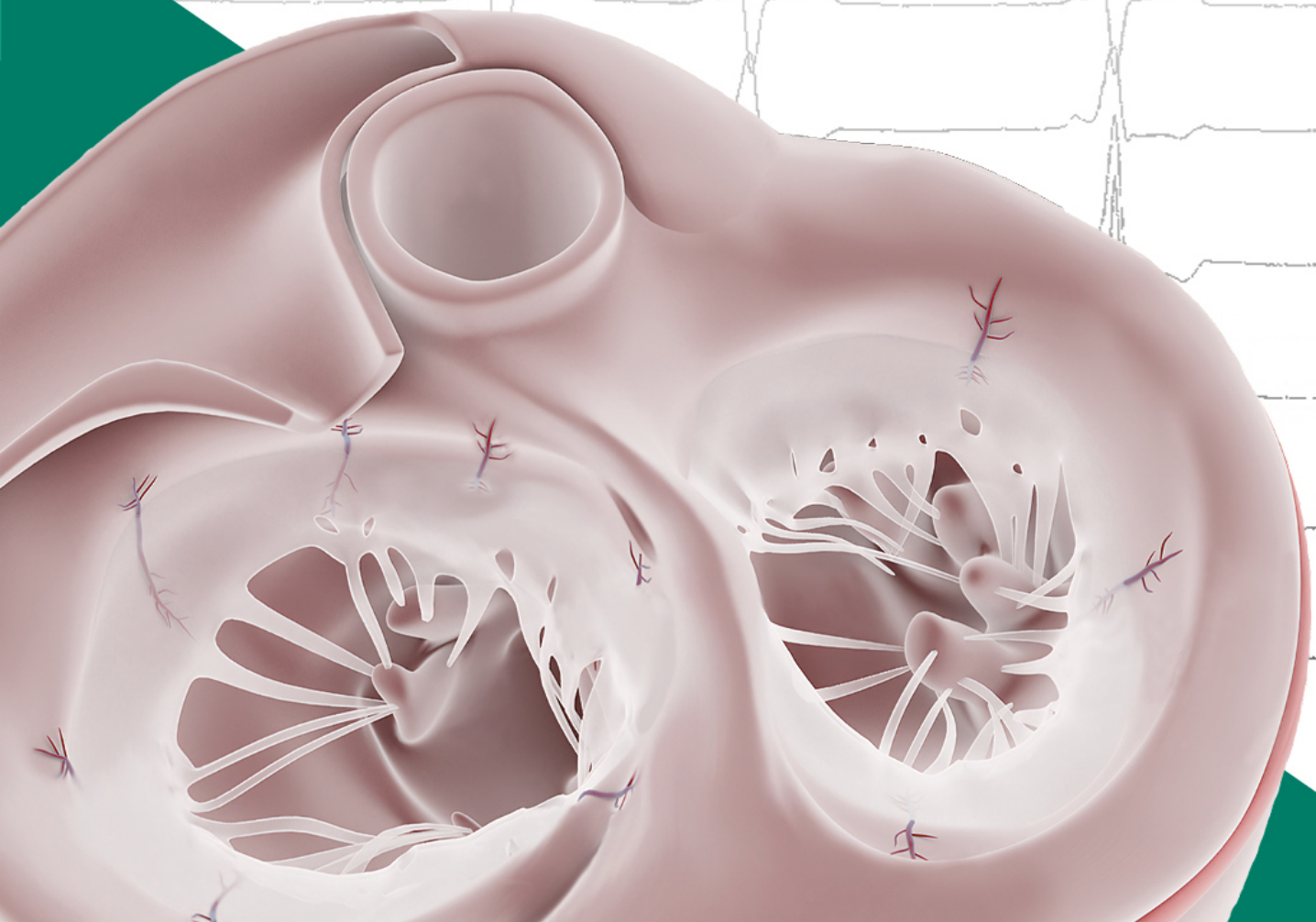
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CARDIAC ARRHYTHMIAS in Dogs and Cats

Mechanisms, diagnosis, and management

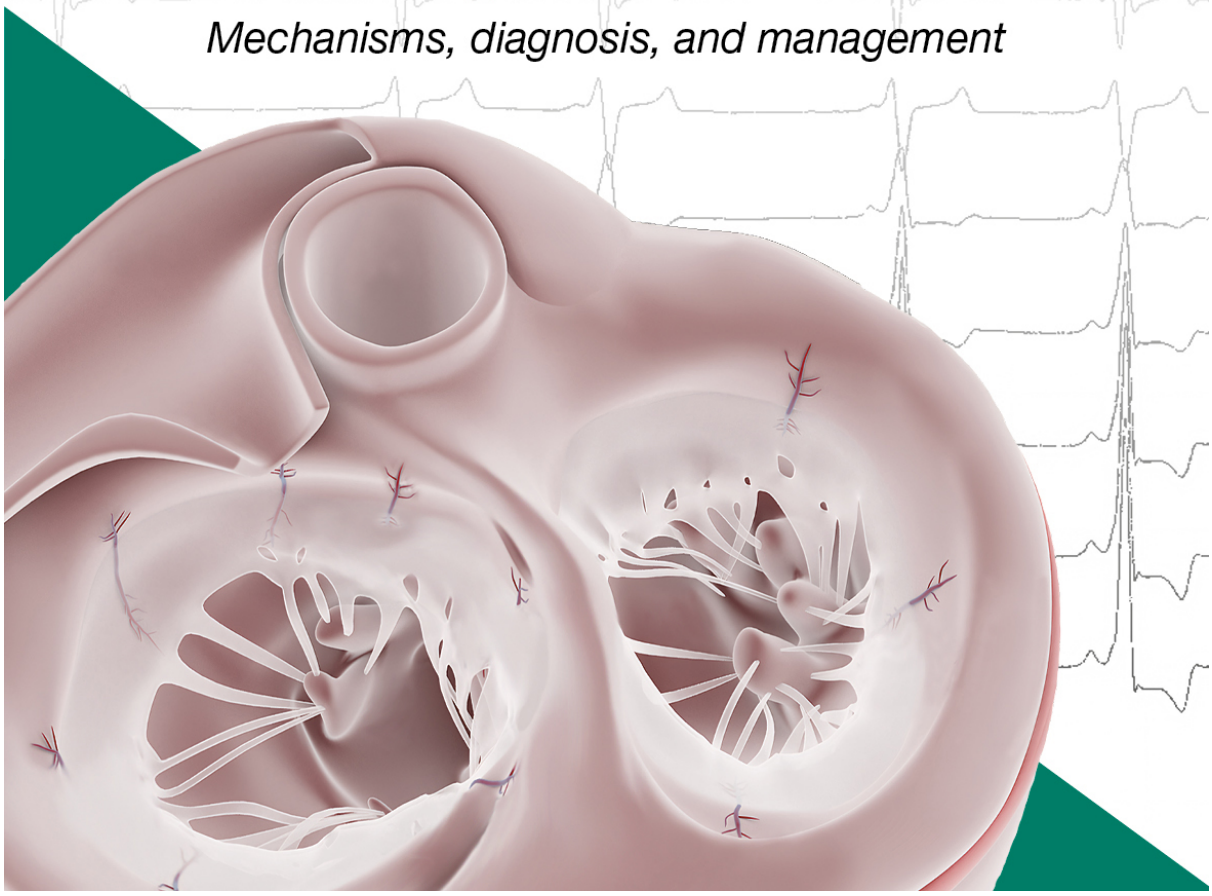


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Roberto Santilli, Romain Pariaut, Manuela Perego
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Roberto Santilli graduated from the College of Veterinary Medicine of the University of Milan, Italy, in 1990. He became a diplomate of the European College of Veterinary Internal Medicine – Companion Animals (specialty of cardiology) in 1999. Between 2004 and 2006, he completed a master's degree in electrophysiology and electrical stimulation at the University of Medicine of Insubria. He then obtained a PhD from the University of Turin – College of Veterinary Internal Medicine in 2010 after completing research on the diagnosis and treatment of supraventricular tachycardias in the dog. Dr. Santilli is the head of the Cardiology Department at Clinica Veterinaria Malpensa, Anicura, in Samarate, Varese (Italy). Since 2014, he has been an adjunct professor of cardiology at the College of Veterinary Medicine of Cornell University, USA, where he is actively involved in the activities of the cardiac electrophysiological laboratory. He is the author of 70

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Romain Pariaut received his degree in veterinary medicine from the National School of Veterinary Medicine in Lyon, France, in 1999. He subsequently became an instructor in emergency and critical care medicine at the same institution. In 2005, he completed a cardiology residency at Cornell University, USA, and attained board certification with the American and European colleges of veterinary internal medicine in 2005 and 2006, respectively. Before coming back to Cornell, Dr. Pariaut was an assistant professor and then associate professor at Louisiana State University. Currently, he is an associate professor and head of the Cardiology Section at Cornell University. His research endeavors have resulted in more than 50 peer-reviewed publications and primarily revolve around unraveling the mechanisms of arrhythmias. Clinically, Dr. Pariaut focuses on the management of arrhythmias and advances in interventional cardiology procedures. He is a coauthor of the textbook *Electrocardiography of the dog and cat* with Drs. Santilli, Moïse, and Perego, and he has been an Associate Editor with the *Journal of Veterinary Cardiology* since 2007.



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Preface

"The aim of science is always to reduce complexity to simplicity"
William James

Following the success of the second edition of *Electrocardiography of the Dog and Cat,* published by Edra Publishing and translated into seven languages (Portuguese, Spanish, French, Italian, Polish, Korean, and Russian), we embarked on a new textbook project to complement our previous work. This collaborative effort stems from a decade-long partnership between the Cardiology departments of Clinica Veterinaria Malpensa, AniCura (Samarate, Italy), under the direction of Professor Roberto Santilli, and of Cornell University (Ithaca, New York, USA), led by Professor Romain Pariaut. Cardiology specialists from both institutions have contributed to this project, coauthoring chapters and providing images and electrocardiographic tracings.

Designed to cater to veterinary specialists in cardiology, anesthesia, intensive care, and emergency medicine as well as to general practitioners seeking to expand their knowledge of the analysis and treatment of arrhythmias in dogs and cats, this book explores rhythm disorders from both clinical and pathophysiological standpoints. For a better understanding of these disorders, each chapter includes detailed information on the cardiac electroanatomy and provides comprehensive descriptions of surface, dynamic, and endocavitary electrocardiographic findings with the latest discoveries in this field. For each rhythm disorder, medical and interventional treatment guidelines are included based on the available literature and the authors' experience.

The book covers a wide spectrum of topics divided into six sections: I – Basic Science, II – Diagnostic Modalities, III – Therapeutic Modalities, IV – Tachycardias, V – Bradycardias, and VI – Specific Diseases. Section I

addresses the electrophysiological mechanisms underlying cardiac arrhythmias and describes their correlation with autonomic nervous system activity, their classification, and their associated clinical findings. In Section II, the focus shifts to surface electrocardiography, offering insights into diagnosing various arrhythmias using specific analytical methodologies. This section also explains the nuances of prolonged dynamic monitoring using Holter devices to help readers in the analysis of electrocardiographic tracings and heart rate variability. Additionally, it provides a detailed description of basic electrophysiological studies and different stimulation techniques, essential for understanding rhythm disorders. Section III begins with a comprehensive review of antiarrhythmic drugs based on the Vaughan Williams classification, with information on their electrophysiological mechanisms, indications, dosages, interactions, and side effects. Anesthesia in dogs and cats is also addressed, given its relevance in treating animals with rhythm disorders. Section III further covers electrical therapy for arrhythmias, including cardioversion, defibrillation, pacemaker or defibrillator implantation, and radiofrequency catheter ablation techniques. Section IV thoroughly discusses clinical, surface electrocardiographic, dynamic, and endocavitary findings of supraventricular and ventricular tachycardias. Each arrhythmia is analyzed in relation to its anatomical and electrophysiological basis, followed by a discussion on clinical, electrocardiographic, and therapeutic characteristics. Diagnostic algorithms proposed by the authors are presented to aid in the understanding of supraventricular arrhythmias. Similarly, Section V focuses on various bradyarrhythmias. Disorders of the sinus node and intra-atrial, atrioventricular, and intraventricular conduction systems are explored, culminating in a discussion on agonal rhythms such as pulseless electrical activity and ventricular fibrillation. The book concludes with Section VI, which describes rhythm disorders associated with various pathological states, including channelopathies, hypertrophic and dilated cardiomyopathies, inflammatory cardiomyopathies, arrhythmia-induced cardiomyopathy, chronic mitral valve disease, and systemic disorders. The final chapters address the causes of syncope and sudden cardiac death in dogs and cats.

We extend our heartfelt gratitude to all our colleagues from the Cardiology departments of Clinica Veterinaria Malpensa, Anicura, and

Cornell University, whose contributions have enriched this book. We also thank our European and North America colleagues who have referred cases for endocardial mapping and radiofrequency ablation over the years. A special expression of gratitude goes to the Silverman family for their encouragement and support through the Henry and Karen Silverman Initiative to Advance Treatment of Canine Arrhythmias, in honor of their beloved dog Rex. The collaboration between our institutions owes much to this generous initiative. We extend our warmest thanks to: Dr. Stefania Scarabelli from the Anesthesia department of Clinica Veterinaria Malpensa, Anicura, whose professionalism and experience have been instrumental in the success of electrophysiological studies, even in the most critical patients; the Anesthesia department at Cornell University for their professionalism; and the Surgery department at Clinica Veterinaria Malpensa, Anicura, led by Dr. Vincenzo Montinaro, for their invaluable assistance and competence during the execution of numerous interventional procedures. We would also like to acknowledge all the Cardiology residents at Clinica Veterinaria Malpensa, Anicura, and Cornell University for their dedication, passion, and eagerness to learn, which have inspired us to advance knowledge in this complex field of cardiology. Finally, we would like to thank Dr. Alessandra Maffei for the accurate research of electrocardiographic tracings, Elena Maria Rossini and Dr. Lucia Ramera for their invaluable help in proofreading, ensuring the accuracy and clarity of the text, and Matilda Bracaloni, Veronica Santilli, and the graphic designers at Edra Publishing for their expertise in executing the iconographic component accompanying the text.

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SECTION I

BASIC SCIENCE

CHAPTER 1

Mechanisms of arrhythmias

Romain Pariaut, Lawrence Santistevan

The mechanisms of arrhythmias can be broadly categorized into abnormalities of impulse conduction, abnormalities of impulse formation, or a combination of both (Table 1.1). Impulse conduction describes how an arrhythmia is perpetuated through the heart. Impulse formation describes how an arrhythmia is initiated.

Abnormalities of impulse conduction include reentry and conduction block; abnormalities of impulse formation include enhanced automaticity and triggered activity.

Usually, it is not possible to identify the exact mechanism of an arrhythmia during routine clinical evaluation and on a surface electrocardiogram. Advanced electrophysiological studies can however provide insight to the underlying mechanism. Importantly, one mechanism may be responsible for the initiation of an arrhythmia and another for its perpetuation. Understanding the mechanisms of arrhythmias remains a helpful tool in the management of rhythm disorders.[1–4]

TABLE 1.1. Summary of arrhythmic disorders, their site of origin and mechanisms (including abnormalities in impulse formation and conduction), and clinical examples.

Disorder	Mechanism/site of origin	Clinical example
Abnormal impulse formation		
Automaticity		
Enhanced normal automaticity	Enhanced automaticity of the sinus node, atrioventricular node, or His–Purkinje fibers	■ Focal junctional tachycardia ■ Nonparoxysmal junctional tachycardia ■ Sinus tachycardia
Enhanced abnormal automaticity	Enhanced automaticity of atrial or ventricular myocardium and tributary veins	■ Focal atrial tachycardia ■ Pulmonary vein firing
Depressed automaticity	Depressed automacity of the sinus node	■ Sinus node dysfunction
Parasystole	Ectopic focus within the myocardium protected by entry block	■ Atrial parasystole ■ Ventricular parasystole
Triggered activity		
Early afterdepolarization	Phase 2 or phase 3 depolarization of the atrial myocardium, ventricular myocardium, or His–Purkinje fibers	■ Inherited ventricular arrhythmias (German Shepherd, English Springer Spaniel) ■ Torsades de pointes ■ Antiarrhythmics with proarrhythmic properties ■ Pulmonary vein firing
Delayed afterdepolarization	Phase 4 depolarization of the atrial myocardium, ventricular	■ Catecholaminergic polymorphic ventricular tachycardia ■ Digitalis toxicity

	midmyocardium, or His–Purkinje fibers	
Abnormal impulse conduction		
Conduction block	Functional, anatomical, physiological, or pathological block within the sinus node, atrioventricular node, or His–Purkinje system	■ Sinus exit block ■ Interatrial block ■ Atrioventricular block ■ Bundle branch block
Reentry	■ Anatomical/functional ■ Phase II reentry, reflection ■ Accessory pathways ■ Ventricular myocardium ■ Atrial myocardium ■ Atrioventricular node ■ His–Purkinje fibers	■ Monomorphic ventricular tachycardia ■ Accelerated idioventricular rhythm ■ Orthodromic atrioventricular reciprocating tachycardia ■ Atrioventricular nodal reciprocating tachycardia ■ Atrial flutter ■ Atrial fibrillation

THE CONCEPT OF HETEROGENEITY

The ventricular myocardium is comprised of different layers of cardiomyocytes that form a mosaic of cells with varying electrical characteristics. These include differences in action potential duration and refractoriness, which is particularly crucial during the repolarization phase. Cardiomyocytes can thus be further categorized as epicardial, mid-myocardial (or M cells), and endocardial myocytes. These differences in refractoriness contribute to the heart's inherent heterogeneity. The action potentials of M cells and epicardial myocytes both exhibit a prominent phase 1 and phase 3 due to the prevalence of an outward potassium current

(I_{to}). However, this current is almost nonexistent in endocardial cells, resulting in the absence of or a discrete phase 1 of the action potential. Epicardial cells exhibit a higher I_{to} density than M cells, which gives their action potential a prominent spike and dome appearance. Conversely, M cells have a longer action potential duration, likely due to a lower I_{Ks} density that prolongs phase 2 of the action potential.[1–4]

These differences in potassium handling create a transmural gradient of repolarization across the myocardium (Fig. 1.1).[1–4] This transmural electrical heterogeneity can serve as a substrate for arrhythmogenesis, particularly in the presence of abnormal conditions such as heart failure, cardiomyopathy, ischemia, and drug therapy.

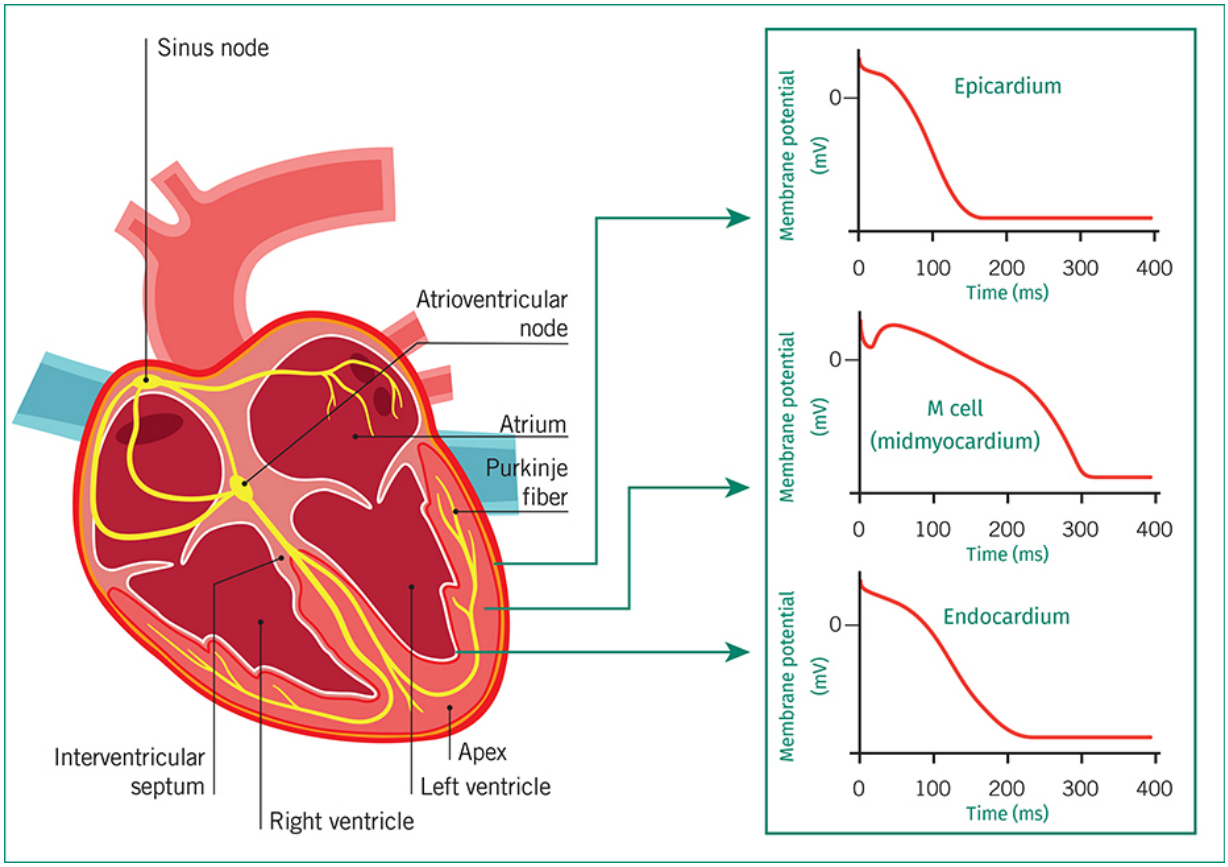


FIGURE 1.1. Concept of heterogeneity within the ventricular myocardium including the epicardium, M cells, and endocardium. Note the differences in action potential morphologies and durations, particularly during repolarization. The endocardial layer displays a slurred phase 1 due to a lower I_{to} current. M cells have longer action potentials due to a lower I_{Ks} current. The epicardial layer maintains a spike and dome appearance because of a prominent I_{to} current.

ABNORMALITIES OF IMPULSE CONDUCTION

REENTRY

Reentry occurs when an electrical impulse becomes entrapped in an abnormal circuit within the heart muscle that allows for its continuous excitation. In the normal heart, the electrical impulses from the sinus node propagate in an orderly manner within the myocardium to stimulate rhythmic contractions. However, if an area of the myocardium is in the refractory state and cannot conduct the normal electrical impulse secondary to a *unidirectional block*, it serves as a potential pathway for that initial impulse to reactivate the myocardial tissue once it has recovered excitability. A persistent re-excitation is known as a reentry and can perpetuate tachyarrhythmias.[5,6]

For a reentry circuit to form, certain prerequisites must be present:

1. An area of nonconducting tissue (anatomical vs. functional).
2. A pathway with a long refractory period where a unidirectional block occurs.
3. A pathway with slow conduction velocity where impulse conduction occurs.
4. An initiating trigger.

Therefore, a reentry circuit is typically comprised of two pathways, or branches, separated by an area of nonconducting tissue. These two branches can be differentiated into an α-*branch,* where antegrade conduction occurs, and a β-*branch,* where retrograde conduction takes place. Figure 1.2 describes the potential outcomes of a reentry circuit. A slow conduction velocity along the α-branch gives enough time for the β-branch to recover from a block, and the impulse conducts retrogradely up the β-branch. Once it reaches the α-branch again, the impulse may stop if the tissue is still in a refractory state or re-excite the α-branch initiating a second loop of reentry.

Initiation and maintenance of reentry depend on two critical parameters: the conduction velocity of electrical impulses along the reentrant pathways and the refractory periods of the circuit's components. These two factors dictate the reentrant wavelength, which is calculated as the conduction velocity multiplied by the refractory period.[5] For reentry to propagate, the

reentrant wavelength must be equal to or shorter than the anatomical circuit available for the electrical impulse to propagate.

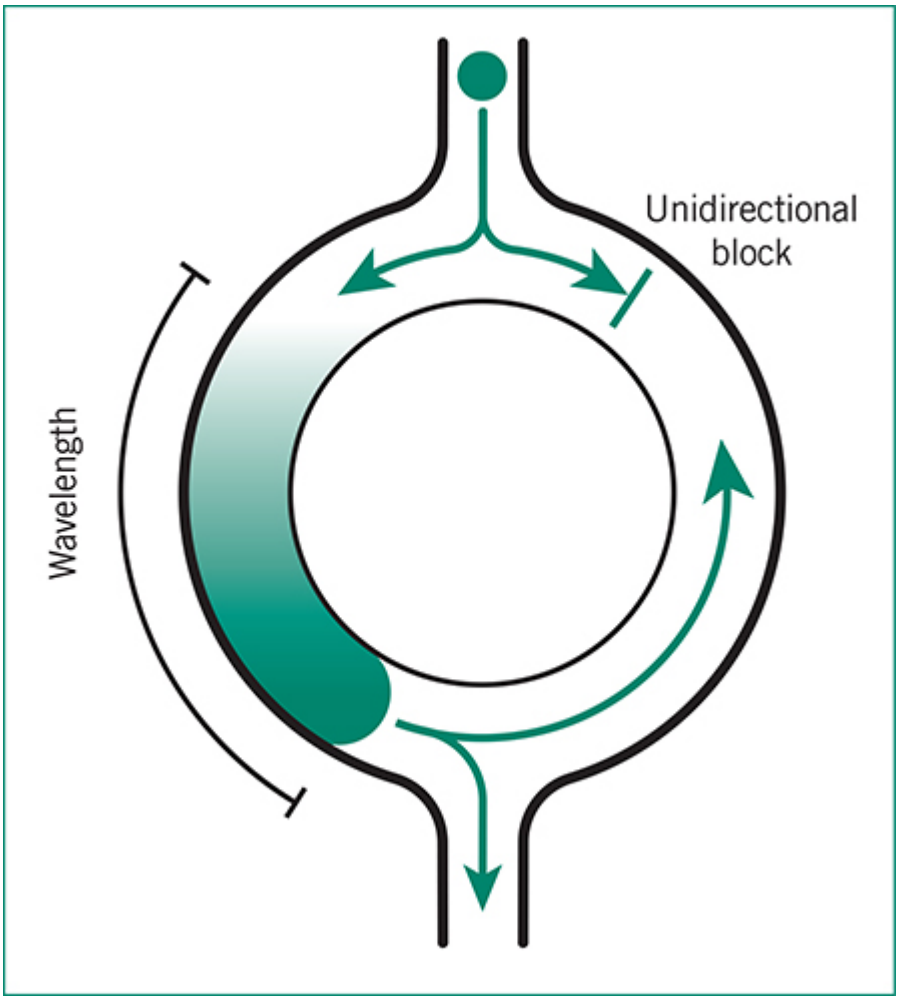


FIGURE 1.2. Schematic representation of a reentry circuit containing two branches of impulse conduction separated by an area of nonconduction.

Reentry can be subdivided into two types: anatomical and functional. Moreover, six different models of reentry have been proposed:

1. Ring model
2. Leading circle model
3. Figure-of-eight model
4. Spiral model
5. Reflection
6. Phase II reentry

Anatomical reentry involves the presence of an anatomical obstacle around which an electrical impulse travels following a fixed path.[5,6] Examples of anatomical obstacles include the valve annulus or areas of fibrotic tissue. As the anatomical circuit is typically slightly longer than the reentrant wavelength, this type of reentry possesses an excitable gap, which is an area of excitable myocardium that exists between the head and the tail of the electrical wavefront and allows for continuous reactivation and propagation of an arrhythmia. An increase in conduction velocity along the α-branch of the circuit or an increase in the refractory period in the β-branch may prevent the reentry from occurring. Conversely, a reduction in conduction velocity or an increase in the refractory period may promote the arrhythmia (Fig. 1.3). This type of reentry is also frequently termed *circus reentry*.

Examples of anatomical reentry circuits include orthodromic atrioventricular reciprocating tachycardia, atrioventricular nodal reciprocating tachycardia, atrial flutter, and some forms of ventricular tachycardia. These arrhythmias are examples of the ring model of reentry (Fig. 1.4).

Functional reentry does not require a fixed anatomical circuit to propagate. Rather, this form of reentry involves an ever-changing central core of functionally refractory tissue and therefore depends on the refractory period of excitable tissue. The wavefront of a functional reentry circuit causes cardiomyocytes within a circuit to be immediately reactivated by the wavefront once they have recovered since the head and the tail of the wavefront nearly overlap, leaving no excitable gap. These types of pathways typically follow the leading circle, spiral, and figure-of-eight models (Fig. 1.5). Circus reentry has also been described with functional reentry circuits but is mostly associated with anatomical reentry. Examples of functional reentry include atrial fibrillation, some forms of ventricular tachycardia, and ventricular fibrillation.

Reflection typically occurs in a linear rather than circular fashion. The impulse travels linearly and parallel to an area of depressed conduction in an antegrade direction. When the wavefront reaches the distal portion of tissue with decreased conduction, that tissue is then re-excitable, and the impulse then reverses its direction to reenter the circuit, and propagates in a retrograde direction, thereby creating a reentry loop (Fig. 1.6).

Phase 2 reentry is the development of an arrhythmia due to a change in the heterogeneity of the layers of the myocardium. Changes in refractoriness secondary to inward or outward ion currents can alter the morphology and duration of action potentials within the myocardial layers and potentially promote reentry during phase 2 (or dome phase) of the action potential. This can be observed with a decreased outward I_{to} current in the epicardium, resulting in changes in its spike and dome appearance. This is also described as the underlying cause of ventricular arrhythmias in humans with Brugada syndrome secondary to a mutation in the inward sodium channels, which has not yet been described in veterinary species.[7]

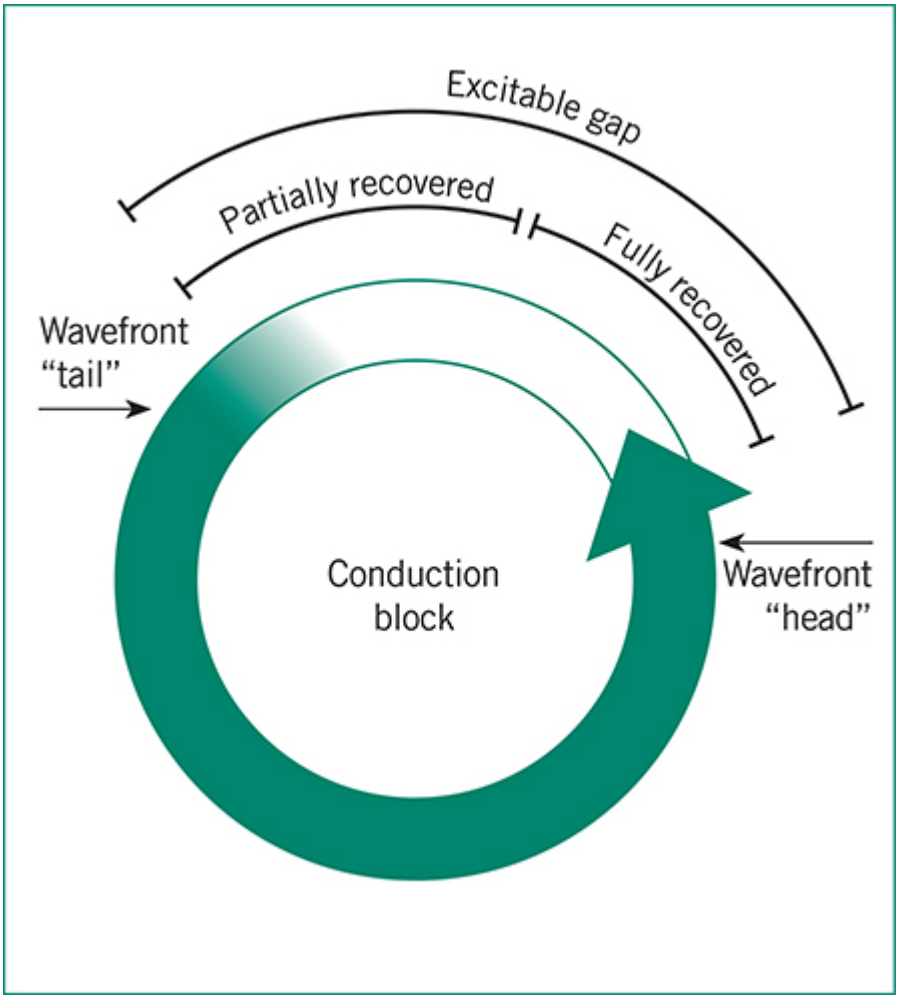
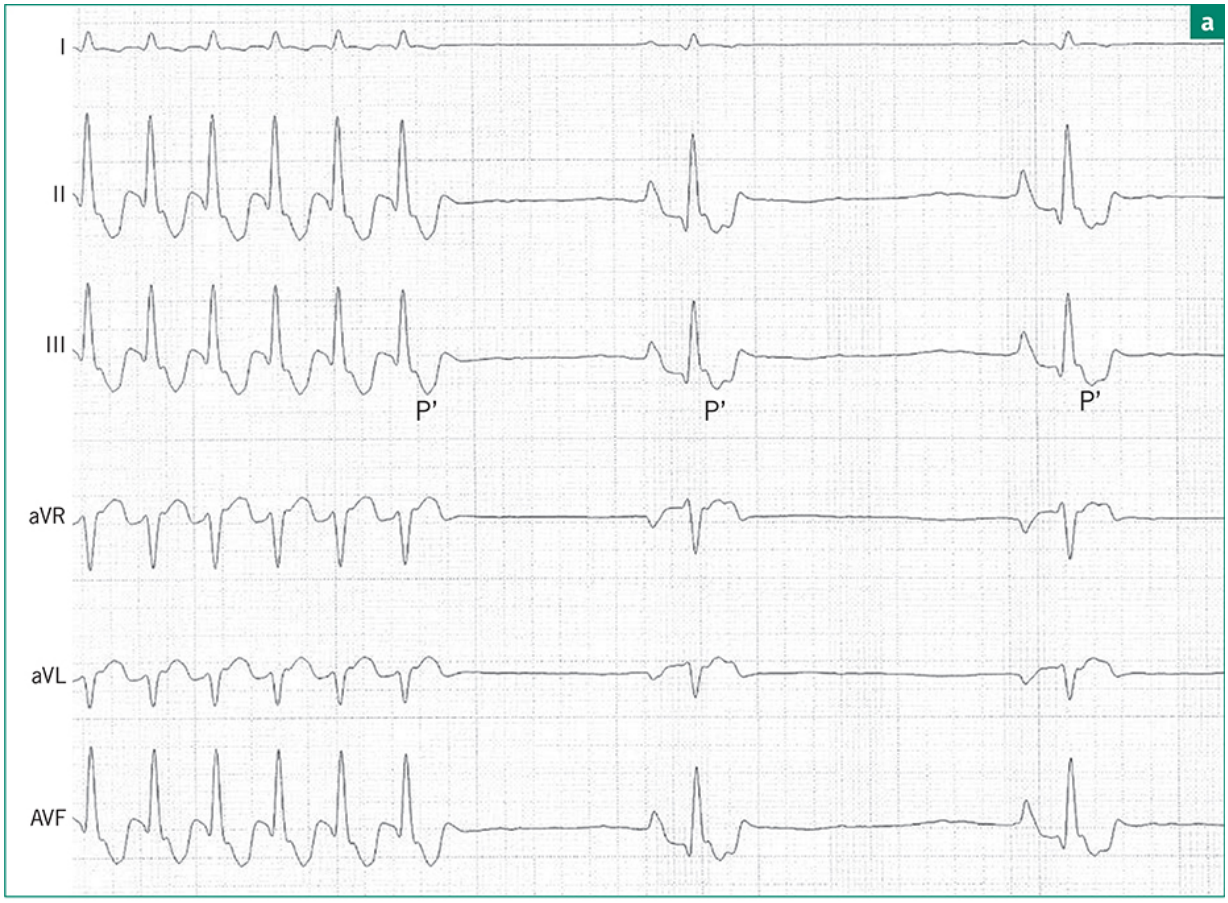


FIGURE 1.3. An excitable gap associated with an anatomical reentry circuit. Notice how the excitable gap maintains an area of fully recovered and partially recovered cells between the head and the tail of the electrical wavefront. This helps potentiate the reentry circuit.



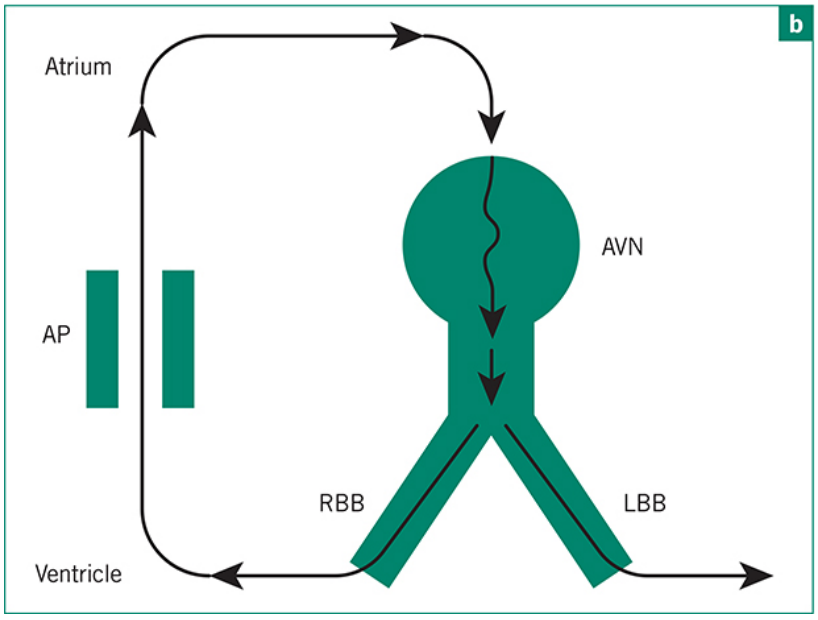


FIGURE 1.4. An example of the ring model of reentry involving the presence of an accessory pathway, responsible in this case for orthodromic atrioventricular reciprocating tachycardia. a) Six-lead electrocardiogram of a dog with an accessory pathway. During the first part of the tracing, orthodromic atrioventricular reciprocating tachycardia is present and terminates abruptly with an atrial depolarization (P') block in the atrioventricular node region. The following sinus beats conduct

retrogradely as evidenced by the presence of a negative P' wave in the ST segment. b) In this circuit, impulses from the atrium conduct antegradely down the atrioventricular node, into the ventricular myocardium, and then retrogradely through the accessory pathway back into the atrial myocardium. AP, accessory pathway; AVN, atrioventricular node; LBB left bundle branch; RBB right bundle branch.

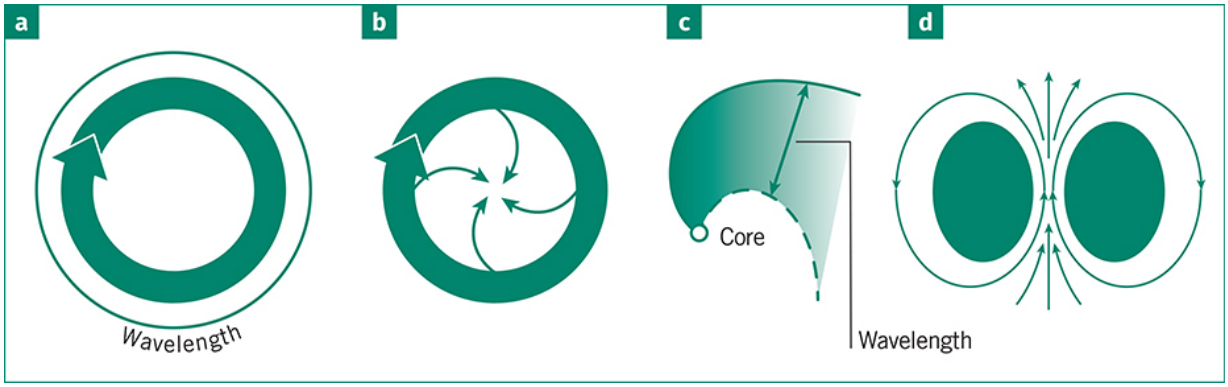


FIGURE 1.5. Examples of the different models of functional reentry. a) Schematic drawing of a functional reentry circuit. Compared to an anatomical reentry circuit, functional reentry circuits commonly do not contain an excitable gap; therefore, the head and the tail of the wavefront almost overlap, allowing for continuous reactivation and propagation of an electrical impulse. b) The leading circle model shows an electrical wavefront revolving around a core in a sustained state of refractoriness due to the constant activation of electrical impulses. There is no anatomical barrier present. c) The spiral model shows a refractory core (sometimes called a filament) around which the electrical wavefront rotates, like in the leading circle model. d) The figure-of-eight model shows two reentrant loops that travel around an area of nonconduction (green portions) and in opposite directions (counterclockwise and clockwise) but share a central portion of their circuits between the two areas of nonconduction.

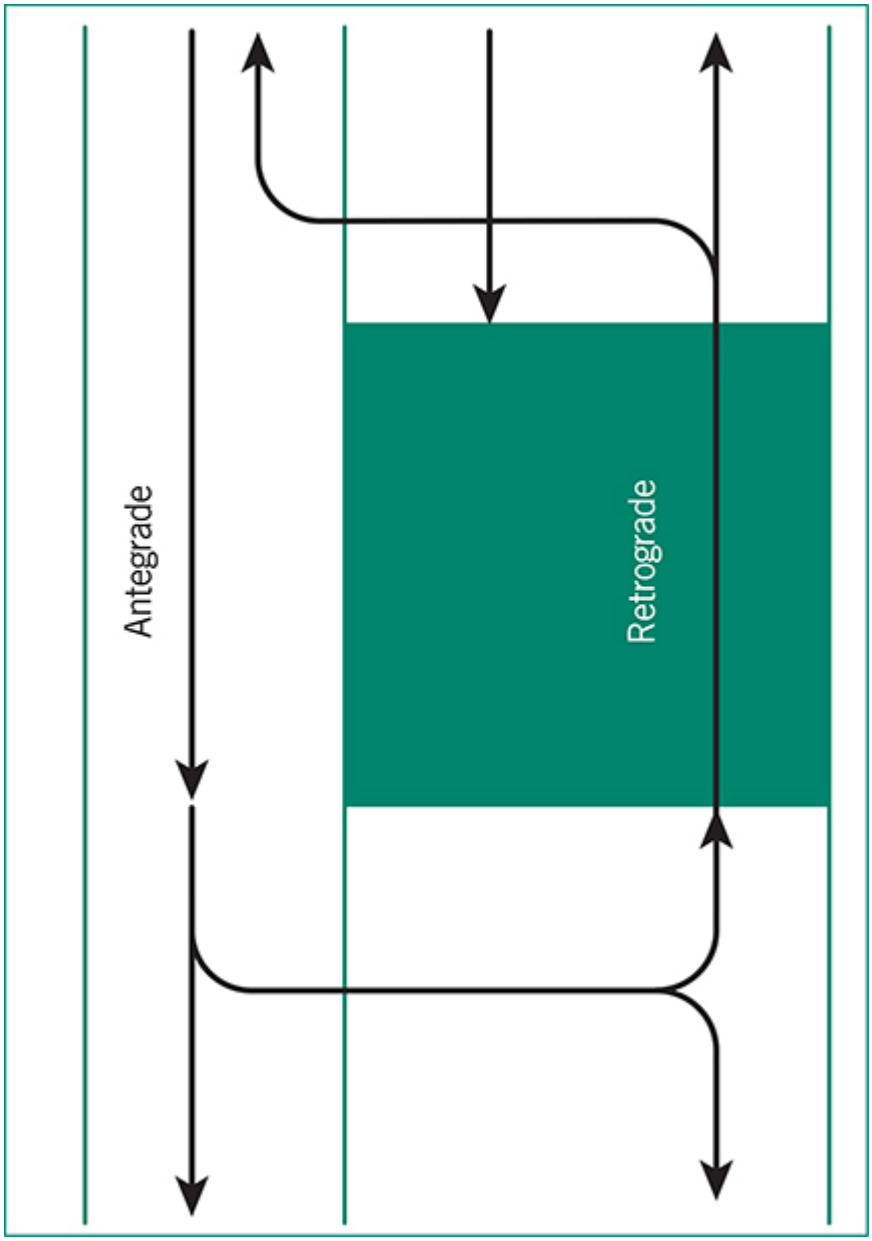


FIGURE 1.6. Reflection. In this model of reentry, a wavefront travels antegradely and parallel to an area of tissue with decreased conduction (green square). Once the wavefront reaches the distal end of the area of depressed conduction, that area is no longer refractory and becomes re-excited. The impulse then travels retrogradely within the tissue and can either be blocked at the proximal region or propagate reentry.

CONDUCTION DISTURBANCES

The impaired transmission of electrical impulses within the cardiac conduction system is known as a *conduction block.* These disruptions can lead to a *partial* or *complete block* of impulse conduction that can be

secondary to a physiological or pathological block due to an *anatomical block* or *functional block*.

A partial block describes a decrease in the conduction velocity of a propagated impulse, while a complete block results in the abrupt termination of the conducted impulse.

A physiological block occurs due to the inherent properties of the cardiac conduction system. If an electrical wavefront is conducted with a short cycle length down a pathway that is still in its refractory state, then the impulse will not be conducted. This can result in complete block or partial block and potential aberrant conduction. These types of blocks are commonly identified with supraventricular tachycardias and result in second-degree atrioventricular block or bundle branch block; they are a mechanism that protects the ventricles from a rapid heart rate.

A pathological block occurs when there has been damage to the electrical conduction system (e.g., fibrosis, inflammation, or ischemia) that prevents impulse propagation. These can result in an anatomical block, which is caused by an anatomical lesion within the conduction system, or a functional block when an electrical impulse attempts to travel through a portion of the conduction system during its refractory state. Functional blocks can be termed *rate-dependent blocks* as different bradyarrhythmias and tachyarrhythmias can result in blocks occurring at different phases of the action potential.

Two types of functional blocks exist (Fig. 1.7):[8]

- A *tachycardia-dependent (or phase 3) block* occurs when electrical impulses are blocked when they arrive at an area that has not yet recovered from refractoriness.
- A *bradycardia-dependent (or phase 4) block* is due to decreased excitability of cardiomyocytes during diastole.

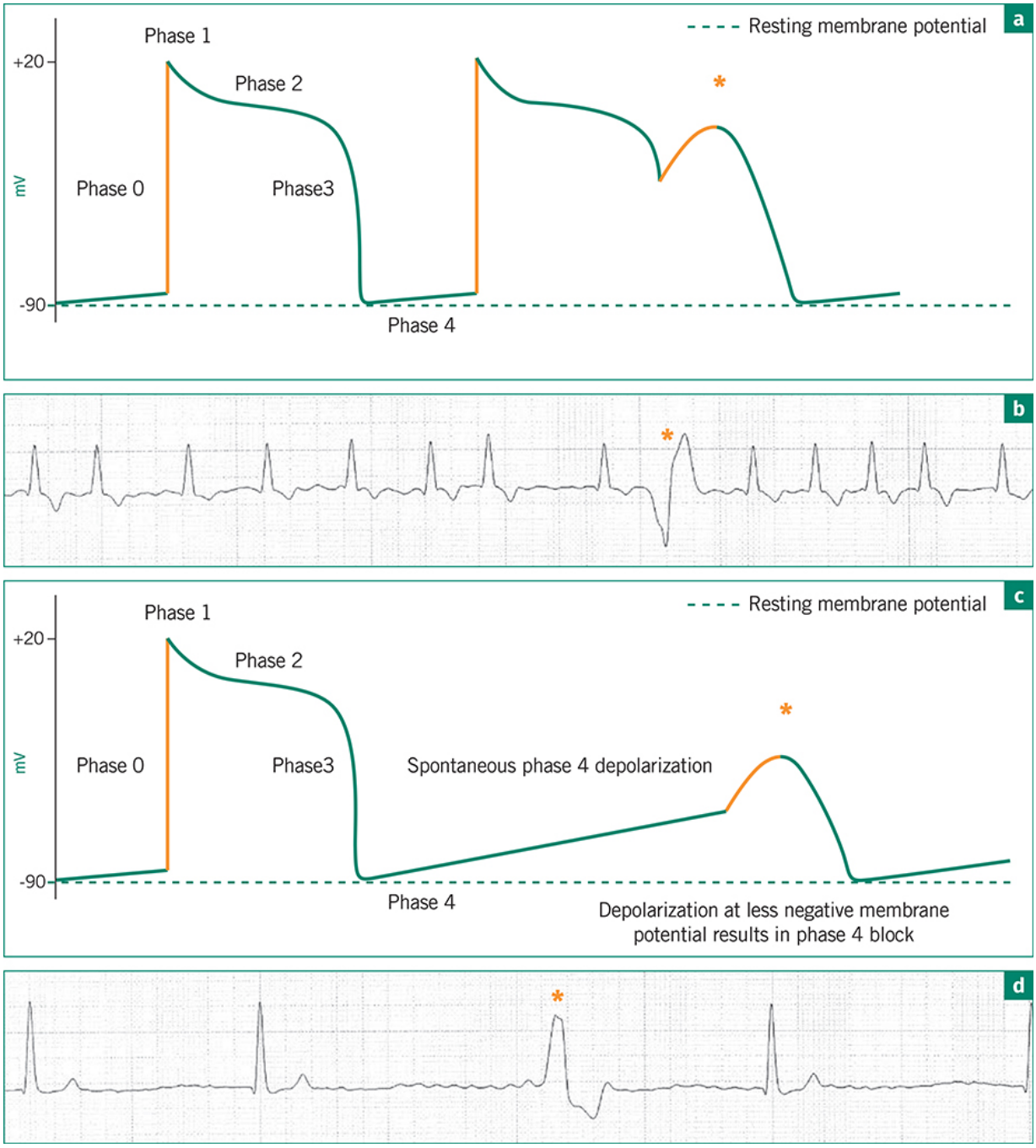


FIGURE 1.7. Rate-dependent conduction block. a) Diagrammatic representation of a phase 3 conduction block, or tachycardia-dependent block. When a stimulus occurs during phase 3 of an action potential, most sodium channels are in an inactivated state and a new action potential is not generated. b) Example of phase 3 aberrancy (rate-dependent right bundle branch block). At the organ level, a phase 3 block limited to some areas of the myocardium leads to phase 3 aberrancy. When the cycle length of an arrhythmia is shortened, or a premature beat occurs, the electrical impulse is blocked (*) in one of the bundle branches that is still in its refractory state. This is commonly associated with a right bundle branch block because the right bundle branch has a longer refractory period than the left. This is also the mechanism of Ashman's phenomenon. c) Diagrammatic representation of a phase 4 block. During periods of bradycardia or abrupt slowing of the heart rate,

phase 4 of the action potential can be associated with spontaneous depolarization of the membrane potential in diseased tissues. As a result of a less negative membrane potential, fewer sodium channels are available, which can result in a conduction block when the next stimulus reaches the tissue. d) Example of phase 4 aberrancy (bradycardia-dependent aberrancy). At the organ level, a phase 3 block limited to some areas of the myocardium leads to phase 4 aberrancy (*).

ABNORMALITIES OF IMPULSE FORMATION

ENHANCED AUTOMATICITY

Automaticity is the ability for cardiac cells to undergo spontaneous depolarization, which results in an action potential and therefore in rhythmic contraction of the working cardiomyocytes. Automaticity is a characteristic of nodal cells due to their inherent ability to spontaneously depolarize.

The sinus node, or "dominant pacemaker", exhibits the highest intrinsic rate of automaticity. In contrast, cells of the atrioventricular node, bundle of His, and Purkinje network—known as *subsidiary pacemakers*— have lower intrinsic rates and thus typically act as latent pacemakers. Tissues with pacemaker properties can also be found in the atrial and ventricular myocardium, particularly within the outflow tracts, tributary veins, and heart valves.[7] However, subsidiary pacemakers can discharge at a faster rate than the underlying sinus rate when the automaticity of the sinus node is depressed or their own automaticity is enhanced.

Under normal conditions, subsidiary pacemaker cells are suppressed via *overdrive suppression* from the sinus node. When these subsidiary pacemaker cells are repeatedly activated, an accumulation of intracellular sodium ions occurs, which triggers the sodium–potassium ATPase pump. This process leads to hyperpolarization, meaning the membrane becomes more negatively charged. Hyperpolarization of the subsidiary pacemaker cells prevents them from initiating an action potential before the sinus node undergoes another depolarization cycle.

The ability for nodal cells to undergo spontaneous depolarization is due to the inherent presence of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, which results in a slow influx of sodium ions, or "funny" current (I_f), and therefore in a continuous slow rise of the membrane resting potential during diastole (phase 4 of the action potential).

Once the threshold is reached, an action potential occurs due to an influx of calcium through T-type and L-type calcium channels (phase 0).

The slope of phase 4 to reach the threshold is also impacted by the autonomic nervous system: heightened sympathetic tone will increase the slope of phase 4 to threshold, thus resulting in an increased discharge frequency (or faster heart rate); conversely, heightened parasympathetic tone will decrease the slope of phase 4 to threshold and result in a decreased discharge frequency (or slower heart rate). These are the characteristics of enhanced or depressed automaticity, respectively. The firing rate of pacemaker cells is influenced by the maximum diastolic potential, the action potential threshold, and the slope of phase 4 of the action potential (Fig 1.8).[3,5]

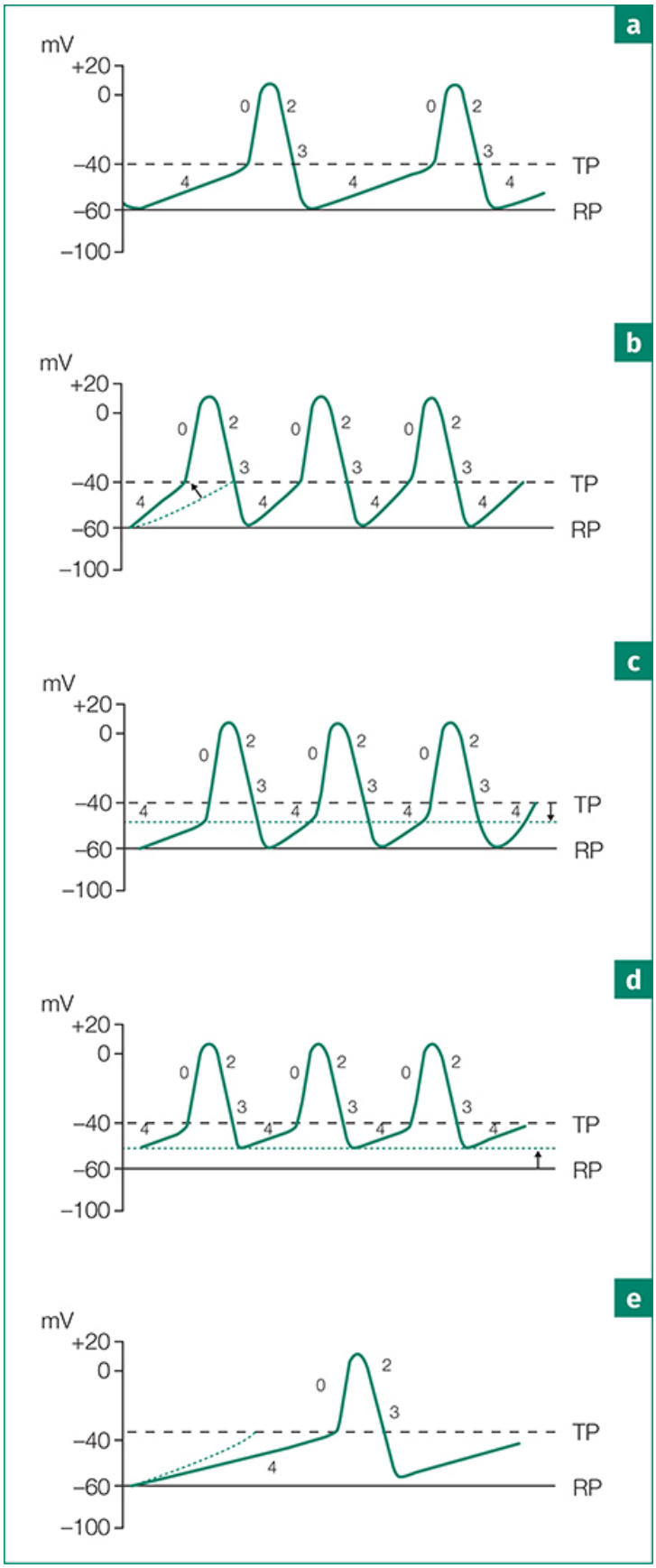

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FIGURE 1.8. Concept of automaticity. Schematic representation of automaticity of the sinus node and the effects of enhanced and depressed automaticity. a) Normal sinus node firing. b) An increased slope of phase 4 results in increased frequency of discharges (faster heart rate). c), d) A more negative threshold potential (c) or a less negative resting membrane potential (d) may also result in more frequent impulse firing (faster heart rate). e) A decreased slope of phase 4 results in a decreased frequency of discharges (slower heart rate). TP, threshold potential; RP, resting potential.

ENHANCED ABNORMAL AUTOMATICITY

Contractile cells of the heart are usually quiescent unless stimulated by nodal cells and therefore do not possess inherent properties of automaticity. However, under abnormal conditions, these cells may acquire automaticity and predispose patients to abnormal rhythms such as premature beats and tachyarrhythmias (e.g., focal atrial tachycardia and ventricular tachycardia).

These acquired mechanisms of enhanced abnormal automaticity can be explained by abnormalities in the membrane potential: a more positive resting membrane potential is closer to the threshold for action potential generation, which may cause underlying contractile cells to become easily excitable. Causes of increased membrane potential include acidosis, hyperkalemia, and increased catecholamines. Enhanced abnormal automaticity is also more resistant to mechanisms of overdrive suppression than enhanced normal automaticity.[5]

TRIGGERED ACTIVITY

Triggered activity occurs when quiescent cells fire prematurely during an action potential due to a triggering event such as changes in autonomic tone, aberrant depolarizations, or drug effects. These triggering events result in oscillations, also known as *afterdepolarizations*, of their membrane potential after the onset of the action potential. Afterdepolarizations are categorized based on the phase during which they take place within the action potential. Whenever these oscillations reach the threshold potential, a new action potential is generated before complete repolarization of the initial action potential and results in a premature beat or a sequence of ectopic beats.

Afterdepolarizations are classified as:

1. Early afterdepolarizations (EADs)
2. Delayed afterdepolarizations (DADs)

EARLY AFTERDEPOLARIZATIONS

Early afterdepolarizations occur during phase 2 or phase 3 of the action potential and are typically associated with a prolonged action potential duration. Therefore, the ventricular mid-myocardial cells (M cells), characterized by their long action potentials, exhibit a higher inherent susceptibility to developing early afterdepolarizations. Moreover, early afterdepolarizations are more likely to occur during bradycardia, a condition associated with an increased action potential duration.

Early afterdepolarizations typically result from a reduction in the outward potassium currents, which are responsible for the repolarizing phases of the action potential. This leads to a prolongation of the action potential, thus allowing for recovery and reactivation of the L-type calcium channels and an influx of calcium. The increase in intracellular calcium then activates the sodium–calcium exchanger, which transports one calcium ion out of the cell for three sodium ions into the cell (net positive charge). This can result in a new, premature action potential if the membrane voltage crosses the threshold potential. An early afterdepolarization can occur when the membrane potential is -30 mV during phase 2 or -60 mV during phase 3 (Fig. 1.9a).[6]

Clinical situations that may promote early afterdepolarizations include heart block, acidosis, hypokalemia, hyperkalemia, and hypothermia. Some antiarrhythmic drugs may also predispose patients to early afterdepolarizations due to an effect on action potential duration, such as class Ia antiarrhythmics (quinidine and procainamide) and class III antiarrhythmics (sotalol via inhibition of the I_{Kr} current). In the German Shepherd dog, early afterdepolarizations have been described as the underlying cause of an inherited ventricular arrhythmia that typically occurs during periods of slower heart rates.[9–12] A *KCNQ1* genetic mutation causing QT prolongation in English Springer Spaniels has also been described and predisposes the breed to early afterdepolarizations and subsequent malignant arrhythmias.[13] A *QIL1* genetic mutation identified in Rhodesian Ridgebacks has also been described as predisposing the breed to ventricular arrhythmias that are likely associated with early afterdepolarizations.[14,15]

DELAYED AFTERDEPOLARIZATIONS

Delayed afterdepolarizations occur during phase 4 of the action potential because of an increased intracellular calcium concentration independent of L-type calcium channels. The increase in cytosolic calcium activates the sodium–calcium exchanger, leading to an influx of three sodium ions and an efflux of one calcium ion. This imbalance results in an intracellular net positive charge, potentially raising the membrane voltage to the threshold potential and triggering another action potential (Fig. 1.9b). Delayed afterdepolarizations are typically associated with disorders causing tachycardia.

Increased circulating catecholamines, digitalis toxicity, hypercalcemia, hypokalemia, and myocardial reperfusion can cause an increased predisposition to delayed afterdepolarizations.

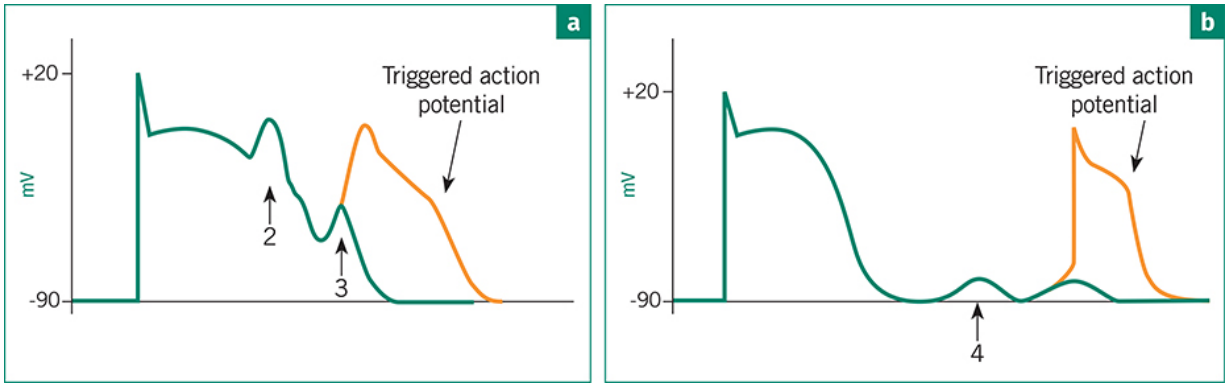


FIGURE 1.9. Triggered activity and afterdepolarizations. a) Early afterdepolarizations occurring during phase 2 (~-30 mV) or phase 3 (~-60 mV) of the action potential. If the early afterdepolarization reaches the threshold, it can generate a new action potential. b) Delayed afterdepolarizations occurring during phase 4 (~-90 mV) of the action potential. Note the shortened action potential duration, usually due to tachycardia. If oscillations (or afterdepolarizations) exceed the threshold, then a new action potential is triggered.

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CHAPTER 2

Influence of the autonomic nervous system on arrhythmias

Manuela Perego, Alessandra Maffei

The autonomic nervous system is made up of the sympathetic and parasympathetic systems. The effects of the autonomic nervous system on the cardiac rhythm are potent and diverse. This is because the autonomic nervous system is regulated by several mechanisms, in particular by afferent signals arising from the kidney, the baroreceptors, the carotid bodies, and the intracardiac ganglionated plexi.[1] The renal nerves are the main regulators not only of renal function but also of the circulating volume, cardiac output, and blood pressure. The carotid baroreflex originates mainly from baroreceptors located in the blood vessels that detect the local blood pressure. The carotid bodies are chemoreceptors located at the bifurcation of the internal carotid arteries; their main function is to regulate respiration so as to maintain normal arterial partial pressures of oxygen and carbon dioxide.[1,2] Ganglionated plexi consist of conglomerations of autonomic ganglia, nerve axons, and interconnected neurons on the epicardial surface of the heart and have an important role in arrhythmia induction and maintenance.[1]

The cardiac nervous system is composed of an extrinsic and an intrinsic part. The extrinsic part includes the ganglia and nerves travelling to the heart. A ganglion is defined as a cluster of neurons located outside the brain. The sympathetic ganglia, also called paravertebral ganglia, are located within the sympathetic chain, while the parasympathetic ganglia, also called intrinsic cardiac autonomic system, are distributed in the epicardial area.

The intrinsic nervous system includes the network of intracardiac ganglia and interconnecting neurons. The ganglia contribute to the modulation of cardiac electrophysiological properties by integrating the inputs from both the extrinsic and intrinsic cardiac nervous systems.[3,4]

While the normal heart can withstand the autonomic system's activity in response to stressful stimuli (both mental and physical), the diseased or aging heart can develop significant rhythm abnormalities. This vulnerability characterizes both the specialized conduction system (i.e., sinus node; interatrial, internodal, atrionodal pathways; atrioventricular node; intraventricular conduction system; and Purkinje fibers) and the atrial and ventricular myocardium, with significant differences in their response to autonomic nervous system stimulation.[1–4]

The effects of sympathetic and parasympathetic activity vary considerably depending on the cardiac structure and/or function under consideration. Sinus node automaticity is particularly responsive to parasympathetic influence, while the atrioventricular node seems to be especially sensitive to sympathetic activity.[1,2]

The response of supraventricular structures to autonomic nervous system activity ranges from rapid compensatory or reflex sinus tachycardia to fast supraventricular arrhythmias, which can degenerate into atrial fibrillation. Derangements in ventricular rhythm due to intense autonomic activity can be most severe and trigger ventricular fibrillation and sudden cardiac death.[1–6]

AUTONOMIC NERVOUS SYSTEM AND SINUS NODE

The heart rate is determined by spontaneous electrical pacemaker activity in the sinus node. The cells within the sinus node (P cells) are the dominant pacemaker in the heart because, although they are characterized as having no true resting potential, they are able to generate regular and spontaneous action potentials. Unlike nonpacemaker cells, the depolarizing current (or funny current, I_f) of the action potential of P cells is mainly achieved through slow Ca^{2+} channels instead of fast Na^{+} channels. This results in a slow depolarization phase (phase 0). P cells are also characterized by

spontaneous repolarization during phase 4 of the action potential; this triggers the next action potential when the membrane potential reaches the threshold (–30/–40 mV). This phase mainly depends on I_f channels. Normal sinus node function results from a balanced interaction between the intrinsic properties of the sinus node and extrinsic factors, among which the autonomic nervous system seems to be of particular importance. The role of the sympathetic and parasympathetic systems is mainly mediated by their influence on I_f channels.[1,2] There is evidence supporting a combined role of I_f channels and Ca^{2+} clocks in the regulation of sinus node activity. The increase in the discharge rate of the sinus node P cells is mediated by an increased slope of phase 4 of the action potential and by an increase in the value of the resting potential, with less negative values. These effects are due to the release of noradrenaline, which causes protein kinase A-dependent phosphorylation of proteins; this regulates intracellular calcium balance and spontaneous sarcoplasmic reticulum calcium cycling.[2] Vagus nerve activity mediated by acetylcholine release decreases the P cell discharge rate by decreasing the slope of phase 4 of the action potential and the value of the resting potential, which reaches more negative values. The more negative values of the resting potential are caused by an increased permeability of the sarcoplasmatic membrane to K^+, which induces a hyperpolarized state of the cell.[2] Sinus node activity is also influenced by other extrinsic factors such as hypoxia, exercise, and temperature.

The rhythmic fluctuation of the heart rate during breathing is called respiratory sinus arrhythmia and is mediated through the Hering–Breuer reflex. This reflex is triggered to prevent overinflation of the lung. After baroreceptor activation during inspiration, action potentials are sent through large myelinated fibers of the vagus nerve to the inspiratory area of the medulla. In response, the inspiratory area is directly inhibited, allowing expiration to occur.[1,2] Because the Hering–Breuer reflex uses the vagus nerve as its neural pathway, it also has some cardiovascular system effects, as the vagus nerve also innervates the heart. During stretch receptor activation, the inhibitory signal that travels through the vagus nerve is also sent to the sinus node, causing an increase in heart rate. The heart rate returns to normal during expiration when stretch receptors are deactivated. When this process is cyclical, it is called respiratory sinus arrhythmia, which is a generally normal physiological phenomenon in which short-term

tachycardia is observed during inspiration. Respiratory sinus arrhythmia constitutes an important measure of cardiovascular health, as it decreases with advancing age, thus reflecting decreases in cardiac and vascular elasticity and compliance and in the capacity of P cells to be activated.[1]

AUTONOMIC NERVOUS SYSTEM AND ATRIOVENTRICULAR NODE

The sinus and atrioventricular nodes respond differently to the same autonomic stimulus. Atrioventricular conduction is preferentially sensitive to sympathoadrenergic activity, whereas sinus node automaticity, like atrioventricular junctional automaticity, is especially responsive to parasympathetic influences.[2]

Most of the delay in conduction time occurs at the level of the atrioventricular node, which is richly innervated by autonomic nervous system fibers. An increased level of vagal stimulation prolongs the atrioventricular conduction time, while sympathetic drive increases conduction. Because the atrioventricular node is innervated by many vagal fibers, even relatively low levels of brief or sustained vagal stimulation may greatly alter atrioventricular node conduction.[1–4]

In normal conditions, there is a sympathetic preponderance over parasympathetic activity in the modulation of atrioventricular conduction velocity. This finding is directly opposed to the accentuated antagonism observed in the sinus node, where the parasympathetic drive is preponderant over sympathetic tone. At the level of the atrioventricular node, this implies that vagal stimuli are less effective when sympathetic activity increases.[2–6]

AUTONOMIC NERVOUS SYSTEM AND ATRIAL FIBRILLATION

The correlation between clinical and experimental models of atrial fibrillation and changes in autonomic system tone is well established. Both adrenergic and vagal stimulation can favor the onset of atrial fibrillation

through complex mechanisms of shortening of the atrial refractory period and heterogeneity of refractoriness and conduction, which finally condition the wavelength of atrial fibrillation.[9] Atrial fibrillation starts with a period of rapid ectopic activity, which may be caused by discharge of an automatic focus or afterpotentials, particularly in case of increased catecholamine levels.[9] Vagal stimulation, on the other hand, causes hyperpolarization of the atrial fibers, which creates the conditions for reentry because P waves may become shorter than the time required to excite the whole atrial chamber.[9] In fact, the delicate balance between these factors for perpetuation or termination of atrial fibrillation has been proven in both clinical and experimental studies. Clinical cases of paroxysmal atrial fibrillation suggesting a predominant vagal mechanism often display a pattern of atrial fibrillation that alternates with atrial flutter (Fig. 2.1).[10] In contrast, electrocardiographic and electrophysiological aspects suggesting ectopic automatic foci predominate in adrenergic-dependent atrial fibrillation.[2] Furthermore, sustained atrial fibrillation has been correlated with increased sympathetic nerve sprouting within the atrial myocardium, suggesting increased sympathetic hyperinnervation may play a role as a substrate for atrial fibrillation.[1] In addition to the complex anatomic and physiological interactions between the various nerve structures, cardiac autonomic innervation is also constantly remodeling, especially during disease states. Pathological examinations of diseased hearts showed findings consistent with cardiac neural remodeling. Studies conducted on the mechanisms of nerve sprouting using a canine model of myocardial infarction revealed a persistent elevation of nerve growth factor levels in the aorta and coronary sinus within 1 month after myocardial infarction. Nerve growth factor and growth-associated protein-43 are transported retrogradely to the left stellate ganglion through retrograde axonal transport. The increased nerve growth factor levels then trigger nerve sprouting at the noninfarcted cardiac chambers. Increased atrial sympathetic innervation is associated with an increased incidence and duration of atrial fibrillation in affected animals.[9] These studies show that, even in case of a cardiac injury at the level of the ventricle, neural remodeling may occur throughout the heart. Cardiac diseases can therefore potentially increase nerve activity and promote the development of both atrial and ventricular arrhythmias. In addition, atrial sympathetic nerve densities have been shown to be

significantly increased in patients affected by atrial fibrillation, and the pathophysiological importance of autonomic remodeling has been documented in various animal models and in humans.[9]

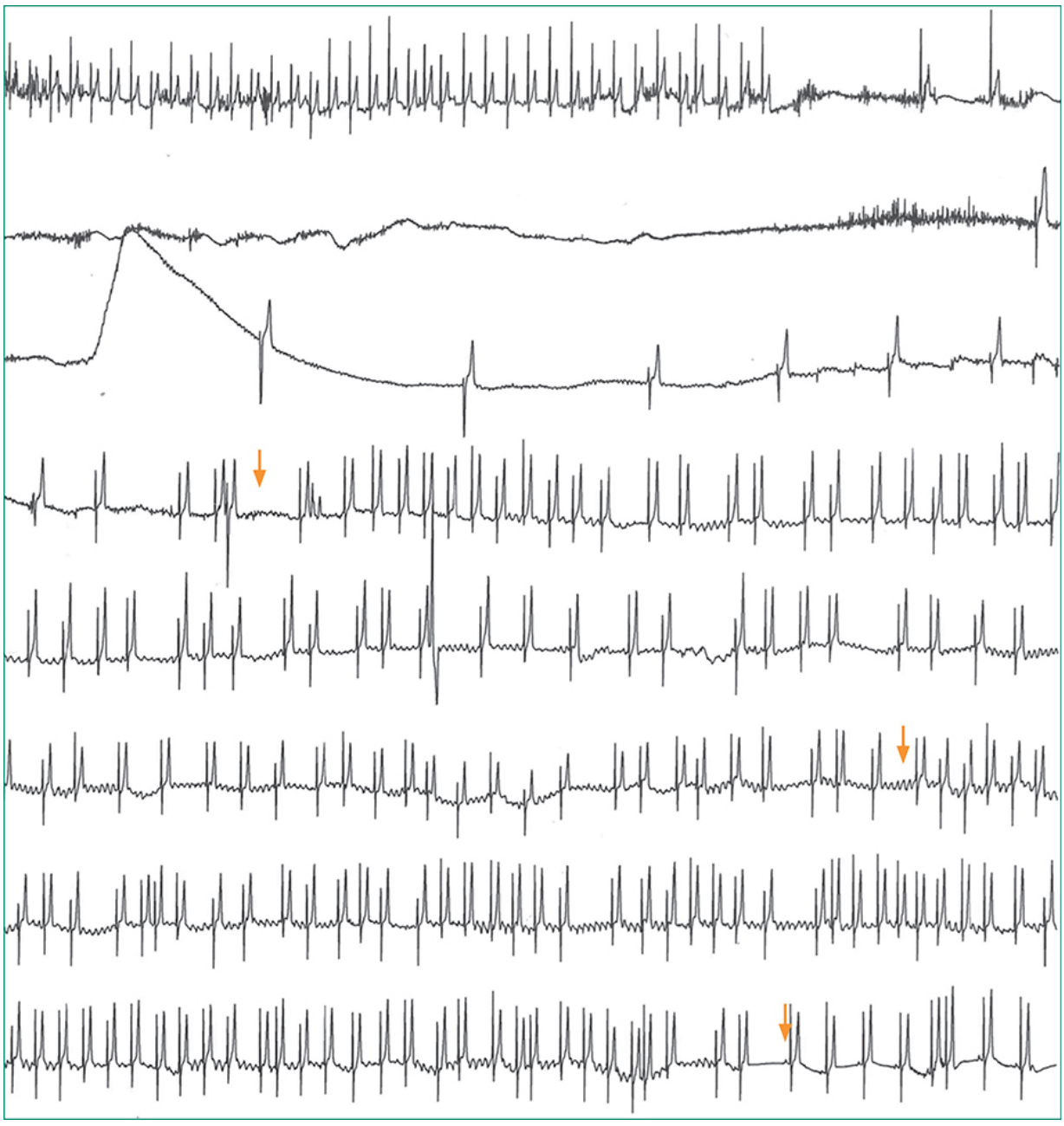


FIGURE 2.1. Ambulatory electrocardiographic recording of a neurally mediated transient loss of consciousness type 1A[16] (see p. 424) due to inappropriate vagal reflex in a 12-year-old male Cavalier King Charles Spaniel. Note the initial sinus tachycardia, followed by progressive sinus bradycardia and then a prolonged sinus arrest (29 seconds), interrupted by a slow idioventricular rhythm. Around 50 seconds postinitiation of sinus arrest, vagal atrial fibrillation occurs (first arrow); it is then cardioverted into functional flutter (second arrow), which lasts around 2 minutes, and finally sinus

rhythm is restored (third arrow). Y lead; each line corresponds to 30 seconds. Speed, 7.5 mm/s; calibration, 5 mm/1 mV.

AUTONOMIC NERVOUS SYSTEM AND FIRING FROM THE PULMONARY VEINS AND OTHER SITES

Pulmonary vein firing has been proven to be a mechanism for induction of atrial fibrillation in both human and veterinary medicine.[11] The main theory explaining this mechanism is the "Ca^{2+} transient triggering" hypothesis, which states that norepinephrine (by sympathetic activation) augments the Ca^{2+} transient, and acetylcholine (by parasympathetic activation) shortens the pulmonary vein action potential duration. The reduced action potential duration causes an even greater myocyte Ca^{2+} overload, which leads to activation of the forward mode of the Na^{+}/Ca^{2+} exchanger. This in turn induces the formation of early afterdepolarizations, and this triggered activity causes pulmonary vein firing. This hypothesis also helps explain why pulmonary vein firing often arises from the distal portion of the pulmonary veins, as this is where the action potential duration is the shortest (Fig. 2.2).[11]

Although pulmonary vein firing accounts for nearly 90% of initiation of paroxysmal atrial fibrillation in human medicine, non–pulmonary vein sites such as the ligament of Marshall and cranial vena cava are alternative sites for rapid firing and atrial fibrillation initiation.[12] The initiation pattern of paroxysmal atrial fibrillation from the ligament of Marshall, cranial vena cava, or pulmonary veins is remarkably similar. The ligament of Marshall is richly innervated and was named "left atrial neural fold" by some anatomists in reference to the abundance of its autonomic neural elements. However, the relative abundance of sympathetic versus parasympathetic innervation in the ligament of Marshall has been a source of discrepancies, and while it has been shown to be a parasympathetic conduit in normal dogs based on both electrophysiological and immunohistochemical findings, other studies have demonstrated a sympathetic predominance in this ligament in dogs with chronic atrial fibrillation.[12] Nevertheless, it is unquestionable that the ligament of Marshall provides an ideal substrate for

triggered firing if the sympathetic versus parasympathetic balance is altered, or if both become hyperactive. Another common site for non–pulmonary vein firing is the cranial vena cava–atrial junction, which has been shown to have a high density of autonomic innervation.[13]



FIGURE 2.2. Ambulatory electrocardiographic recording of pulmonary vein firing that degenerates into paroxysmal atrial fibrillation in a 5-year-old male Dogue de Bordeaux. Note the presence of rapid atrial activity (500 bpm) with different atrioventricular conduction ratios that degenerates into atrial fibrillation (arrow). X, Y, Z leads; speed, 25 mm/s; calibration, 10 mm/1mV.

AUTONOMIC NERVOUS SYSTEM AND SUPRAVENTRICULAR TACHYCARDIAS

Influences of the autonomic nervous system may cause modifications of the initiation, continuation, and discontinuation of supraventricular rhythm disturbances.[1–6] In case of orthodromic atrioventricular reciprocating tachycardia, the arrhythmogenic substrate is well defined: the anatomical macroreentrant circuit is formed by the atrial myocardium, the atrioventricular node, the ventricular myocardium, and the accessory pathway. Manipulation of the autonomic nervous system has been extensively studied. Interestingly, sudden onset tachycardia has been demonstrated to cause an increase in sympathetic tone due to the drop in cardiac output and consequently in blood pressure.[1–6] The adrenergic reaction may sometimes explain the occurrence of atrial fibrillation complicating the accessory pathway–mediated tachycardia. In case of increased vagal tone, early termination of the reentrant tachycardia may be achieved by blocking the impulse at the level of the atrioventricular node, thus decreasing the conduction velocity through this structure. The mode of

initiation of reentrant tachycardia is more difficult to investigate than its termination, because the degree of vagal and sympathetic influence on the antegrade or retrograde limb of the circuit that favors the induction of the reentrant circuit is unknown.[1–6] Focal atrial tachycardia depending on abnormal enhanced automaticity can be triggered by sympathetic stimulation, which can modify phase 4 of the action potential and thereby increase the discharge rate of the ectopic focus.[2]

AUTONOMIC NERVOUS SYSTEM AND VENTRICULAR ARRHYTHMIAS

The mechanism underlying the generation of ventricular tachycardia results from a complex interaction between multiple factors, one of them being the autonomic nervous system, in particular its adrenergic limb.[1–6] The adrenergic nervous system can exert influence on the cardiac muscle through the nerve endings (neurogenic origin) or via epinephrine release from the adrenal glands to the bloodstream (humoral origin). The sympathetic stimulation caused by exercise can produce different effects on the cardiac tissue, depending on how it is transmitted. Neurogenic stimulation is characterized by a sudden appearance, short duration, and effects that are unequally distributed in the cardiac tissues.[14] Humoral stimulation is more progressive, has a longer duration, and its effects are homogeneous. Exercise can cause ventricular tachycardia in both diseased and structurally normal hearts.[14] Changes in the adrenergic tone can be crucial to the induction and maintenance of ventricular tachycardias. In addition, the increased adrenergic tone in heart failure plays a central role in the development of ventricular arrhythmias.[14]

The anatomical distribution of the sympathetic and parasympathetic nerves and their functional effects on the working myocardium and His–Purkinje tissue are still under active investigation.[14] Both the vagal and sympathetic systems have direct and indirect effects on the ventricular tissue. In contrast to what occurs in the atria, vagal modulation usually does not have any detrimental effects, and adrenergic influences bear the responsibility for many ventricular arrhythmias.[14] Benign forms of repetitive tachycardia are examples of the interplay between rate and

adrenergic dependence. The rate dependence of some ventricular rhythm disturbances can explain the disappearance of premature ectopic ventricular beats at rest as well as during exercise, but there is also a strong correlation between the repetitive activity that follows the initial premature beat and the preceding heart rate.[14] These mechanisms can be explored during prolonged electrocardiographic monitoring. Ventricular arrhythmias with a prolonged QT interval, either congenital or acquired, are preceded by abnormal ventricular repolarization. In these cases, the sympathetic drive can induce malignant polymorphic ventricular tachycardias or torsades de pointes mediated both by α- and β-adrenergic stimulation. In this syndrome, the vagal influence is considered protective.[2]

AUTONOMIC NERVOUS SYSTEM AND ARRHYTHMIAS IN HEART DISEASES

The refinement of experimental procedures has produced remarkable models for studying the mechanism of sudden death by combining acute ischemia and adrenergic stimulation, evaluating variations in the balance between sympathetic and parasympathetic tone, and exploring possibilities to treat the trigger and electrophysiological substrate of arrhythmias. Both α- and β-adrenergic effects may exacerbate arrhythmias by increasing afterpotentials in healed myocardial tissue.[1–6] The role of the autonomic nervous system and more specifically the sympathetic nervous system in the occurrence of ventricular tachycardia and ventricular fibrillation is well established.[2] Myocardial injury and infarction lead to cardiac sympathetic afferent activation, which in turn increases cardiac sympathetic outflow to the heart via the stellate, middle cervical, and thoracic sympathetic ganglia.[1–6]

In structural heart diseases, remodeling may have significant adverse effects at multiple levels, including the intrinsic cardiac nervous system, the extracardiac ganglia, and the central nervous system. Remodeling is aimed at improving cardiac performance (cardiac contractility and cardiac output) in the short term, but these changes become detrimental in the long term if left uncorrected. In fact, neurohormonal activation has been demonstrated to have a pivotal role in the development of congestive heart failure, which

is usually associated with increased systemic levels and decreased cardiac levels of catecholamines. Myocardial infarction and fibrosis lead to denervation of sympathetic fibers in the scar area, which no longer responds to sympathetic stimulation. Myocardial scars also cause the loss of efferent sympathetic innervation in close noninfarcted areas, and attempted reinnervation or nerve sprouting occurs at the border zone of the damaged area. Localized nerve sprouting potentially exacerbates the heterogeneous cardiac activation and repolarization during sympathetic activation and promotes the onset and maintenance of ventricular tachycardia, which can potentially degenerate into ventricular fibrillation and sudden cardiac death.[15]

Studies in cats and canine models of ischemia revealed that sympathetic stimulation represents the trigger for ventricular tachycardia and ventricular fibrillation, by reducing the action potential duration, increasing dispersion of repolarization, and causing early afterdepolarizations.[2] Experimental studies have shown that an increase in sympathetic tone predisposes to ventricular tachycardias and ventricular fibrillation, while an increase in parasympathetic tone had a protective effect. It is well known that circulating catecholamine levels are elevated in patients with congestive heart failure, thereby indicating an increased sympathetic tone.[2] (Fig. 2.3).

Other than ventricular rhythm disturbances, structural heart diseases can also be associated with supraventricular arrhythmias. Atrial fibrillation is the most common arrhythmia and is associated with important morbidity and mortality rates. The electrophysiological and anatomical substrates underlying atrial fibrillation include atrial fibrosis, atrial stretch, oxidative stress, and abnormalities in calcium handling. An increase in the parasympathetic and sympathetic tone is involved in the genesis and maintenance of atrial fibrillation. On the one hand, sympathetic stimulation increases calcium transients and atrial ectopy from the pulmonary veins, which triggers atrial fibrillation by decreasing the duration of the effective refractory period and causes a nonuniform anisotropic conduction. On the other hand, an increase in parasympathetic tone reduces the duration of the action potential, thus favoring the induction of atrial fibrillation. Studies in canine models suggested that the development of atrial fibrillation may be associated with concurrent activation of both the sympathetic and parasympathetic limbs, rather than isolated overactivity in either one.[16]

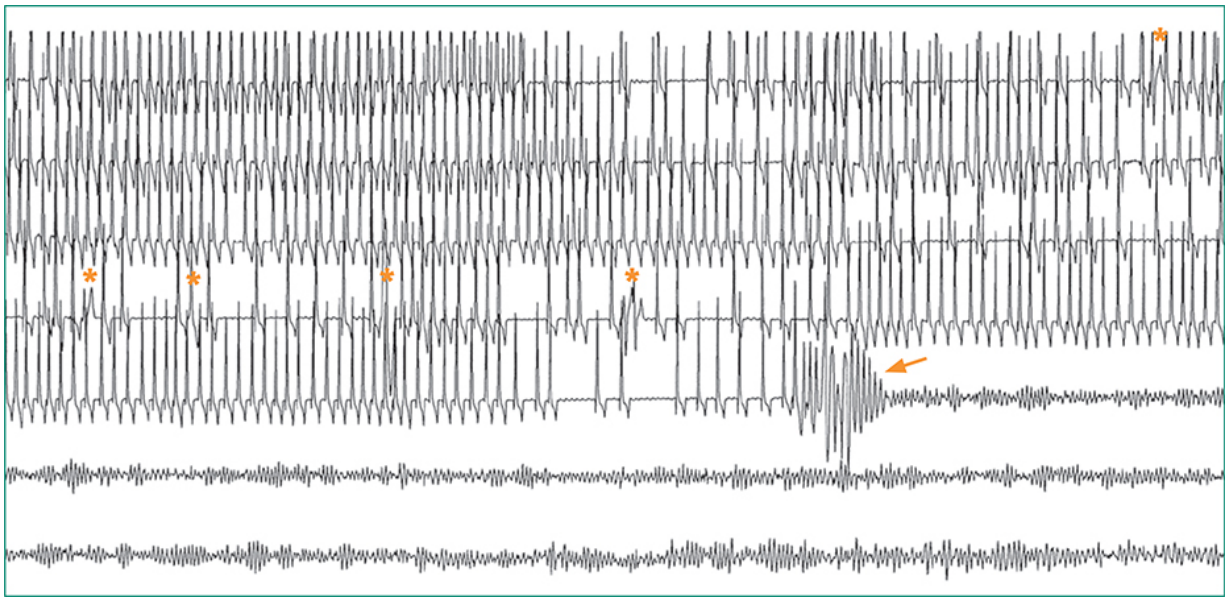


FIGURE 2.3. Ambulatory electrocardiographic recording of sudden cardiac death occurring due to ventricular fibrillation in a 10-year-old female German Shepherd. The initial part of the tracing shows a persistent atrial fibrillation interrupted consecutively by three ventricular ectopic beats and one couplet (*), then a polymorphic ventricular tachycardia (arrow), which degenerates into ventricular fibrillation. Y lead; each line corresponds to 30 seconds. Speed, 7.5 mm/s; calibration, 5 mm/1 mV.

Myocardial infarction represents an uncommon structural heart disease in dogs and cats. A heterogeneous interruption of neurotransmission is present in both acute and chronic myocardial infarction.[17] A transmural myocardial infarction can interrupt neural innervation and thus exert an effect on the noninfarcted, otherwise apparently normal, myocardium. Nonuniform electrophysiological effects of right and left sympathetic nerve stimulation have been shown to have an arrhythmogenic potential in several experimental settings.[17] In particular, it has been hypothesized that the presence of myocardial infarction may create an area of autonomic nervous system imbalance not only in the damaged ischemic myocardium but also in the normal areas surrounding the ischemic lesion.[17] In case of severe ischemia and infarction, neurotransmission to the infarcted area may cease. In addition, normal regions surrounding the infarction are characterized by heterogeneous sympathetic innervation for at least 3 weeks.[17] The importance of restructuring of cardiac innervation due to ischemic disease is correlated to the phenomenon of nerve sprouting. Myocardial infarction leads to increased local release of nerve growth factor in the peri-infarct area, with a consequent increase in the density of sympathetic nerve

endings. These structural changes lead to an increased risk of developing ventricular tachycardia and degeneration into ventricular fibrillation, with concomitant macro T wave alternans (Fig. 2.4).[1]



FIGURE 2.4. Repetitive polymorphic ventricular tachycardia in a 9-year-old female Labrador Retriever with a myocardial infarct secondary to hypothyroidism and dyslipidemia. Note the presence of wide QRS complex tachycardia runs always preceded by a sinus beat with a beat-to-beat variation of the QRS morphology. The left precordial leads (V2–V6) show ascending ST elevation suggestive of myocardial hypoxia. Twelve leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6); speed, 50 mm/s; calibration, 5 mm/1 mV.

AUTONOMIC NERVOUS SYSTEM AND HEART FAILURE

Different structural heart diseases are complicated by heart failure, which is characterized by a reduced cardiac output and increased myocardial stretch.[18] The pathophysiology of heart failure is characterized by hemodynamic abnormalities that lead to neurohormonal activation and

autonomic nervous system imbalance, with an increase in sympathetic tone and withdrawal of vagal activity. The presence of an autonomic imbalance directly contributes to the progression of the cardiostructural disease.[18] In addition to the cardiac and extracardiac neural remodeling mentioned above, these changes further cause activation of sympathetic afferent fibers, which effectively increases sympathetic efferent outflow, and potentially reduces parasympathetic afferent neurotransmission from the carotid and aortic baroreceptors, thus decreasing vagal tone.[15] Most of the data regarding the role of the autonomic nervous system in patients affected by heart failure were obtained in individuals with dilated cardiomyopathy and a reduced ejection fraction. In the acute setting, increased catecholamine levels help to increase ventricular contractility and heart rate in order to maintain cardiac output. Increased sympathetic activity also induces vasoconstriction of the arteries and veins, which contributes to the maintenance of systemic blood pressure by increasing systemic vascular resistance, venous return, and therefore ventricular preload. At the renal level, the increased sympathetic tone induces vasoconstriction of the efferent arterioles, which is mainly mediated by angiotensin II. This leads to an increased filtration fraction that allows glomerular filtration to be relatively well maintained, despite a decrease in blood flow through the afferent arterioles. The increased levels of noradrenaline and angiotensin II also stimulate proximal tubule sodium reabsorption, contributing to sodium retention and volume expansion.[18,19] Studies in animal models have found a direct relationship between increased angiotensin-converting enzyme in the ventricles and the degree of ventricular dilation. Aldosterone has direct proinflammatory effects and leads to interstitial and perivascular fibrosis as well as hypertrophy.[15] The chronic upsurge of the renin–angiotensin–aldosterone system activity leads to fibrosis and alterations in gap junctions and enhances dispersion of repolarization and electromechanical feedback.[15] Finally, release of angiotensin II directly promotes ventricular arrhythmias, not only due to loss of urinary potassium and magnesium but also by directly increasing catecholamine (including norepinephrine) release from nerve endings through activation of prejunctional angiotensin II receptors.[15]

The elevated sympathetic tone in chronic phases of congestive heart failure leads to chronically elevated stimulation of the cardiac β-adrenergic

receptor system, which in turn has a detrimental effect on the structural heart disease complicated by congestive failure. Recent studies in humans have shown that in chronic congestive heart failure, cardiomyocyte β-adrenergic receptor signaling and function are significantly altered and the heart presents a reduced adrenergic reserve. Cardiac β-adrenergic receptor dysfunction is characterized by a selective reduction in β-1 adrenergic receptor density at the plasma membrane (downregulation) and by uncoupling of β-1 and β-2 adrenergic receptors from G proteins (functional desensitization). Furthermore, chronic exposure of cardiomyocytes to catecholamines has been shown to have a toxic effect, as it causes cAMP-mediated calcium overload of the cell, with a resulting decrease in cardiomyocyte viability.[18]

AUTONOMIC NERVOUS SYSTEM AND SUDDEN DEATH

An increasing wealth of clinical and experimental research supports the epidemiological evidence that stressful stimuli, either physical or psychological, may trigger acute cardiovascular events, including cardiac arrhythmias and degeneration into ventricular fibrillation, and thus cause sudden cardiac death.[20] Sympathetic activation represents the main aspect of the trigger for malignant cardiac arrhythmias.[20] Furthermore, activation of either the sympathetic or the parasympathetic nervous system can not only alter heart rate and blood pressure but also play a fundamental role in the modulation of the electrophysiological properties of the atrial and ventricular myocardium, such as the depolarization and repolarization times and repolarization heterogeneity.[16] Experimental studies have shown that sympathetic nervous system stimulation may be proarrhythmic on the ventricular myocardium, by favoring the induction of ventricular tachycardia and degeneration into ventricular fibrillation, while vagal nerve stimulation, partly by antagonizing sympathetic activity, reduces the potential for the development of malignant ventricular arrhythmias (see Fig. 2.3).[20] In veterinary medicine, it has also been shown that sudden cardiac death can be caused by an imbalance of the autonomic nervous system characterized by increased vagal tone and concurrent sympathetic

withdrawal.[21] When this occurs, progressive sinus bradycardia followed by sinus arrest is associated with extreme coronary vasodilation with consequent myocardial hypoperfusion (Fig. 2.5) (see p. 439).

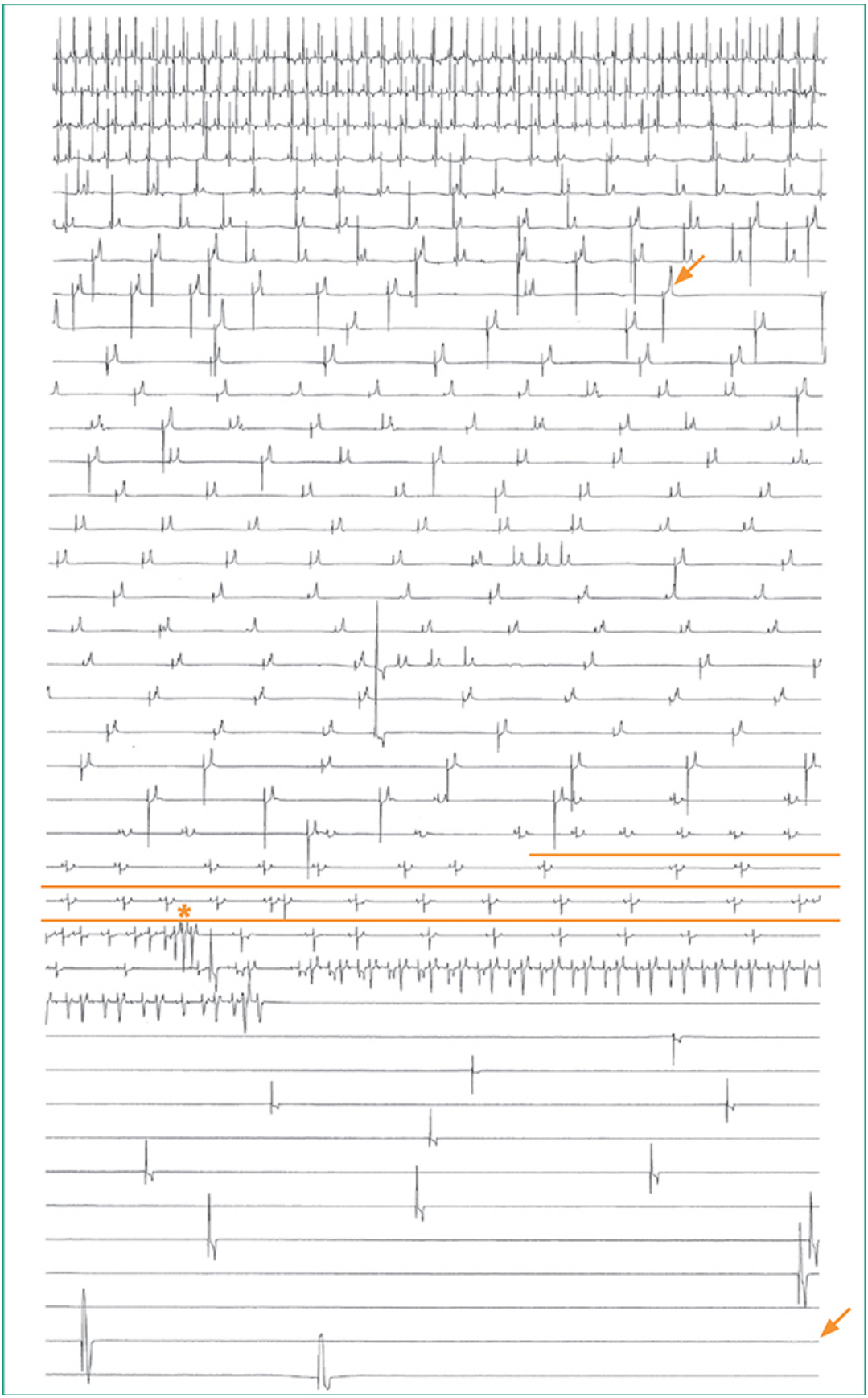


FIGURE 2.5. Ambulatory electrocardiographic recording of repetitive neurally mediated transient losses of consciousness (type 1A)[16] due to inappropriate vagal reflexes in an 8-year-old male Miniature Schnauzer. The initial part of the tracing shows sinus tachycardia, followed by progressive sinus bradycardia and sinus arrest interrupted by a slow idioventricular rhythm and then a slow junctional rhythm, which lasted 7.5 minutes. This is followed by a recurrence of the idioventricular rhythm (first arrow), interrupted by profound sinus bradycardia with ST segment depression (horizontal line) and a ventricular triplet (*). Sinus bradycardia is then restored for a few seconds and interrupted by an accelerated idioventricular rhythm, which culminates in a new sinus arrest lasting 32 seconds, a slow junctional escape rhythm, and, finally, electromechanical dissociation occurs and induces sudden death (second arrow). Y lead; each line corresponds to 30 seconds. Speed, 7.5 mm/s; calibration, 5 mm/1 mV.

AUTONOMIC NERVOUS SYSTEM AND NEURALLY MEDIATED SYNCOPE

Neurally mediated syncope is the most common form of transient loss of consciousness in both humans and dogs.[22,23] It has a negative impact on quality of life and is associated with the owners' psychological distress. Although neurally mediated syncope is a very common clinical entity, its mechanisms are not yet fully understood. The main mechanism involved is a dysregulation of the autonomic nervous system. The key elements in the occurrence of neurally mediated syncope are the role of the central and peripheral nervous systems in triggering the event, the role of the efferent parasympathetic and sympathetic branches, and the potential role of neurohumoral autonomic mechanisms. In predisposed individuals, different stimuli have been shown to trigger neurally mediated syncope. Depending on the stimulus (central or peripheral), an activation or inhibition of different pathways can occur. Neurally mediated syncope results from sympathetic nervous system withdrawal after an initial activation (accentuated antagonism), which induces venous and arterial vasodilation, and concurrent activation of the parasympathetic nerves, which induces sinus bradycardia or sinus arrest. However, while the final situation is a loss of consciousness, the initial trigger may activate different pathways, thereby leading to a different and complex autonomic response that may produce neurally mediated syncope with different patterns. Variations in sympathetic withdrawal and parasympathetic activation can therefore be seen, with a variable cardiovascular response. In fact, neurally mediated syncope can be

characterized by a predominant vasodepressor reflex, by a predominant cardioinhibitory reflex, or it can present as a mixed type.[23]

Different studies in human medicine identified four different phases characteristic of neurally mediated syncope:

- Phase 1: early stabilization
- Phase 2 circulatory instability (early syncope)
- Phase 3: terminal hypotension (late syncope)
- Phase 4: recovery

Phase 1 is characterized by vasodilation with venous pooling at the level of the abdomen. The decrease in right venous return is associated with a 10–20% decrease in cardiac output, but because of the concomitant increase in heart rate, the stroke volume remains stable. At the same time, there is a decrease in systolic blood pressure associated with an increase in diastolic pressure; the mean systemic arterial pressure is therefore maintained. The increase in diastolic blood pressure is the consequence of a baroreflex-mediated vasoconstriction in both the skeletal and splanchnic arterioles.[24–26] It has been demonstrated in anesthetized animals that the main mechanism maintaining cardiac output during phase 1 is decreased splanchnic vasoconstriction with filling of the downstream capacitance venules, which contain 20% of the blood volume. The decrease in transmural pressure determines their reaction, allowing more volume of blood to return to the right atrium by passive venous recoil and consequently increasing left preload. After a variable period of stability, all people experiencing neurally mediated syncope enter phase 2, which is characterized by a fall in cardiac output and systemic blood pressure. In phase 2, a gradual fall in cerebral blood flow velocity is also seen, which is proportional to the decrease in the mean arterial pressure. After another variable period of time, the individuals enter phase 3, which is characterized by a marked drop in systolic arterial blood pressure. In addition to this finding, which is mediated by sympathetic tone withdrawal, the concurrent increase in parasympathetic tone causes a decrease in heart rate. This period coincides with the signs reported by the owners, such as weakness and loss of posture. When the systolic blood pressure decreases below 60 mmHg, loss of consciousness occurs.[23] Although most studies suggest that bradycardia is preceded by a fall in blood pressure, this may not be

completely true, and in some cases, prolonged sinus arrest or third-degree atrioventricular block with concomitant sinus bradycardia can occur early in phase 3. These patients should be considered for pacemaker implantation.[27] The final part of phase 3 is characterized by a fall in cardiac output and a significant increase in systemic vascular resistance. In adult humans, the decrease in cardiac output remains the dominant mechanism explaining hypotension, since the systemic vascular resistance is always above the baseline levels. Phase 4 corresponds to the recovery phase. The mechanism explaining the recovery of systolic blood pressure is mainly cardiac in origin and is based on increased venous return, which results in rapid recovery of left preload, stroke volume, and cardiac output following the Frank–Starling law. Not all individuals recover rapidly after phase 4. In fact, some patients can manifest a prolonged hypotensive state characterized by pale mucous membranes, a heart rate below normal limits (<60 bpm), and hypotension (systolic blood pressure <80 mmHg) for up to 5 minutes or even longer. The presence of pronounced bradycardia, abdominal discomfort, and nausea is consistent with increased vagal outflow from the nucleus ambiguus to the heart. A delayed recovery may also be associated with a prolonged decrease in stroke volume and cardiac output due to decreased contractility of the ventricles. This finding has been attributed to a combination of excess vagal activity and decreased sympathetic neural outflow to the heart. When the arterial baroreflex is impaired and there is a persistent inappropriately low heart rate and blood pressure, a sustained suppression of excitatory mechanisms occurs. In other words, the patient is not able to activate the central sympathetic pathways in order to overcome the exaggerated vagal activity.[28]

A different pathological entity is represented by vagal overactivity. Vagal overactivity may affect sinus node function, inducing prolonged sinus arrest, or atrioventricular node function, inducing third-degree atrioventricular block associated with sinus bradycardia.[29] This condition is associated with an enhanced density of M_2 and M_3 muscarinic receptors at nodal structures. In experimental studies on rabbits, a significant correlation was found between the severity of bradycardia and cardiac muscarinic receptor expression levels, thus indicating that vagal overactivity was dependent on muscarinic receptor density. The increase in M_2 receptor density is correlated with a negative chronotropic effect, and recent studies

have shown that stimulation of M_3 receptors mediates K^+ currents inducing a hyperpolarized state of the cell.[29,30]

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CHAPTER 3

Classification and clinical manifestations of arrhythmias

Roberto Santilli, Dolores María Porteiro Vázquez

The term *arrhythmia* refers to any type of rhythm caused by an electrical impulse that does not originate from the sinus node, does not follow normal conduction pathways, and/or results in a heart rate that is different from the physiological ranges.[1] Rhythm disturbances can lead to severe hemodynamic effects if the cardiac output is affected; however, the presence or absence of a concomitant cardiac disease and peripheral vascular tone may play an important role in the maintenance of proper organ perfusion.[2–5]

The most common clinical signs associated with low cardiac output during arrhythmias are weakness, loss of postural tone, and syncope. Congestive heart failure signs, such as dyspnea due to pulmonary edema or ascites, can also be present if the hemodynamic changes last long enough to induce impaired myocardial function (arrhythmia-induced cardiomyopathy) (see p. 395).[6,7]

CLASSIFICATION OF ARRHYTHMIAS

Arrhythmias in dogs and cats can be classified according to the heart rate (bradycardia or tachycardia), origin (supraventricular or ventricular), anatomical substrate, electrophysiological mechanism (impulse formation

or conduction disorders), rhythm (regular or irregular) or mode of presentation (single or organized ectopic beats) (Table 3.1).[1,8]

TABLE 3.1. Classification of rhythm disorders in dogs and cats.

Supraventricular	Ventricular	Bradycardia and conduction disturbances	Ectopic beats and rhythms
■ Sinus tachycardia ■ Atrioventricular nodal reciprocating tachycardia ■ Focal junctional tachycardia ■ Nonparoxysmal junctional tachycardia ■ Atrioventricular reciprocating tachycardias (orthodromic atrioventricular reciprocating tachycardia, antidromic atrioventricular reciprocating tachycardia) ■ Focal atrial tachycardia ■ Multifocal atrial tachycardia or chaotic atrial rhythm ■ Macroreentrant atrial tachycardia (cavotricuspid isthmus dependent atrial flutter, cavotricuspid isthmus nondependent atrial flutter) ■ Atrial fibrillation	■ Idioventricular rhythm ■ Accelerated idioventricular rhythm ■ Monomorphic ventricular tachycardia (nonsustained, repetitive, sustained, incessant, ventricular flutter) ■ Polymorphic ventricular tachycardia ■ Torsade de pointes ■ Bidirectional ventricular tachycardia ■ Ventricular fibrillation	■ Sinus bradycardia ■ Sinus arrest ■ Sinus standstill ■ Atrial standstill ■ Sinoventricular rhythm ■ Asystole or ventricular arrest ■ Pulseless electrical activity or electromechanical dissociation ■ Intra-atrial conduction delay or block ■ Atrioventricular blocks (first-degree, second-degree Wenckebach, second-degree Mobitz, second-degree fixed 2:1, advanced second-degree, third-degree) ■ Intraventricular blocks (monofascicular, bifascicular, trifascicular)	■ Supraventricular ectopic beats and rhythms (atrial ectopic beats, atrial ectopic rhythm, junctional ectopic beats, junctional ectopic rhythm, atrial parasystole, dissociation or unilateral atrial rhythm) ■ Ventricular ectopic beats and rhythms (ventricular ectopic beats, idioventricular rhythm, ventricular parasystole)

Source: Santilli R. et al.[8]

Bradycardia is defined as a heart rate below 60 bpm in the dog and 140 bpm in the cat.[8] Healthy dogs can have heart rates lower than 60 bpm while sleeping, and cats can have heart rates below 140 bpm.[8] The maximum heart rate is more variable and is closely related to the degree of sympathetic activation. Generally, a heart rate greater than 180 bpm in the dog and 220 bpm in the cat is considered tachycardia.

Bradycardia can be classified according to the disorder of origin: abnormal sinus node automaticity (sinus bradycardia, sinus arrest, sinus standstill), abnormal sinoatrial or intra-atrial conduction (sinoatrial or intra-atrial conduction block or delay), abnormal atrioventricular conduction (atrioventricular blocks or delay), or atrial mass (atrial standstill and sinoventricular rhythm).[1,8]

Tachycardias are classified as supraventricular or ventricular based on their anatomical substrate.[1,8] A tachycardia is classified as supraventricular when it depends on one or more supraventricular structures, i.e., the sinus node, atrial myocardium, tributary veins, and atrioventricular node. The

atrioventricular node can be critical to the perpetuation of tachycardia or a bystander, and for this reason supraventricular arrhythmias can be subclassified into atrioventricular node–independent (sinus tachycardia, focal atrial tachycardia, multifocal atrial tachycardia, atrial flutter, and atrial fibrillation) and atrioventricular node–dependent (focal junctional tachycardia, nonparoxysmal junctional tachycardia, atrioventricular nodal reciprocating tachycardia, and atrioventricular reciprocating tachycardia). Atrioventricular reciprocating or nodal reciprocating tachycardias also include the ventricular myocardium in their circuit.[1,8]

Ventricular tachycardias originate from ventricular anatomical structures including the ventricular walls, the specialized intraventricular conduction system, the Purkinje fibers, the left and right outflow tracts, the aortic root, and the initial segment of the pulmonary artery.[1,8] Anatomical structures are important in the development of ventricular arrhythmias, but autonomic tone and other modulators play an important role in the onset of rhythm disturbances.[9,10] Ventricular arrhythmias can be classified based on the QRS morphology on the surface electrocardiogram, which is a reflection of the electrophysiological mechanism.[1,8] Ventricular tachycardia is described as monomorphic when all QRS complexes have the same morphology, pleomorphic if there is more than one QRS morphology during a run of tachycardia but the QRS complexes are not continuously changing, and polymorphic when the QRS complex morphology varies on a beat-to-beat basis. A bidirectional ventricular tachycardia is characterized by an alternating QRS morphology, characterized by a 180° shift of the electrical axis between consecutive QRS complexes.[1,8]

Tachycardias are defined as regular when the RR interval duration is constant, and irregular when the RR interval is variable.[1,8] When the RR interval presents sudden or progressive changes in its duration (at least 20 ms), this can be defined as cycle length irregularity. This type of irregularity occurs in focal atrial tachycardia, in which a “warm-up” phase (progressive shortening of the RR interval) is observed, followed by a “cool-down” phase (progressive prolongation of the RR interval), and in atrial flutter with different atrioventricular conduction ratios. Finally, cycle length alternance refers to RR intervals that vary on a beat-to-beat basis.[1,8]

Depending on their duration, tachycardias can be classified as nonsustained (i.e., lasting less than 30 s), sustained (i.e., lasting more than

30 s or inducing loss of consciousness), incessant or permanent (i.e., lasting more than 12 hours), repetitive (i.e., runs of tachycardia alternating with sinus beats or sinus rhythm) and paroxysmal (i.e., initiating and terminating abruptly).[1,8]

Interatrial and intraventricular conduction abnormalities (interatrial and intraventricular blocks) are classified as a different identity.[1,8]

HEMODYNAMIC CONSEQUENCES OF ARRHYTHMIAS

The main factors contributing to a compromised cardiac output during arrhythmias are the ventricular rate, atrial activity (atrioventricular ratio, atrial contraction), the sequence of ventricular activation, and cycle length irregularity. Other important factors associated with hemodynamic effects are the duration of the arrhythmia, cardiac function, vasomotor tone, and drug therapy.[2–5] If conditions promoting a low cardiac output are maintained for a long time, they can have an impact at the systemic and myocardial levels (arrhythmia-induced cardiomyopathy).[6]

Heart rate is an important determinant of myocardial function when there are changes in cardiac volume and myocardial contractility.[2–5] A moderate increase in heart rate improves cardiac output because it increases the stroke volume by summation and improves the heart's force of contraction (force–frequency relationship).[2–5] Indeed, a faster heart rate facilitates the influx of calcium into the cytosol, thereby inducing a positive inotropic effect (positive staircase or Bowditch effect).[2–5] However, beyond a certain heart rate, this inotropic effect is no longer seen (Fig. 3.1). This is because a shorter diastole reduces the cytosolic calcium levels available (negative staircase or Woodworth effect) and worsens ventricular ejection according to the Frank–Starling law as a result of reduced preload (length–tension relationship).[2–5] A severely increased stimulation rate therefore decreases myocardial contractility and cardiac output. Conversely, a slow heart rate facilitates cardiac filling and improves cardiac performance (Frank–Starling law), but an extremely slow heart rate or prolonged ventricular arrest will not maintain an adequate cardiac output due to a reduced number of ejections (Fig. 3.2).



FIGURE 3.1. Pressure tracing before and after the onset of orthodromic atrioventricular tachycardia in a 6-month-old male Labrador Retriever. The surface electrocardiogram (leads I, II, III, V1, V6) and endocardial mapping at different levels of the heart [coronary sinus ostium (CSp), great cardiac vein (CS2–CS4), posterior left atrium (CSd), His bundle (HBEp-HBEd), and ablation catheter placed at the right posteroseptal tricuspid valve annulus (ABLp-ABLd)] show 5 sinus beats followed by a sudden onset of orthodromic atrioventricular reciprocating tachycardia. Notice the drop in the systolic, mean, and diastolic pressures (arrow) after the onset of tachycardia. Speed, 25 mm/s; calibration, 5 mm/1 mV; pressure tracing scale in mmHg.

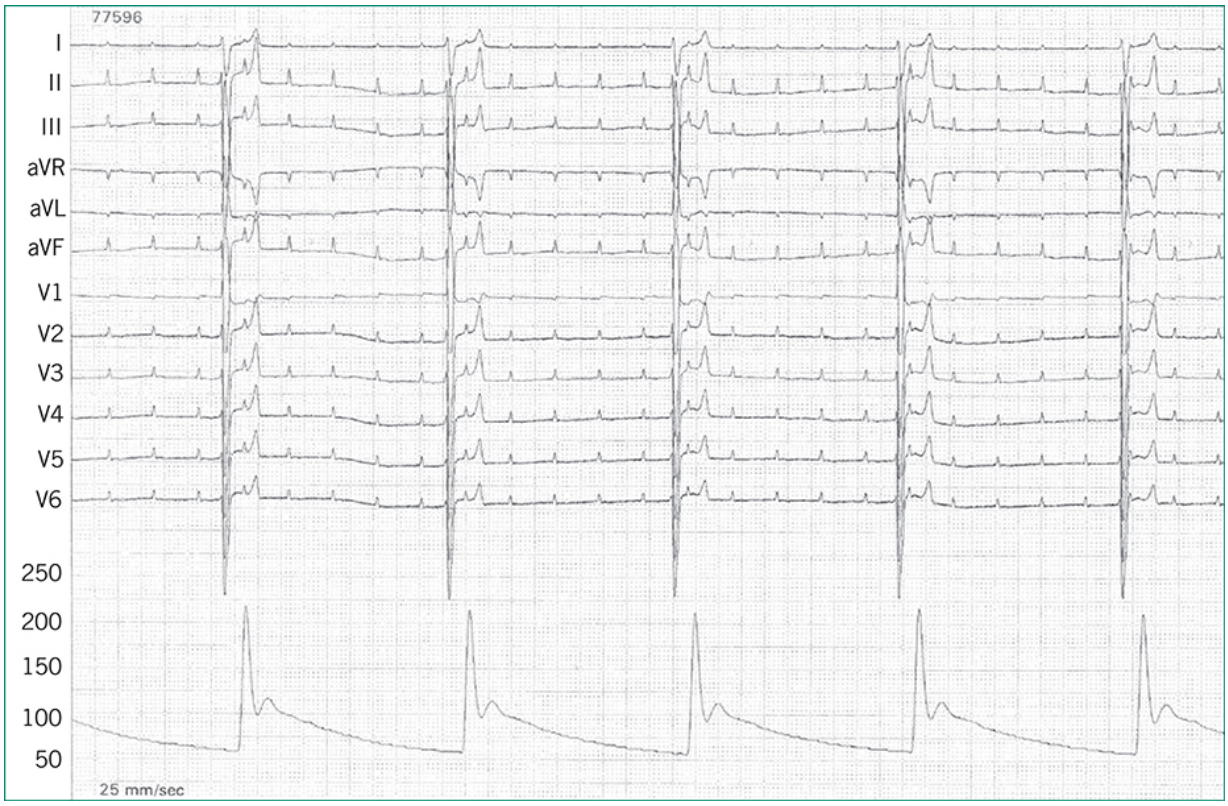


FIGURE 3.2. Third-degree atrioventricular block in a 9-year-old female German Shepherd. Note the slow idioventricular rhythm (30 bpm) with dissociated P waves at a faster rate (160 bpm). The simultaneous peripheral arterial pressure tracing shows a very high systolic pressure with a progressive fall in diastolic pressure during the long diastolic phase. The stroke volume in these cases is increased, while the cardiac output decreases. Twelve leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6); speed, 25 mm/s; calibration, 5 mm/1 mV. Pressure tracing scale in mmHg.

Another example of improved myocardial contractility associated with arrhythmias is post-extrasystolic potentiation after premature ectopic beats.[2–5] Even though cardiac output can be affected during premature ectopic beats (reduced contractile force due to decreased diastolic time), the beat that follows the compensatory pause produces a stronger cardiac contraction, thus increasing the stroke volume. Ectopic beats increase the duration of calcium channel opening during the absolute refractory period of the previous beat, so higher calcium currents are available in the next beat to increase the contractile force. The post-extrasystolic pause improves cardiac filling and contraction due to the length–tension relationship (Frank–Starling law) (Fig. 3.3).[2–5]

Sequential atrioventricular electrical and mechanical activity is important during the cardiac cycle to maintain a correct diastolic and systolic volume.

Diastolic ventricular filling depends on atrial function and occurs in two phases, passive filling and active filling (atrial contraction). Atrial contribution to ventricular filling can be affected if atrioventricular dissociation is present (i.e., third-degree atrioventricular block, ventricular arrhythmias) or if atrial contraction is absent (atrial fibrillation).[2–5] Atrial contraction contributes 10–15% of the end-diastolic ventricular filling volume. Loss of atrial contraction can compromise cardiac output but also increases the atrial and pulmonary arterial pressures, leading to congestive heart failure (forward failure) (Fig. 3.4).

Left bundle branch block or ventricular ectopic beats with left bundle branch block morphology produce abnormal ventricular activation and can induce hemodynamic effects impacting systolic function (interventricular dyssynchrony) (see p. 395).[3]

The irregularity of the cycle length during arrhythmias has important hemodynamic effects and is related to the length–tension relationship (Frank–Starling law) as explained above. The stroke volume changes according to variations in the end-diastolic volume; it decreases during a short RR interval and increases during a prolonged RR interval. A classic example of an arrhythmia associated with high blood flow variations due to irregular RR intervals is atrial fibrillation.[3]

Neurohumoral activation, metabolic changes, and cellular alterations caused by hemodynamic changes lead to impaired myocardial function called arrhythmia-induced cardiomyopathy.[6] Rhythm and conduction disorders may also contribute to the worsening of an underlying previous myocardial disorder (e.g., familial dilated cardiomyopathy). Arrhythmias can be potentially fatal, especially in those patients that present an anatomical substrate (e.g., ischemia, cardiomyopathies, systemic diseases) or triggering factors (e.g., stress). The reduction in cardiac output triggers compensatory systems (i.e., adrenergic system, renin–angiotensin–aldosterone system, and vasopressin release) to maintain systemic perfusion.[2] Over time, the increase in circulating volume combined with the elevation in atrial pressure can lead to bradycardia-induced cardiomyopathy and heart failure.

Adequate organ perfusion during arrhythmic disorders depends on a correct compensatory hemodynamic response, for example, with changes in peripheral vascular resistance and blood pressure regulated by vasomotor

tone.[2] An example of inadequate systemic blood pressure associated with bradycardia is reflex syncope (vasovagal syncope).[11] This inappropriate reflex produces a cardioinhibitory (bradycardia) and vasodepressor (vasodilation) stimulation, such that the circulatory system is not able to maintain blood pressure even though cardiac output may be maintained during bradycardia.[11]



FIGURE 3.3. Ventricular ectopic beats, atrial ectopic beats, and focal atrial tachycardia in a 7-year-old male Boxer. After three initial sinus beats, a late ventricular ectopic beat occurs and induces a pulse deficit (arrows), followed by a ventricular triplet, two couplets and one atrial ectopic beat, which induce different degrees of pulse deficit (arrows) and post-extrasystolic potentiation (*) (see text for explanation). The last part of the tracing shows a run of focal atrial tachycardia inducing mechanical alternans (horizontal line). Two mechanisms have been proposed to explain this phenomenon. Based on the Frank–Starling relationship, a strong beat leaves a small residual end-systolic volume, which then results in a decreased end-diastolic volume and in decreased contractile force development. After the weak beat, the end-diastolic volume is greater due to decreased ejection, which results in a greater contractile force in the next beat. The second mechanism proposed as a possible cause for mechanical alternans involves a beat-to-beat alternation of myocardial contractility. Leads I, II, III; speed, 25 mm/s; calibration, 10 mm/1 mV. Pressure tracing scale in mmHg.

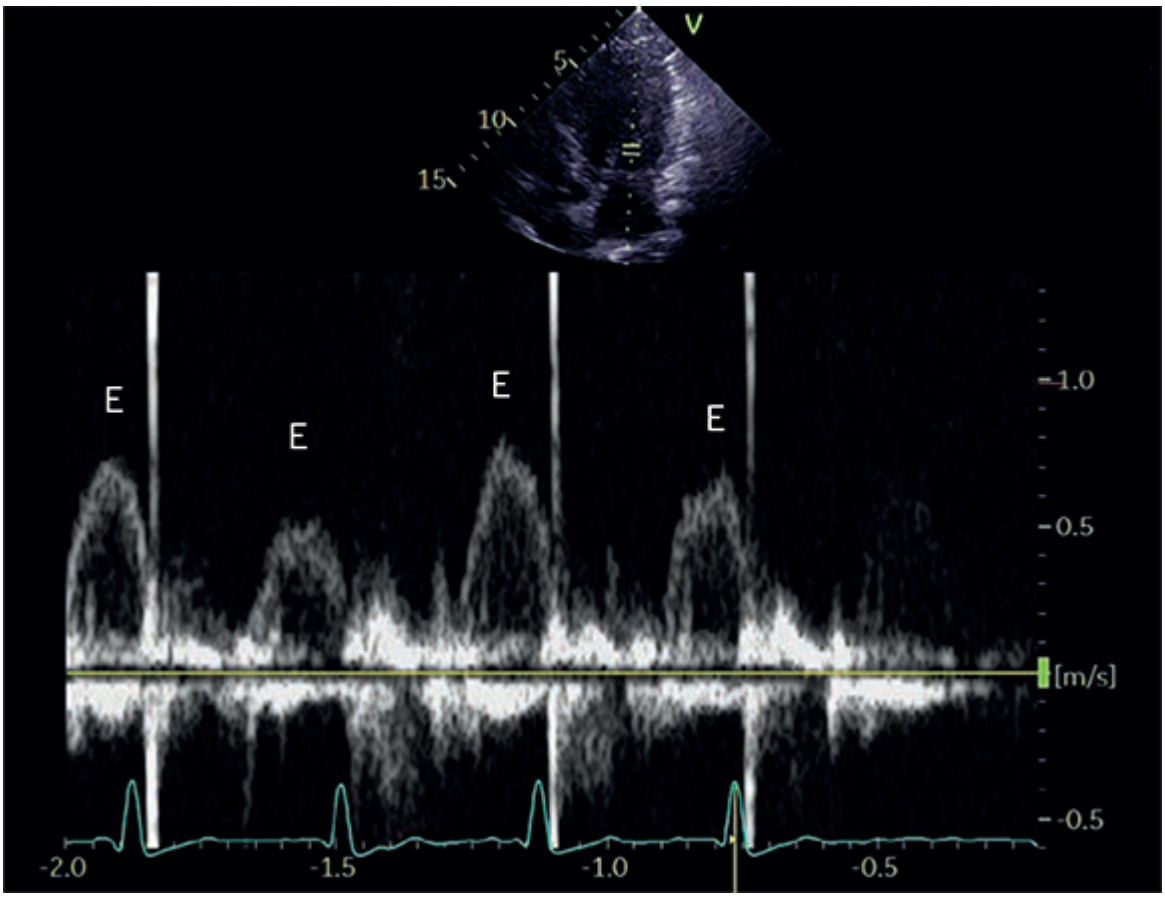


FIGURE 3.4. Pulse-wave Doppler profile of the mitral inflow during atrial fibrillation in an 8-year-old male Golden Retriever with persistent atrial fibrillation. Note the presence of early filling waves (E waves) without atrial contraction waves (A waves). Speed, 100 mm/s.

CLINICAL FINDINGS

The clinical signs associated with cardiac arrhythmias include weakness, exercise intolerance, collapse, and syncope.[7] Syncope is defined as a transient loss of consciousness due to transient global cerebral hypoperfusion and is characterized by a rapid onset, short duration, and complete spontaneous recovery (see p. 421).[11] Episodes are usually brief (5–20 seconds) and characterized by a loss of postural tone with no tonic-clonic movements; the mucous membranes are usually pale, and recovery is very rapid. In some cases, if the syncopal episode lasts longer than usual, tonic-clonic movements or sphincter relaxation (urination or defecation) may appear due to prolonged cerebral hypoxia.[12] Collapse is defined as a sudden loss of postural tone that is not necessarily associated with a loss of

consciousness.[11] Arrhythmias can be associated with syncope and loss of postural tone when the fast or slow heart rate compromises the cardiac output and cerebral perfusion.[11] Episodes of transient loss of consciousness in dogs are mainly associated with ventricular arrest (69%) and less frequently with sinus bradycardia (8.7%), sinus rhythm or sinus tachycardia (19.5%), and supraventricular or ventricular tachycardia (2.2%) (see p. 423).[13] The presence of a cardiac structural disease can aggravate the clinical signs associated with the rhythm disturbance due to the compromised stroke volume (forward heart failure). If cardiac function is correct and the arrhythmia is not severe enough, it may just result in weakness or exercise intolerance.

Although this is less common, signs such as anxiety or odd behavior can sometimes be identified by owners. These signs are nonspecific of cardiac disease but could be caused by palpitations during fast rhythm, as described in human medicine.[14] Another uncommon clinical sign of fast arrhythmias is head bobbing, which can sometimes be observed in dogs with supraventricular tachycardias, together with precordium bobbing.[14]

If a rhythm disturbance is associated with a structural cardiac disease (primary or secondary), the animal may present with clinical signs resulting from backward heart failure (congestive heart failure). The main sign of left-sided congestive heart failure is pulmonary edema, although cats can also present with pleural effusion. Tachypnea and respiratory distress are the most common signs associated with pulmonary edema or pleural effusion. The clinical signs caused by right-sided congestive heart failure include abdominal distension caused by ascites or pleural effusion. If ascites are severe, they may compromise the patient's ability to breathe. Swollen extremities and ventral edema can be present in severe cases of right-sided heart failure.

While some highly symptomatic arrhythmias may not be associated with any adverse outcomes, some asymptomatic arrhythmias are life-threatening due to the risk of sudden cardiac death.[3–4]

PHYSICAL EXAMINATION

Mucous membranes appear pale in animals with a reduced cardiac output during severe tachycardia or bradycardia, and they may be cyanotic if the arrhythmia is associated with congestive heart failure and the animal has difficulty breathing.[3–6]

Jugular venous distension is indicative of high central venous pressure and can be seen when right-sided volume overload is reached in cases of advanced arrhythmia-induced cardiomyopathy. Jugular venous pulsation can be evident during atrioventricular dissociation (i.e., third-degree atrioventricular block, ventricular tachycardia) due to the contraction of the atrium against a closed tricuspid valve (cannon A wave in the venous waveforms). Pulsations of the carotid artery can easily be felt in patients with tachyarrhythmias.[15]

The femoral and tarsal artery pulse can be easily palpated in small animals. The palpable pulse is an indicator of pulse pressure (difference between the systolic and diastolic pressures) and is correlated with cardiac output and vasomotor tone.[15] A weak pulse may be felt during tachycardia due to a reduced stroke volume or cardiac output associated with systolic dysfunction (arrhythmia-induced cardiomyopathy), while a bounding pulse may be palpated in bradycardias without ventricular arrest and is attributed to increased cardiac output during a prolonged diastolic time. A pulse deficit generally occurs with supraventricular or ventricular ectopic beats and with irregular supraventricular arrhythmias, such as atrial fibrillation.[3–5] Pulse bigeminy is a beat-to-beat difference in pulse strength during ventricular bigeminy. Blood pressure should be measured in patients with arrhythmic disorders, but the value obtained may not be reliable when a pulse deficit is present and the oscillometric method is used.

Cardiac sounds can be abnormal during arrhythmic disturbances.[16] The intensity of the first sound (closure of atrioventricular valves in systole) is increased during tachycardia and decreased during long PQ intervals. Physiological or paradoxical splitting of the second sound (closure of semilunar valves) occurs during ventricular ectopic beats. An atrial gallop (audible fourth heart sound) may be heard during a third-degree atrioventricular block. Rhythm variations can also be identified upon auscultation. Single ectopic beats are auscultated as early or delayed heart sounds when compared with the dominant rhythm, while series of ectopic beats may occur as self-limiting or sustained runs of tachycardia and can

easily be distinguished from sinus rhythm. Finally, changes in cycle length (regularity or irregularity) can also be heard on auscultation and are sometimes helpful to identify arrhythmias such as atrial fibrillation (delirium cordis).[17,18]

Heart murmurs during arrhythmias are generally associated with valvular insufficiency in response to structural and functional changes of the ventricle and mitral annulus.[16] Most murmurs are systolic, but mid-diastolic murmurs can be audible during third-degree atrioventricular block.

Abdominal distension, as described previously, can be related to ascites and splenomegaly or hepatomegaly in dogs with arrhythmia-induced right-sided congestive heart failure. Organomegaly can sometimes be confused with severe ascites. Jugular distension may be observed during abdominal compression (hepatojugular reflux) and suggests an elevated central venous pressure.

Physical maneuvers during tachycardia can have both a diagnostic and therapeutic value. Carotid sinus massage, eyeball pressure, and nasal planum massage cause a transient increase in vagal tone and tachyarrhythmias depending on the atrioventricular node for continuation can terminate or slow down with these maneuvers.[19,20]

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SECTION II

DIAGNOSTIC MODALITIES

CHAPTER 4

Use of the electrocardiogram in the diagnosis of arrhythmias

Manuela Perego, Roberto Santilli

VALUE AND LIMITATIONS OF ELECTROCARDIOGRAPHY

The surface electrocardiogram was introduced more than 100 years ago by Willem Einthoven and still is to date the most common technique to evaluate heart rhythm.[1]

Electrocardiography is a very useful tool to investigate transient loss of consciousness or transient loss of posture and is the gold standard to investigate cardiac arrhythmias, conduction disturbances, preexcitation syndromes, channelopathies, and some aspects of acute ischemic heart diseases.[2–7]

It is also useful for epidemiological studies, screening of diseases (e.g., dilated cardiomyopathy or arrhythmogenic cardiomyopathy), and checkups of athlete dogs.[8–10]

Electrocardiography is an invaluable diagnostic tool if performed correctly, although normal electrocardiograms should be interpreted with

caution. It is important to bear in mind that a relatively high percentage of dogs and cats presenting with transient loss of consciousness may have a normal electrocardiogram despite the presence of severe conduction disturbances or severe impulse formation abnormalities.[2] Therefore, a normal electrocardiogram is not completely reassuring because the patient may still present with a severe disease with an increased risk of sudden cardiac death. However, in the absence of clinical signs or a family history of sudden death, this possibility is very remote.[11]

Conversely, electrocardiographic abnormalities with no evidence of structural heart disease may occasionally be observed. In case of channelopathies and preexcitation syndromes, the electrocardiogram plays a pivotal role.[6,12,13]

Normal variations may be observed in the electrocardiogram and are related to the patient's chest morphotype, age, and other factors. Transient abnormalities due to hyperventilation, hypothermia, or ionic abnormalities caused by drugs must also be considered.[14–16]

The importance of the electrocardiogram goes beyond its role in the diagnosis of arrhythmias; it has become a tool to determine prognosis and stratify risk in many clinical situations because it can provide insights into the electrophysiological mechanisms of diseases by ascertaining abnormalities at the molecular level, as in the case of channelopathies.[13]

These considerations should be kept in mind before starting to learn about electrocardiography, because the interpretation of electrocardiograms must be done within the context of a given clinical condition. This chapter will provide a description of electrocardiographic devices, normal electrical activation, the characteristics of a normal electrocardiogram, and the main findings in patients with bradycardia, narrow QRS complex tachycardia, and wide QRS complex tachycardia.

ELECTROCARDIOGRAPHIC DEVICES

THE ELECTROCARDIOGRAPH

An electrocardiograph is a galvanometer able to record electrical potentials generated by the heart from several electrodes positioned on the body surface, at the level of the limbs and thorax.[17]

An electrocardiograph can convert the electrical potentials measured between the different electrodes into electrocardiographic waves recorded on a calibrated paper.[18–20] Electrocardiographs can be analog or digital. Analog electrocardiographs acquire the electrical signal and print it on calibrated paper as electrocardiographic waves. Digital electrocardiographs record and postprocess the signal and store the information in a hard drive of the device. Digital electrocardiographs can simultaneously record the 12 leads and allow manual or automatic electrocardiogram measurement using different degrees of zoom as well as the transfer of files to other computers and long-term storage of electrocardiographic tracings.[21]

HOLTER MONITORING

In 1949, Dr. Norman Holter invented a system to record a continuous electrocardiogram for 24 hours.[22]

Nowadays, Holter monitoring is a basic diagnostic method used for the detection and characterization of transient arrhythmias. Thanks to technological advances and design improvements, the method has been refined and made user-friendly, and miniaturization of the recorder has allowed the use of Holter monitoring in veterinary practice not only in large but also in small animals.[23]

Routine electrocardiography is commonly performed in veterinary medicine to assess patients for the presence of cardiac arrhythmias. This technique is quite reliable when arrhythmias are sustained or very frequent; however, transient arrhythmias are often not present at the time of the consultation. This limitation is quite apparent when we consider that a 5-minute rhythm strip comprises only 0.34% of the daily electrocardiographic activity.[24] Furthermore, most animal patients undergoing a hospital visit and routine electrocardiography experience elevations in sympathetic tone that may significantly increase the sinus node discharge rate and the conduction velocity of the atrioventricular node. Electrocardiography in clinical settings has been demonstrated to increase the heart rate of normal cats by 54% (from 118 to 182 bpm) compared with rates measured at home.[25,26]

EVENT RECORDERS

Due to the advancements in semiconductor memory technologies, the more recently developed ambulatory Holter systems can monitor and store electrocardiograms for more than 48 hours.[27]

These memory-efficient ambulatory Holter devices and patch monitors are portable and can be employed to monitor heart rhythm for a few days and up to 1 or 2 weeks. Intermittent long-term monitoring devices store the patient's electrocardiographic data only when the monitoring device is activated either by the human patient when he/she experiences symptoms such as syncope or palpitations or by the occurrence of any abnormal cardiac episodes detected by the automated algorithms embedded in the monitoring device.[27]

Cardiac loop recorders can be further classified into two groups: external loop recorders and implantable loop recorders.[20] The latter devices are implanted underneath the chest skin, in the left hemithorax near the heart, while the former can be worn externally on the body (like Holter or patch recorders) and do not require any invasive procedures. The leadless, subcutaneously implanted device records a one-lead electrocardiogram signal through two electrodes embedded within the device. The latest versions of implantable loop recorders enable remote transmission of data and have a battery lifetime of 36 months. External loop recorders and implantable loop recorders typically record 1 to 6 minutes of new electrocardiographic data, replace any previously recorded data, and save the data only if a trigger occurs. Once activated, either by the patient experiencing the symptoms or by the internal abnormal rhythm detection algorithm, the episodic electrocardiographic data are stored for a fixed (preset) amount of time before the activation and after the activation (looping memory), and the recorder can transmit the data to the central monitoring station for clinical intervention.[28] The main advantages of these systems are portability and the capability of very long-term monitoring, which allows detection of the underlying causes of infrequent and intermittent events such as transient loss of posture or transient loss of consciousness.[28–30]

ELECTROPHYSIOLOGICAL STUDY

The field of cardiac electrophysiology has greatly advanced over the past decades.[31–36]

Consequently, the use of electrophysiological studies in clinical practice has also significantly increased, with a gradually increasing number of certified electrophysiology centers and specialists. A cardiac electrophysiological study is a minimally invasive procedure in which catheters are introduced through the venous or arterial system to record the heart's electrical activity. An electrophysiological study is typically performed in an electrophysiological laboratory or cardiac catheter laboratory. These laboratories are equipped with a C-armed fluoroscope, a polygraph that records surface and intracardiac electrical signals, a stimulator able to pace the heart, and an ablation device for the delivery of radiofrequency energy.[36] An electrophysiological study is indicated in the diagnosis of narrow and wide QRS complex tachycardias. The term "narrow QRS complex tachycardia" is a general term that encompasses several types of supraventricular tachycardias characterized by a heart rate >180 bpm and a QRS complex duration <70 ms: sinus tachycardia, focal atrial tachycardia, focal junctional tachycardia, nonparoxysmal junctional tachycardia, accessory pathway–mediated tachycardias, and atrial macroreentrant tachycardias.[3] Although all the above-mentioned supraventricular tachycardias have specific characteristics on the 12-lead electrocardiogram, their differential diagnosis is not always possible by standard noninvasive methods. The role of the electrophysiological study in patients with supraventricular tachycardias is to identify the tachycardia mechanism and guide catheter ablation.[33,34,37] An electrophysiological study precedes any catheter ablation procedure and has the following goals:[38]

1. Baseline characterization of the normal His–Purkinje conduction system.
2. Identification of the presence of an arrhythmia substrate, such as abnormal atrioventricular connections (accessory pathways)/dual atrioventricular nodal physiology and areas of conduction block.
3. Initiation of tachycardia to determine its underlying mechanism, with or without pharmacological provocation (isoprenaline, atropine, and adrenaline).
4. Application of electrophysiological maneuvers for the differential diagnosis.
5. Establishing the correct diagnosis.

Several electrophysiological maneuvers are also performed after catheter ablation to confirm success of the procedure, assess the integrity of the His–Purkinje conduction system, and confirm the presence or absence of additional tachycardia substrates.[17] Wide QRS complex tachycardias are characterized by a QRS width >70 ms in the presence of a heart rate of >180 bpm. Depending on the underlying mechanism, there are three possible types of wide QRS complex tachycardia: ventricular tachycardia, supraventricular tachycardia with preexisting or functional bundle branch block, and ventricular preexcitation. It should be mentioned that, in human medicine, up to 80% of times, a wide QRS complex tachycardia is ventricular in nature; supraventricular tachycardias with bundle branch block account for 15–25% of cases.[36]

Several electrocardiographic algorithms have been developed to aid in the diagnosis of arrhythmias, but these algorithms have limitations, and a correct diagnosis is not always possible using a surface electrocardiogram only, particularly when trying to differentiate some forms of ventricular tachycardia from ventricular preexcitation. Doubtful cases can be evaluated with an electrophysiological study.[36]

ELECTROCARDIOGRAM LEAD SYSTEMS

By placing several exploring electrodes on the body surface at a fixed distance from the heart, it is possible to record the magnitude and direction of cardiac vectors.[11] The electrocardiogram detects the variations in the electric potentials over time between a point on the body surface and an indifferent (or reference) electrode, or between a pair of electrodes. The lines joining pairs of electrodes are named leads. The electrocardiogram is evaluated by examining the limb and precordial lead systems. The voltage changes recorded by the different leads are displayed graphically as waves of variable amplitude, polarity, and duration.[11]

Bailey's hexaxial system records the electrocardiographic waves in the frontal plane using three bipolar leads (I, II, III) and three unipolar leads (aVR, aVL, aVF) (Fig. 4.1).

The precordial leads are recorded by placing the exploring (positive) electrodes at predefined positions on the chest surface. The precordial lead

system uses only unipolar leads.

In veterinary medicine, different precordial lead systems have been used. The first system used was Lannek's lead system, later modified by Dettweiler and Patterson in 1965. It is based on the use of a fourth unipolar lead placed at the level of the chest. In 1964, Takahashi developed a more complex system based on experimental studies in the dog. This system is based on 12 precordial leads, six of which are placed on the left hemithorax and six on the right.

In 2002, Kraus et al. adapted Wilson's precordial lead system, which is used in human beings, for veterinary medicine.[39] This system consists of six unipolar leads (from V1 to V6) exploring the right and left hemithoraces. The exploring electrode V1 is placed on the right hemithorax in the fifth intercostal space at the sternochondral junction and the left precordial leads at the sixth intercostal space. In 2019, Santilli et al. optimized the 12-lead electrocardiogram developed by Kraus et al. for veterinary patients, with a new position for lead V1 that is feasible in all thoracic morphotypes in the canine species. Lead V1 is placed in the first intercostal space at the costochondral junction to allow correct evaluation of the cardiac vectors (Fig. 4.2). The exploring electrode V2 is placed on the left hemithorax, in the sixth intercostal space, at the sternochondral junction. The exploring electrode V3 is placed on the left hemithorax, in the sixth intercostal space, midway between V2 and V4. The exploring electrode V4 is placed on the left hemithorax, in the sixth intercostal space, at the costochondral junction. The exploring electrode V5 is placed on the left hemithorax, in the sixth intercostal space dorsal to V4. The distance between V5 and V4 is the same distance as that between V4 and V3. The exploring electrode V6 is placed on the left hemithorax, in the sixth intercostal space, dorsal to V5. The distance between V6 and V5 is the same distance as that between V5 and V4.[40]

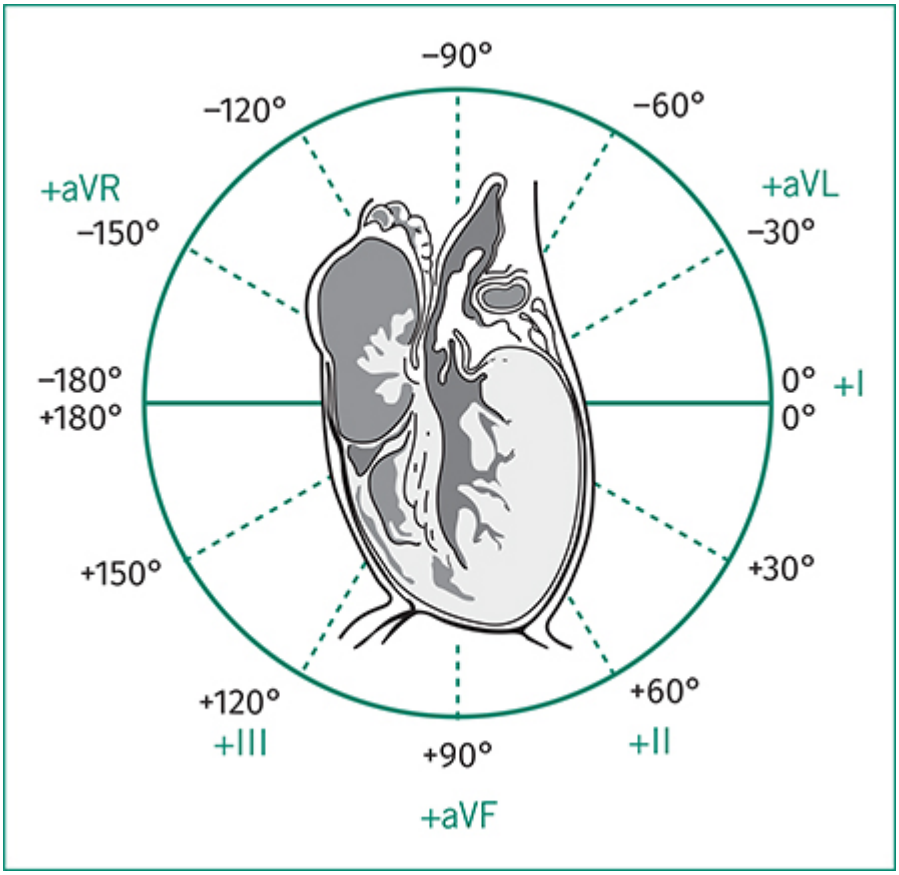


FIGURE 4.1. Bailey's hexaxial system representing the combination in the frontal plane of triaxial systems of bipolar (I, II, III) and unipolar leads (aVL, aVR, aVF). The axis of each lead is identified by increments of 30° from 0° to +180° (I: 0°; II: +60°; aVF: +90°; III: +120°) and from 0° to –180° (aVR: –150°; aVL: –30°).

Lead V1 is the lead reading the right atrial and right ventricular vectors, while leads V2 to V6 are usually the leads reading the left atrial and left ventricular vectors.[22] When lead V1 is placed in the first right intercostal space at the sternochondral junction (reading the right chambers), it shows a negative P wave and a fairly consistent QRS pattern with a R/S<1 in most dogs, regardless of the thoracic morphotypes, in a manner similar to that observed for V1 in humans.[40]

The atrial activation wavefront from the sinus node to the atrioventricular node is directed leftward in an anterior-to-posterior and superior-to-inferior direction. Ventricular depolarization is represented by vector 1 and vector 2, which is simultaneous to vector 3. Ventricular depolarization starts with septal activation (vector 1), which shows an inferior-to-superior, left-to-right, and posterior-to-anterior direction. Right ventricular activation

(vector 2) shows an inferior-to-superior, left-to-right, and posterior-to-anterior direction, while left ventricular activation (vector 3) shows a superior-to-inferior, right-to-left, and anterior-to-posterior direction. Consequently, the P wave is typically positive in leads V2 to V6 and negative in V1 (and sometimes in V2). Additionally, the QRS complex in lead V1 has an rS morphology with an R/S <1, while in leads V2–V6 it has a qRs morphology. In the left precordial leads (V2–V6), the QRS complex is characterized by a progressive increase in amplitude of the R wave from V2 to V5 and then a decreased amplitude of the R wave from V5 to V6. These findings confirm the correct position of the unipolar precordial leads because alterations in the amplitude of the R wave, particularly a decrease in amplitude between V5 and V6, can be the result of an attenuating effect of the lungs or by the more dorsal position of V6 on the thorax relative to V5. The amplitude of the R wave is also affected by the thoracic morphotype.[40]

Brachymorphic dogs present the lowest R wave amplitude in both limb and precordial leads compared with mesomorphic and dolicomorphic dogs.[40]

The voltage recorded by the precordial leads depends on the direction and magnitude of the resulting cardiac vector generated from the cardiac dipole. Some cardiac causes (myocardial infarctions, infiltrative cardiomyopathies, impaired cardiac volume, or pericardial diseases) and extracardiac causes (increased distance between the heart and thoracic wall, abnormally decreased pulmonary impedance, and position of precordial leads) can alter the transfer of electrical potentials generated by the heart to the body surface and consequently produce a QRS complex with a low voltage in the frontal and precordial leads.[40]

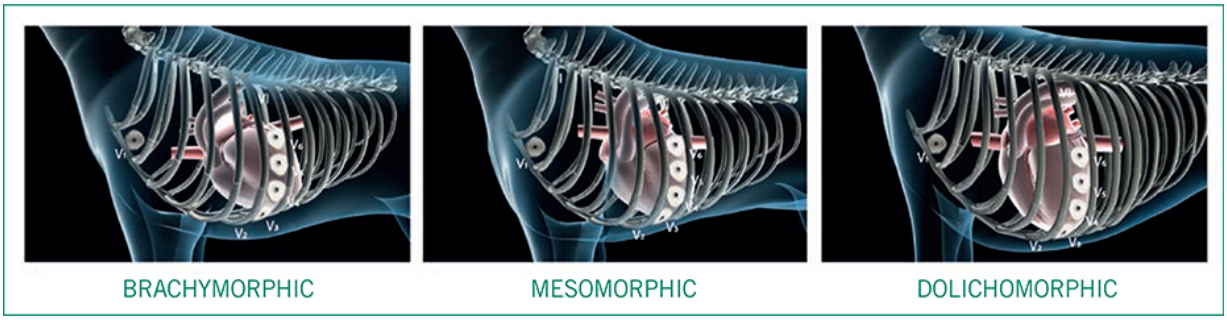


FIGURE 4.2. Schematic images of the transversal and lateral aspects of the thorax for dogs with brachymorphic, mesomorphic and dolichomorphic thorax conformations, showing the placement of

the precordial lead V1 in the first right intercostal space at the sternochondral junction. The sixth left intercostal space is used for all the left precordial leads (V2–V6). Source: Santilli R. et al.[40]

Brachymorphic dogs have a great heart-to-thoracic wall distance, likely because of their round thoracic shape. These characteristics, in conjunction with a horizontal electrical axis in the frontal plane, could induce a low QRS amplitude on the surface electrocardiogram.[40]

Precordial leads are useful in the diagnosis of chamber enlargement or intraventricular conduction abnormalities to detect normal P waves and ectopic P' waves and in the differential diagnosis of both narrow and wide QRS complex tachycardias.[40]

The orthogonal bipolar lead system, used to record Holter tracings, was designed to simultaneously record the vector of cardiac activation from the three planes of the Cartesian system. The X lead records the cardiac vectors in the frontal plane from right to left and is similar to lead I; the Y lead records the cardiac vector in the sagittal plane in a superior-to-inferior direction and is comparable to aVF; the Z lead records the cardiac vectors in the horizontal plane in an anterior-to-posterior axis and is comparable to V10 (see p. 57).[41]

Another electrocardiogram lead system developed based on the Bailey's system is the Cabrera system. In the Cabrera sequence (also called "panoramic display" or "anatomical format"), the leads are anatomically arranged and lead aVR is inverted (Fig. 4.3). Lead aVR is considered as -aVR, and corresponds to its reciprocal vector or inverted image, with the same direction and opposite sense (lead aVR is at +30°). This arrangement allows visualization of all the electrocardiographic waves with a progressively increasing and decreasing amplitude.[42]

This system can have some advantages, such as helping to understand the pathway followed by the wavefront from right to left, which favors the visual appreciation of the gradual change at each angle (in the same way that the precordial leads progress sequentially from V1 to V6).[42]

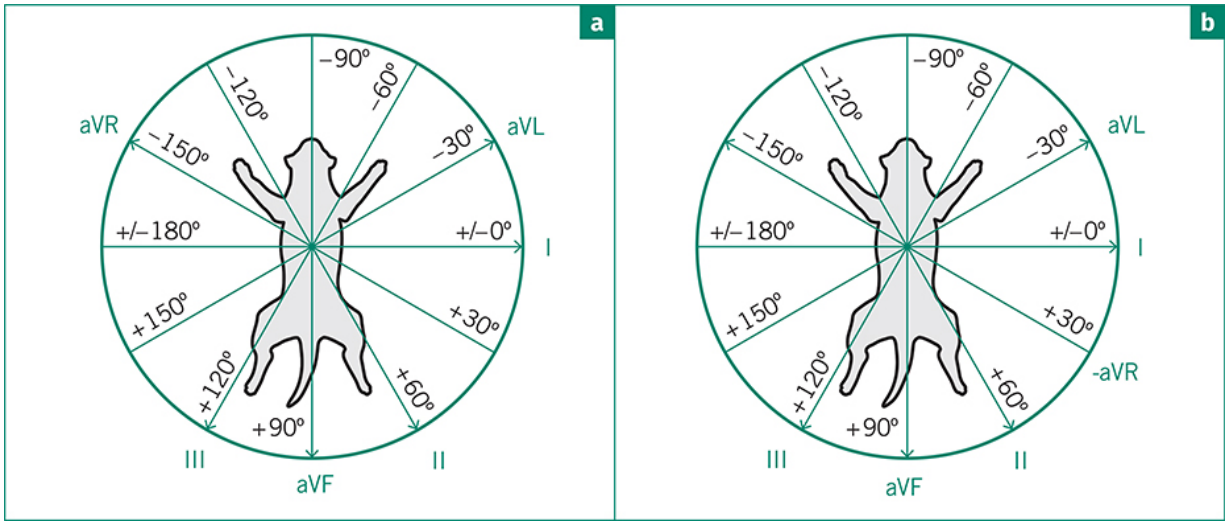


FIGURE 4.3. Schematic images of Bailey's hexaxial lead system (a) and of Bailey's hexaxial lead system adapted with the Cabrera format, with the -aVR lead (b). Adapted from images courtesy of Dr. Federico Curra Gagliano.

SYSTEMATIC INTERPRETATION OF THE ELECTROCARDIOGRAM

The normal waves on the electrocardiographic trace are named P waves, Ta waves, QRS complexes, T waves, and U waves. These waves can vary in morphology, polarity, duration, and amplitude. In pathological conditions, other waves can be recorded, such as delta waves in case of preexcitation (see p. 205) or Osborne waves in case of hypothermia. Different parameters should be routinely assessed when interpreting an electrocardiogram. The following sections will discuss the most important aspects of the normal limits of these electrocardiographic parameters.

HEART RATE

The normal heart rate is considered to be 60–180 bpm in adult dogs, 60–220 bpm in puppies, and 140–220 bpm in cats (Table 4.1).

TABLE 4.1. Reference ranges of electrocardiographic measurements in dogs and cats.

Electrocardiographic parameters	Dogs	Cats

Heart rate	Adults: 60–180 bpm Puppies: 60–220 bpm	140–220 bpm
P wave ▪ **Amplitude** ▪ **Duration** ▪ **Mean electrical axis in the frontal plane**	 ≤0.4 mV ≤40 ms (<50 ms in giant breeds) From -18° to + 90°	 ≤0.2 mV ≤35 ms From 0° to + 90°
Ta wave ▪ **Amplitude** ▪ **Duration** ▪ **P–Ta interval**	 0.006 mV 105–175 ms 149–227 ms	
PQ interval	60–130 ms	50–90 ms
QRS complex ▪ **R wave amplitude** ▪ **Duration** ▪ **Mean electrical axis in the frontal plane**	 >0.5 mV in II, III, aVF ≤0.5 mV in V1 >1 mV in V2–V6 R/S ≤1 in V1 ≤70 ms From +40° to +100°	 ≤0.9 mV ≤40 ms From 0° to +160°
J wave **ST segment**	0.19 mV (0.10–0.50 mV) in II Isoelectric	Isoelectric
QT interval	150–240 ms	160–220 ms
T wave ▪ **Amplitude** ▪ **Polarity** ▪ **Mean electrical axis in the frontal plane**	 ≤0.05 to 1 mV in all leads Concordant with QRS complex in lead II (70–80% of the cases). From –45° to +147°	 From ±0.03 Variable in all leads

U wave ▪ **Amplitude** ▪ **Duration** ▪ **Polarity** ▪ **T–U interval**	 Absent or ≤0.05 mV 70–90 ms Concordant with the T wave 40 ms	

RHYTHM

The normal cardiac rhythms in the dog are the sinus rhythm, respiratory sinus arrhythmia, and nonrespiratory sinus arrhythmia.[43,44] In the cat, the normal rhythm is the sinus rhythm.[45]

In normal conditions, P waves have a positive polarity in inferior leads (II, III, aVF) and a negative polarity in aVR and aVL (with maximum negative polarity in aVR), and are positive or isoelectric in lead I. Each P wave must be followed by a QRS complex with a normal and usually constant PQ interval. The PQ interval ends with the Q wave in leads I, II, III, and aVF and is followed by an R wave with a maximal amplitude in lead II. In leads aVR and aVL, an S wave is usually present with a maximal negative amplitude in aVR.[45]

Sinus rhythm is characterized by regular PP and RR intervals (less than 10% variation) and normal P waves with a constant morphology. In addition, every P wave is followed by a QRS complex, and every QRS complex is preceded by a normal P wave with a normal and constant PQ interval.[11]

In the dog, respiratory sinus arrhythmia is characterized by cyclic variations of the RR interval in association with respiratory phases; this interval is decreased during inspiration and increased during expiration.[11] Respiratory sinus arrhythmia can be associated with a wandering pacemaker, with a variable morphology and amplitude of the P wave. The P wave decreases in amplitude after a long PP or RR interval associated with expiration and increases in amplitude after a short PP or RR interval associated with inspiration. The cyclic variations in the P wave characteristics in a wandering pacemaker are due to changes in the site of impulse initiation within the sinus node and/or the exit pathways from the sinus node.

Nonrespiratory sinus arrhythmia is characterized by a variation in PP intervals that is not correlated with the respiratory phases.[11]

P WAVE

The P wave is the electrocardiographic deflection that represents the sequential depolarization of the right and left atria. In normal conditions, it originates from the sinus node located in the roof of the right atrium and disperses first through the right atrium and then through the left atrium. In particular, once the electrical impulse exits the sinus node area, it typically travels rapidly along the crista terminalis and moves anteriorly in the inferior part of the right atrium, where it reaches the atrioventricular node.[46] At the same time, rapid propagation of the electrical impulse also takes place across the interatrial septal muscle, allowing near synchronous activation of the right and left atria. Interatrial propagation of the impulse from the right to the left atrium is also guaranteed by Bachmann's bundle. Conduction across Bachmann's bundle at both the endocardial and epicardial aspects allows the left atrium to depolarize in a superior-to-inferior direction; the last area to be depolarized is the inferioanterior portion of the left atrium.[46] This pattern of depolarization produces P waves; when these are evaluated in lead II, the ascending segment typically corresponds to right atrial depolarization while the descending segment corresponds to left atrial depolarization.[46] A P wave begins at the point where the wave separates from the isoelectric line and ends when the deflection returns to the isoelectric line. The duration of a P wave is measured from the point of first visible departure from the isoelectric line to the last point of intersection with this line. The P wave amplitude is measured from the isoelectric line to the peak of the wave (see Table 4.1). An increased P wave duration associated with a bifid or bimodal morphology is caused by interatrial conduction block. An increased duration associated with abnormalities in P wave polarity (negative polarity of the second part of the P wave in inferior leads and positive polarity of the second part of the P wave in lead V1) is associated with third-degree interatrial conduction block (see p. 310).[46]

While P waves represent the electrical potentials generated during excitation or depolarization of the atrial myocardium, the potentials generated during atrial recovery (repolarization phase) are part of the PQ

segment and QRS complex and are called Ta waves.[47] In normal conditions, P waves and Ta waves have opposite polarity in all leads. Ta waves have been described to be longer in duration and smaller in amplitude than their respective P waves, although both waves have a similar area under the curve. A segment between the P wave and the Ta wave (PTa segment) does not exist, and the end of the P wave corresponds to the beginning of the Ta wave. The amplitude of the Ta wave has been estimated to be 24% of the amplitude of the T wave, and a linear correlation was detected between P wave and Ta wave amplitude (see Table 4.1).[47]

PQ INTERVAL AND SEGMENT

The PQ interval corresponds to the time the electrical impulse generated by the sinus node takes to activate the atrial myocardium, travel through the atrioventricular node, and reach the His bundle.[48]

The atrioventricular node represents the connection between the atrial and ventricular myocardium; it is located at the atrioventricular junction, on the right side of the heart. The main role of the atrioventricular node is to conduct the electrical impulse from the atria to the ventricles. Clusters of P cells are present at the atrioventricular node so that it serves as a subsidiary pacemaker in case of sinus node dysfunction. Due to its decremental and concealed conduction properties, the atrioventricular node also acts as a filter that regulates the ventricular response in case of fast supraventricular tachycardia. In addition, the atrioventricular node serves as the slow antegrade conduction pathway of the circuit in cases of accessory-pathway mediated tachycardias.[49,50]

The electrical impulse arriving from the atrial myocardium undergoes a significant delay in conduction at the atrioventricular node. This delayed conduction is important to allow complete filling of the ventricles during the diastolic phase.[50,51] Slow conduction of the electrical impulse in this area of the heart is due to different factors. Two important causes are the smaller diameter of the nodal myocytes and the complex architecture of the atrioventricular node, which includes extensive areas of connective tissue. The slow velocity of the wavefront as it goes through the atrioventricular node is also attributable to the poor expression of Na^+ channels, with a consequent slow upstroke of the action potential during phase 0. Finally, the

small number of gap junctions in the atrioventricular node does not favor electrical coupling between adjacent myocytes.[51,52]

On the electrocardiogram, the delay in conduction is represented by the PQ interval, i.e., the interval between the beginning of the P wave and the beginning of the QRS complex. In normal conditions, the PQ interval lasts 60–130 ms in dogs and 50–90 ms in cats (Table 4.1). Although the PQ interval also includes the conduction time across the atrial myocardium and the His–Purkinje system until the first ventricular activation vector appears, its duration in large part reflects the slow conduction along the atrioventricular node. The PQ interval may be decreased or increased in duration. A short PQ interval (less than 60 ms in dogs and less than 50 ms in cats) is present in case of ventricular preexcitation. This condition is associated with the presence of an accessory pathway that connects the atrial myocardium to the ventricular myocardium bypassing the atrioventricular node and presents antegrade conduction.[6,12] Another cause of a short PQ interval is enhanced atrioventricular conduction, a condition in which physiological slowing of atrioventricular conduction is diminished.[53]

Prolongation of the PQ interval more than 130 ms in the dog and more than 90 ms in the cat is termed first-degree atrioventricular block. It is a frequent condition in clinical practice and is considered a benign finding.[54] First-degree atrioventricular block can be a consequence of increased vagal tone or structural diseases, which are more frequent in the older population and are characterized by conduction system fibrosis (see p. 306).[55] In individuals with heart failure, the PQ interval duration can be prolonged and associated with an increased risk of morbidity and mortality,[56] and a significantly increased PQ duration has also been reported in experimental models of myocardial infarction and congestive heart failure.[57] If the increased duration of the PQ interval is the consequence of delayed conduction along the atrioventricular node, it could be the result of a dysregulation of gap junctions and connexins. A prolongation of the PQ interval and the presence of first-degree atrioventricular block is also associated with aging and with exercise [58–60]

QRS COMPLEX

The QRS complex corresponds to ventricular depolarization. Based on the direction of the three different ventricular vectors (Fig. 4.4), the QRS complex is composed by the Q wave, which is the first negative wave preceding the R wave; the R wave, which is the first positive deflection after the PQ segment; and the S wave, which corresponds to the negative wave following the R wave. A second positive deflection after a R wave is named R' wave. The end of ventricular depolarization can be difficult to identify, and by convention, it corresponds to the point where the last deflection of the QRS complex intersects the isoelectric line. This point is also named J point or ST junction. In normal conditions, the QRS complex lasts less than 70 ms in dogs and less than 40 ms in cats.

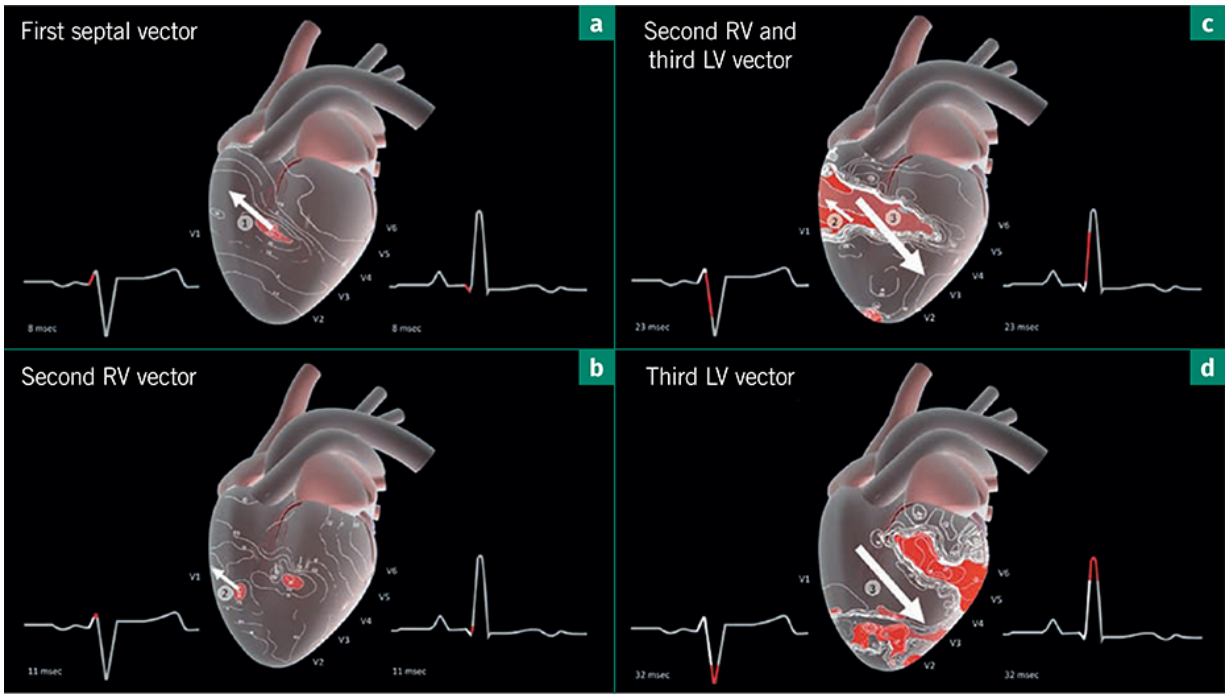


FIGURE 4.4. Graphic representation of the ventricular depolarization wavefronts with epicardial breakthroughs and their electrocardiographic appearance in the right precordial lead (V1) and left precordial leads (V2–V6). a) Vector 1 indicates the activation of the interventricular septum and has an inferior-to-superior, left-to right, posterior-to-anterior direction. b and c) Vector 2 is simultaneous to vector 3, indicates right ventricular activation, and shows an inferior-to-superior, left-to-right, and posterior-to anterior direction. LV, left ventricular; RV, right ventricular. d) Vector 3 represents the activation of the left ventricle and has a superior-to-inferior, right-to-left, and anterior-to-posterior direction. Source: Battaia S. et al.[4]

A QRS complex lasting more than 70 ms is called a wide QRS complex. A QRS complex duration that ranges from 70 ms to 80 ms is associated with delayed intraventricular conduction. A QRS complex >80 ms may be

due to a ventricular ectopic beat, a supraventricular beat conducted with intraventricular conduction disturbances (both anatomical or functional), and ventricular preexcitation. The time interval between the beginning of the QRS complex and the apex of the R wave is called R-peak time. R-peak time is an electrocardiographic parameter that corresponds to the time taken for electrical activation to spread from the endocardium to the epicardium; it is measured form the earliest onset of the QRS complex to the peak of the R wave (or R' wave if present).[60] The R-peak time is statistically shorter in V1 than in the other precordial leads. This finding could be related to the thickness of the right ventricular wall compared to that of the left ventricular wall (Table 4.2). The R-peak time also differs between thoracic morphotypes (brachymorphic, mesomorphic, and dolichomorphic) in the precordial leads. This finding is likely due to the variations in the cardiac shape and dorsoventral diameter of the thorax from one thoracic conformation to another.[60] The R-peak time in the precordial leads can also be used to establish the interventricular dyssynchrony index. This index is calculated using the absolute value of the difference between the R-peak times in leads V5 and V1, which reflect left and right endo-epicardial activation, divided by the QRS complex duration (Fig. 4.5).[4] Evaluation of the interventricular dyssynchrony index is very important since it has been shown in human medicine that ventricular dyssynchrony reduces pump function and energetic efficiency in an acute setting, while on a chronic basis, it reduces regional and global molecular signaling, thus altering excitation-contraction coupling, energetic requirements from the myocytes, arrhythmia susceptibility, and myocyte survival. In dogs, it has been proven that normal values of interventricular dyssynchrony index are 16–29%. This value increases in case of complete bundle branch block and ranges from 23 % to 41% in complete left bundle branch block and from 30 % to 38 % in complete right bundle branch block.[4]

TABLE 4.2. Median (25–75th percentile in ms) R-peak times (in milliseconds) in dogs with different morphotypes.

Lead	Brachymorphic dogs	Mesomorphic dogs	Dolicomorphic dogs
I	24 (22–29.5)	30 (25–32)	27.5 (23–30)
II	22 (19–27.5)	30 (27–33)	35 (31.5–36)
III	19 (14.5–25)	30 (27–32)	34 (29.5–36.5)
aVR	9.5 (6–12)	10 (9–11)	11.5 (8.5–13.5)
aVL	26 (0–32)	9 (7–12)	10 (10–15)
aVF	21.5 (17–27.5)	30 (26–33)	35.5 (30–37)
V1	10.5 (10–12)	16 (14–18)	15 (13–17)
V2	18 (16.5–20)	22 (20–24)	29 (26–32.5)
V3	9 (18–22)	23 (21–25)	30 (27–33.5)
V4	20 (17–23.5)	23 (22–25)	29.5 (26–35)
V5	21 (18.5–24)	25 (23–27)	30 (28–34)
V6	22 (18.5–25.5)	28 (25–30)	31.5 (28–35)

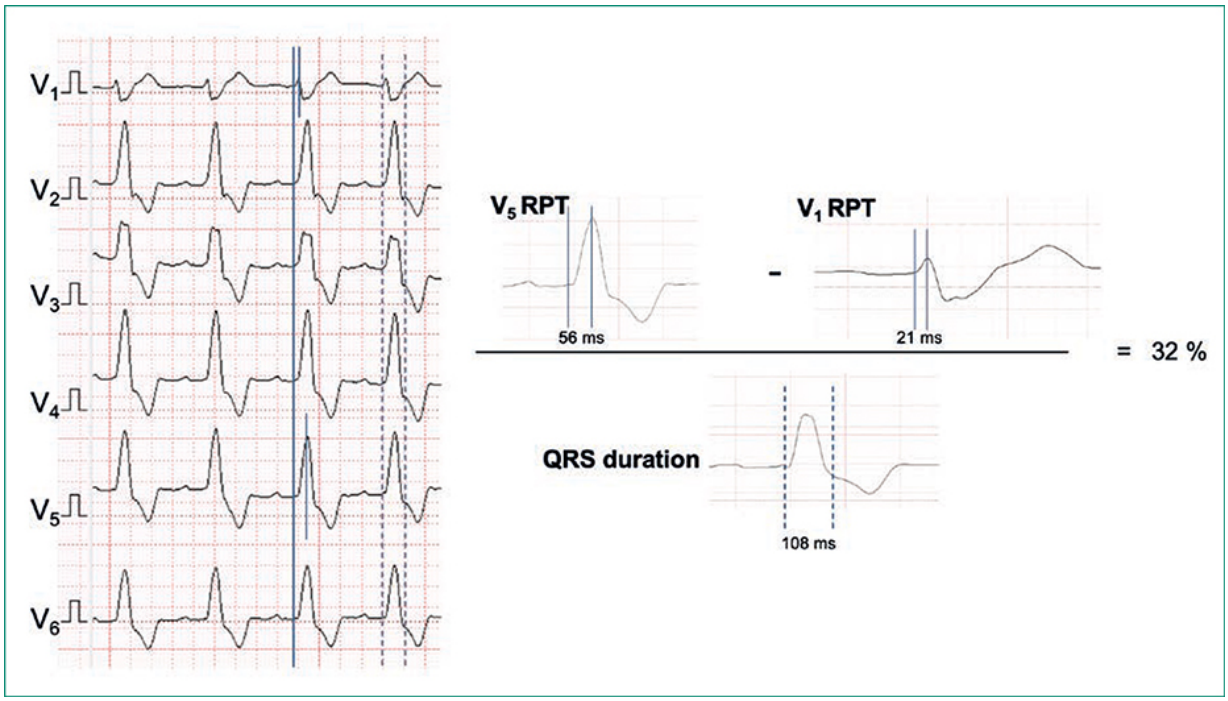


FIGURE 4.5. Interventricular dyssynchrony index calculation in a case of left bundle branch block. The index is estimated by calculating the absolute value of the difference between the duration of the R-peak time in V5 and the duration of the R-peak time in V1, divided by the duration of the QRS complex. Source: Battaia S. et al. [4]

The QRS complex can have an altered morphology with multiple waves or peaks. Notching is always positive (it does not go to the negative side of the baseline) and can occur in any part of the ascending R wave (R'sR or

r'sR), in the R peak (RsR' or Rsr'), or in the upper part (>50%) of the descending R wave (RsR' or Rsr'). (Figs. 4.6 and 4.7); it is present only in one lead.[61–63] Fragmented QRS complexes are defined as notched QRS complexes in two or more contiguous leads in the frontal plane: leads I and aVL, which correspond to the anterior area of the left ventricular wall, and leads II, III, or aVF, which correspond to the posterior area of the left ventricular wall (Fig. 4.7). In human beings with ischemic heart disease, it has been proven that the fibrotic area is sufficient to generate a terminal conduction delay with consequent fragmentation of the QRS complex.[64]

Fragmented QRS complexes have also been associated with hypertrophic cardiomyopathy,[65] nonischemic dilated cardiomyopathy,[66] or myocardial infarction.[67,68] All these conditions are associated with large areas of fibrotic tissue.[69]

A splintered QRS complex is characterized by an rR', Rr', RR', or rr' morphology or prominent notching in which the second deflection does not cross the baseline to be classified as a secondary R wave (Fig. 4.7). A splintered QRS complex is described as a common feature of dogs and cats with right atrioventricular valve malformation. Although the underlying mechanism is currently unknown, potential causes of the alteration of ventricular depolarization include fibrosis and ischemia.[70]

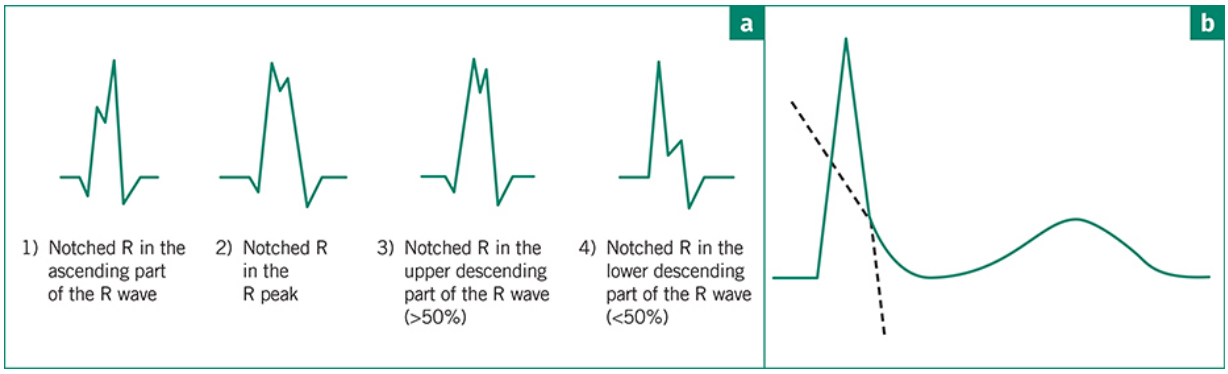


FIGURE 4.6. a) Graphic representation of a notched QRS complex with multiple waves or peaks altering the normal morphology. Notching is always positive and can occur in any part of the ascending R wave (R'sR or r'sR), in the R peak (RsR' or Rsr') or in the descending part of the R wave (RsR' in the upper part or Rsr' in the lower part). b) A slurred QRS complex is defined as a change in the slope of the R wave descending branch in inferior leads.

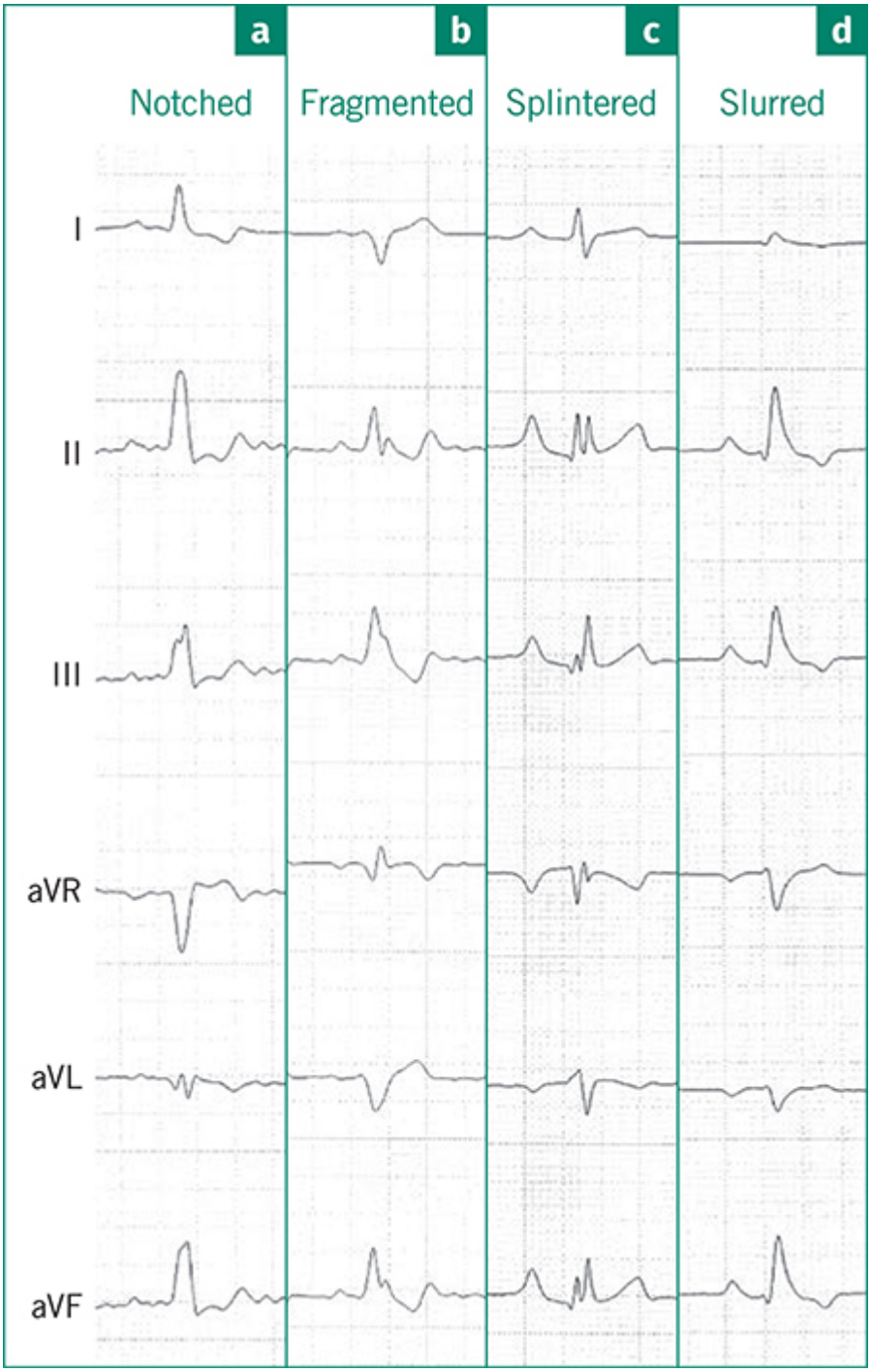


FIGURE 4.7. Different QRS complex morphologies in six leads (I, II, III, aVR, aVL, and aVF). a) Notched QRS complex. Note the RR' morphology in lead III (speed, 50 mm/s; calibration, 10 mm/1 mV). b) Fragmented QRS complex. Note the Rr' morphology in leads II, III, aVF (speed, 50 mm/s; calibration, 5 mm/1 mV). c) Splintered QRS complex. Note the prominent notched QRS complex in leads II, III, and aVF, in which the second deflection does not cross the baseline (speed, 50 mm/s; calibration, 10 mm/1 mV). d) Slurred QRS complex. Note the distinctive change in the slope of the descending branch of the R wave in inferior leads (speed, 50 mm/s; calibration, 10 mm/1 mV).

A deflection of the QRS complex is slurred (slurring of the QRS complex) when it displays a distinctive change in the slope of the descending branch of the R wave in the inferior leads (Fig. 4.7). This can be distinguished from a notched QRS complex, which is characterized by an abrupt change in the direction of a deflection (Fig. 4.6).[71] Slurring of the QRS complex is correlated with anatomical islands of viable myocardial cells in an area of fibrosis.[72]

Notched, splintered, and slurred QRS complexes are presumed to have a common mechanistic basis involving areas of fibrosis in the ventricular myocardium.[71]

ST SEGMENT

The ST segment begins at the end of the QRS complex and extends up to the beginning of the T wave. The ST segment corresponds to phase 2 of the action potential and ventricular systole. The point where the QRS complex ends is called J point and represents the point of intersection of the descending branch of the R wave or the ascending branch of the S wave, when present, and the isoelectric line. In dogs, the J point is more visible in leads II and aVF. ST segment deviation describes the displacement of the entire segment above (elevation of the ST segment) or below (depression of the ST segment) the isoelectric line by more than 0.20 mV in the standard limb leads and by more than 0.25 mV in the precordial leads. The ST segment deviation must be measured at a specific point, which is typically 40 ms after the J point. In normal dogs, a mild ST segment deviation is not an uncommon finding and ST depression is more common than ST elevation. ST depression and elevation have a similar amplitude that is usually below 0.2 mV. In dogs, horizontal and concave morphological patterns are overrepresented compared with other morphologies (upsloping or downsloping depression).[73]

ST segment deviations are associated with significant changes in the voltage gradient during the plateau phase of the action potential. ST depression occurs when the ventricular gradient is directed towards the epicardium; the opposite gradient has been postulated as the cause for ST elevation. In particular, ST elevation is the hallmark of myocardial infarction caused by transmural ischemia. Transmural heterogeneities in the properties of sodium and ATP-sensitive potassium channels may contribute

to the genesis of ST–T wave changes during mild or moderate transmural ischemia, while ST elevation may be induced without the contribution of heterogeneity in case of severe transmural ischemia.[74]

T WAVE

The T wave is the electrocardiographic representation of the final phase of ventricular repolarization following the ST segment. The morphology, polarity, and amplitude of the T wave should be evaluated. In normal conditions, the T wave in dogs and cats can be positive, negative, diphasic, isodiphasic, or flat (especially in leads I, aVR, and aVL). When the T wave has the same polarity as that of the QRS complex it is called concordant; if the polarity is opposite, it is named discordant. The amplitude of a normal T wave in dogs does not exceed 0.05–1mV in all leads. The T wave has asymmetrical branches, with an ascending slope that is slower than the descending slope. The ventricular repolarization vector has an epi-endocardial direction, and the repolarization phase is slower at the epicardium and mid-myocardium than at the endocardium, giving the classical asymmetrical morphology to the T wave. Positive T waves occur most frequently in dogs followed by negative T waves and isodiphasic T waves.[75]

In some dogs, a U wave can be detected in inferior leads (II, III, aVF) as a small positive deflection within the TP segment, approximately 40 ms after the T wave. The U wave corresponds to the repolarization of midmyocardial cells, which have a longer action potential duration than epicardial and endocardial myocytes.[76]

In pathological conditions, T waves can present changes in morphology during the recording of an electrocardiogram. This condition is called macroscopic T wave alternans and is characterized by beat-to-beat alternations in T wave amplitude, width, morphology, or even polarity when there are no variations in heart rate. These alternations are clearly visible in all or most of the 12 leads on the electrocardiogram.[78] Macro T wave alternans during which two different T waves and QT intervals are respectively occur every other beat is linked with mechanical alternans and is promoted by bradycardia often heralds the onset of malignant ventricular tachycardias such as of torsades de pointes.[78]

QT INTERVAL

The QT interval represents the duration of the depolarization phase (QRS complex) and repolarization phases (ST segment and T wave) and is measured from the beginning of the QRS complex to the end of the T wave. If a U wave is present, it should not be included in the calculation of the duration of the QT interval.[79] In normal conditions, the QT interval lasts 150–240 ms in dogs and 160—220 ms in cats (see Table 4.1). The duration of the QT interval varies depending on the heart rate: if the animal is not tachycardic, the QT interval should not be longer than 50% of the duration of the previous RR interval. In general, an increase in heart rate is associated with a reduction in the QT interval duration, while a decrease in heart rate is associated with an increase in the QT interval duration. In human medicine, different formulas have been validated to calculate the correct QT interval based on the previous RR interval or on the average heart rate, but extensive research in recent years has highlighted the inaccuracy of these formulas.[79] In fact, although the QT interval is known to depend on the preceding RR interval, this interval does not vary during respiratory sinus arrhythmia in dogs, despite a wide variation in heart rate. The QT interval response therefore depends on the number of heart beats following a sudden change in heart rate (QT memory).[80]

A more accurate mean for assessing the risk of a prolonged repolarization phase, in particular in dogs presenting with respiratory sinus arrhythmia with a variable RR interval duration, is the QT/TQ restitution curve. This parameter provides insight into the ability of the heart to recover from one beat to the next by giving information on the relationship between a QT interval and the next. The number of beats presenting a QT/TQ interval ratio below 1 is calculated from a 24-hour Holter recording to give an appreciation of the increased risk of arrhythmias.[81]

ELECTROCARDIOGRAPHIC CLUES TO THE ELECTROPHYSIOLOGICAL MECHANISM OF ARRHYTHMIAS

Although histological characterization of tissue is often difficult or impossible, electrocardiographic findings may allow the identification of the underlying electrophysiological mechanism of an arrhythmia with some degree of reliability. The presence of enhanced abnormal automaticity explaining a tachycardia is suggested by gradual acceleration and deceleration of the arrhythmia (Fig. 4.8), long coupling intervals, variable coupling of monomorphic complexes, and gradual emergence of the arrhythmia. Some examples of rhythm disturbances include some forms of focal atrial tachycardia, nonparoxysmal junctional tachycardia, accelerated idioventricular rhythm, and some forms of ventricular tachycardia. The electrocardiographic findings that suggest the presence of a reentrant mechanism include a fixed and relatively short coupling interval of the ectopic beats, paroxysmal behavior of the arrhythmia characterized by sudden initiation and termination of the arrhythmia, onset of the arrhythmia accompanied by prolongation of atrioventricular conduction, and evidence of dual atrioventricular nodal conduction (Fig. 4.9). Some examples of reentrant arrhythmias include: isolated atrial, junctional, or ventricular ectopic premature beats; orthodromic atrioventricular reciprocating tachycardia; atrial flutter; some forms focal atrial tachycardia; and some forms of ventricular tachycardia.

Triggered activities can be evoked in different cardiac areas and lack specific electrocardiographic criteria. Many electrocardiographic findings of reentry and triggered activities are common to both mechanisms, making the differential diagnosis difficult. However, some criteria may be helpful in differentiating triggered activities from enhanced abnormal automaticity or reentrant mechanisms:

- Induction of the arrhythmia favored by a slow sinus rate (early afterdepolarization; Fig. 4.10) or by a rapid sinus rate (delayed afterdepolarization).
- Decrease in the cycle length of the arrhythmia parallel to the decrease in the cycle length of the dominant rhythm.



FIGURE 4.8. Crystal automatic focal atrial tachycardia in an 8-year-old female Rottweiler. Notice, after the first sinus beat, the progressive decrease in RR interval duration (warm-up phenomenon) and the progressive increase in RR interval duration after the 10th QRS complex (cool-down phenomenon) until the tachycardia terminates and sinus rhythm is restored (last beat). Six limb leads (I, II, III, aVR, aVL, aVF); speed, 50 mm/s; calibration, 5 mm/1 mV.



FIGURE 4.9. Repetitive runs of orthodromic atrioventricular reciprocating tachycardia in a 1-year-old female Labrador. The first sinus beat is followed by paroxysmal supraventricular tachycardia with a sudden onset, narrow QRS complexes, regular RR intervals, and a negative atrial deflection in

the inferior leads (arrow) with a short RP' interval. After the 6th QRS complex, the tachycardia suddenly stops and is followed by a sinus beat with ventriculo-atrial conduction along the accessory pathway (negative atrial deflection embedded in the ST segment). After the 2nd sinus beat, orthodromic atrioventricular reciprocating tachycardia occurs with a paroxysmal behavior. Six limb leads (I, II, III, aVR, aVL, aVF); speed, 50 mm/s; calibration, 10 mm/1 mV.

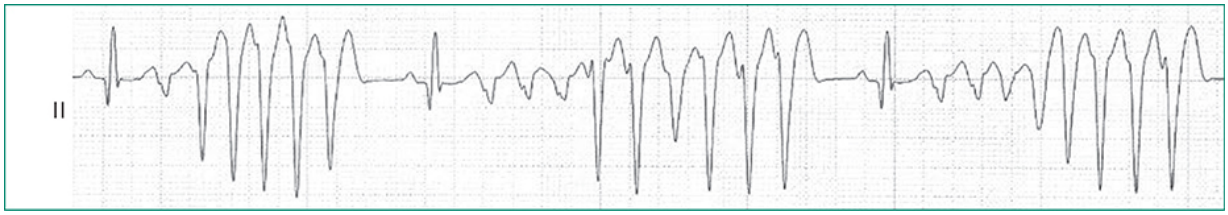


FIGURE 4.10. Polymorphic ventricular tachycardia in a 4-month-old female German Shepherd. Note, after the first sinus beat, the repetitive nonsustained runs of wide QRS complex tachycardia characterized by a change in the QRS complex morphology on a beat-to-beat basis. Lead II; speed, 50 mm/s; calibration, 5 mm/1 mV.

ELECTROCARDIOGRAPHIC FEATURES OF NARROW QRS COMPLEX TACHYCARDIAS

Narrow QRS complex tachycardia (QRS duration ≤70 ms in dogs and ≤40 ms in cats) is almost always supraventricular in origin. Narrow QRS complex ventricular tachycardia is uncommon, and it is usually diagnosed based on the same criteria used to diagnose ventricular tachycardias (see section on wide QRS complex tachycardias). The differential diagnosis of narrow QRS complex tachycardia includes sinus tachycardia, focal atrial tachycardia, orthodromic atrioventricular reciprocating tachycardia, permanent junctional reciprocating tachycardia, focal junctional tachycardia, nonparoxysmal junctional tachycardia, atrial flutter, and atrial fibrillation. Data regarding the electrocardiographic diagnosis of these types of tachycardia are summarized in Table 4.3.

The differential diagnosis of supraventricular tachycardias is based on the analysis of atrial deflections and the relationship between atrial deflections and QRS complexes and on initiation and termination of the tachycardia.[3]

Usually, the rate of supraventricular tachycardia provides little help in establishing the mechanism underlying the condition because there is much overlap between the heart rate in different types of supraventricular tachycardias.

The presence of atrial depolarizations and their morphology and timing in relation to ventricular activity are the cornerstones of electrocardiographic evaluation in supraventricular tachycardia (Fig. 4.11).[3]

Determining the presence or absence of atrial depolarization is the first step in establishing the underlying mechanism of a supraventricular tachycardia. However, atrial depolarization can be difficult to distinguish if a limited number of electrocardiographic leads are available. A 12-lead electrocardiogram should be obtained whenever possible. After careful evaluation of all electrocardiographic leads, the absence of obvious atrial depolarization in a supraventricular tachycardia with regular RR intervals suggests focal junctional tachycardia with P waves embedded in the QRS complex. In focal junctional tachycardia, it is sometimes possible to observe a negative atrial deflection that occurs shortly after the QRS complex and alters the very end of the QRS complex as a pseudo-S wave in the inferior leads (II, III, aVF) and a pseudo r' wave in the left precordial leads (V2–V6).[82] Often, these subtle alterations in the QRS complex can only be appreciated after comparison with an electrocardiographic trace obtained during normal sinus rhythm. Atrial depolarization may also be apparently absent during focal atrial tachycardia as a result of being embedded in the T wave. This is often due to a prolonged atrial depolarization (AD)-R interval caused by a slower atrioventricular conduction velocity. This situation can be clarified by comparing the electrocardiographic traces during tachycardia and during sinus rhythm. However, rate-dependent changes in repolarization phases (variations in the duration of the QT interval or T wave morphology related to the previous RR intervals) may make this task challenging. Atrial activity may become obvious with a chest thump or vagal maneuvers that can alter the AD-AD interval or atrioventricular conduction.[3]

TABLE 4.3. Electrocardiographic and mechanistic characteristics of supraventricular tachycardias in the dog.

Rhythm	HR (bpm)	Anatomical substrate	AD axis and R-AD interval AD-R interval	QRS complex	Atrioventricular conduction ratio
ST	185–220	Enhanced automaticity Sinus node	AD axis: 52°/73° Long R-AD >200 ms (192–222 ms) (variable in 14%) AD-R interval: 81±16 ms (variable in 20%) R-AD/AD-R: 2.25–3.08	Duration: 48–60 ms	1:1 – 100%
OAVRT	190–300	Anatomical macroreentry along atrioventricular accessory pathways	AD axis: -90°/-78° Short R-AD interval <100 ms (65–80 ms) (variable in 20%) AD-R interval:140±32 ms (variable in 23%) R-AD/AD-R: 0.45–0.64	Duration: 50–63 ms QRS alternans in 46% of cases (V2–V6) First beat aberrancy or linking	1:1 – 100%
PJRT	230–250	Anatomical macroreentry along accessory pathways with decremental retrograde conduction	AD axis: –90°/–78° Long R-AD interval (>100 ms)	Duration: ≤70 ms	1:1 – 100%
FAT	210–330	Enhanced automaticity, triggered activity, or microreentry of ectopic foci of atrial myocardium and tributary veins	AD axis: -72°/76° Long R-AD interval >100 ms (124±29 ms) (variable in 50%) AD-R interval:120–200 ms (variable in 24%) R-AD/AD-R: 0.92–1.67	Duration: 50–63 ms QRS alternans in 12% of cases	1:1 – 97% 2:1 – 3%
AFL	Dependent on atrioventricular conduction ratio	Anatomical reentry within the atrial myocardium	Right-sided: AD axis, 72°/81°; left-sided: AD axis, –150° R-AD interval: 72–144 ms (variable in 60%) AD-R interval: 126±43 ms (variable in 34%) R-AD/AD-R: 0.63–1.13	Duration: 50–60 ms Different QRS complex amplitude due to AD embedded in the QRS complex	1:1 – 41% 2:1 – 41% Variable – 18%
AF	130–260	Functional reentry within atrial myocardium		Normal unless rate dependent aberrancy (Ashman's phenomenon)	Variable
FJT	100–160	Enhanced automaticity junctional focus	AD axis: 52°/73° during IAVD AD axis: –80°/-100° during retrograde conduction with 1:1 ventriculo-atrial conduction ratio	Duration: ≤70 ms	IAVD
NPJT	100–160	Enhanced automaticity junctional focus	AD axis: –80°/–100°	Duration: ≤70 ms	PQ ≤60 ms

HR, heart rate; AD, atrial depolarization; ST, sinus tachycardia; OAVRT, orthodromic atrioventricular reciprocating tachycardia; PJRT, permanent junctional reciprocating tachycardia; FAT, focal atrial tachycardia; AFL, atrial flutter; AF, atrial fibrillation; FJT, focal junctional tachycardia; NPJT, nonparoxysmal junctional tachycardia; IAVD, isorhythmic atrioventricular dissociation.

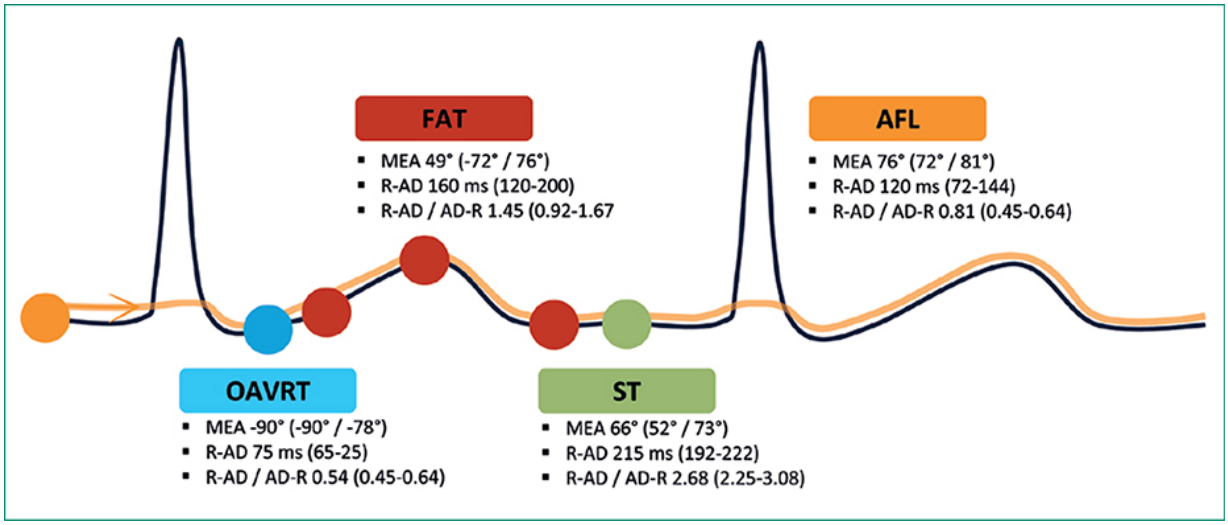


FIGURE 4.11. Schematic depiction of the position and features of atrial deflections in orthodromic atrioventricular reciprocating tachycardia (OAVRT), focal atrial tachycardia (FAT), atrial flutter (AFL), and sinus tachycardia (ST). Given that the position of the atrial deflection is variable in most cases of AFL, it is represented as a continuous line throughout the electrocardiographic tracing. MEA, mean electrical axis; AD, atrial depolarization. Source: Battaia S. et al.[3]

The absence of atrial depolarizations associated with irregular RR intervals is indicative of a diagnosis of atrial fibrillation.

When atrial depolarizations are visible, these have positive polarity in the inferior leads (II, III, and VF) with a superior-to-inferior axis in sinus tachycardia, variable polarity in focal atrial tachycardia that depends on the site of the ectopic focus, negative polarity in the inferior leads with an inferior-to-superior axis in orthodromic atrioventricular reciprocating tachycardia, positive polarity in the inferior leads in reverse typical or atypical atrial flutter, negative polarity with a saw-tooth morphology in the inferior leads in typical atrial flutter, and negative polarity in left septal atrial flutter. Atrial fibrillation is typically characterized by fine oscillations of the isoelectric line with a different duration, polarity, morphology, and atrial cycle length (ranging from 85–190 ms).

The values for the mean electrical axis of atrial depolarization in the frontal plane have been reported: 66° (52°/73°) in sinus tachycardia, 49° (–72°/76°) in focal atrial tachycardia, –90° (–90°/–78°) in orthodromic atrioventricular reciprocating tachycardia, and 76° (72°/81°) in atrial flutter.[3] Nonparoxysmal junctional tachycardia has a concentric retroactivation with an atrioventricular depolarization axis between –80° and -100°.

The mean electrical axis of atrial depolarization in focal atrial tachycardia is characterized by a wide range of values (from –72° to 76°) because of the different localization of the ectopic foci. The reported mean electrical axis in left septal atrial flutter was –150°.

The median duration of atrial depolarization in different supraventricular tachycardias has been reported as 41 ms (35–45 ms) in sinus tachycardia, 50 ms (40–52 ms) in focal atrial tachycardia, 46 ms (40–54 ms) in orthodromic atrioventricular reciprocating tachycardia, and 50 ms (40–60 ms) in atrial flutter. Atrial depolarization in atrial flutter has a significantly longer duration in comparison with atrial depolarization in other supraventricular tachycardias.[3]

The mean atrial cycle length during supraventricular tachycardias (AD-AD interval) has been reported as 292 ± 31 ms in sinus tachycardia, 270 ± 38 ms in focal atrial tachycardia, 213 ± 30 ms in orthodromic atrioventricular reciprocating tachycardia, and 199 ± 57 ms in atrial flutter. The AD-AD interval is the shortest in atrial flutter, followed by orthodromic atrioventricular reciprocating tachycardia, focal atrial tachycardia, and sinus tachycardia. These data could be useful to differentiate between cases of atrial fibrillation with prominent fibrillatory waves ("coarse fibrillatory waves") and cases of atrial flutter with a different atrioventricular conduction ratio. Most dogs with atrial flutter present with an atrial rate below 500 bpm (120 ms). In atrial flutter, the AD-AD interval is regular in 100% of cases, while in orthodromic atrioventricular reciprocating tachycardia, the AD-AD interval is regular in 96% of cases and alternating in 4% of cases. Cycle length alternans (AD-AD and RR intervals) is defined as interval variations on a beat-to-beat basis (two alternating cycle length durations). The atrial cycle length is longer in focal atrial tachycardia than in orthodromic atrioventricular reciprocating tachycardia and atrial flutter, and it is regular in 55% of cases and regular with cycle length irregularity in 45% of cases. The atrial cycle length in sinus tachycardia is also significantly longer than in focal atrial tachycardia, orthodromic atrioventricular reciprocating tachycardia, and atrial flutter.[3] Cycle length irregularity is defined as variations in the AD-AD and RR intervals of at least 20 ms and is particularly present in cases of atrioventricular blocks or at the beginning and termination of the supraventricular tachycardia (warm-up and cold-down phenomena).

The second step in the differential diagnosis of narrow QRS complex tachycardias is to analyze the relationship between atrial depolarizations and QRS complexes. The atrioventricular conduction ratio is 1:1 in all dogs with sinus tachycardia and orthodromic atrioventricular reciprocating tachycardia. Dogs with atrial flutter have a 1:1 conduction ratio in 41% of cases, a 2:1 ratio in another 41% of cases, and a variable ratio in 18% of cases.[3] In focal atrial tachycardia, 97% of dogs have a 1:1 conduction ratio, and only 3% of dogs have a 2:1 conduction ratio.[37] The presence of atrioventricular blocks during supraventricular tachycardia effectively excludes any macroreentrant rhythm requiring the ventricular myocardium as a part of the circuit, such as orthodromic atrioventricular reciprocating tachycardia. A 2:1 atrioventricular block often results in an electrocardiographic pattern in which an atrial depolarization is present halfway between two consecutive QRS complexes, and the second atrial depolarization is buried within the QRS complex. The most common cause of a 2:1 atrioventricular conduction ratio is atrial flutter. Atrioventricular dissociation can be observed in focal junctional tachycardia. In such a case, the accelerated atrioventricular junctional automaticity has a junctional rate similar to the sinus rate, thus allowing the presence of isorhythmic atrioventricular dissociation.[82]

The R-AD interval values are 215 ms (192–222 ms) in sinus tachycardia, 160 ms (120–200 ms) in focal atrial tachycardia, 75 ms (65–80 ms) in orthodromic atrioventricular reciprocating tachycardia, 120 ms (72–144 ms) in atrial flutter, with a significant statistical difference between the four types of supraventricular tachycardias. The relative variability of the R-AD interval is lower in sinus tachycardia (14%), followed by orthodromic atrioventricular reciprocating tachycardia (20%), focal atrial tachycardia (50%), and atrial flutter (60%) (Fig. 4.11).[3]

The AD-R interval is 81 ± 16 ms in sinus tachycardia, 124 ± 29 ms in focal atrial tachycardia, 140 ± 32 ms in orthodromic atrioventricular reciprocating tachycardia, and 126 ± 43 ms in atrial flutter, with a significant statistical difference between sinus tachycardia, focal atrial tachycardia, and orthodromic atrioventricular reciprocating tachycardia. The relative variability is lower in sinus tachycardia (20%), followed by orthodromic atrioventricular reciprocating tachycardia (23%), focal atrial tachycardia (24%), and atrial flutter (34%). In case of nonparoxysmal

junctional tachycardia, the AD-R interval is short (usually ≤60 ms) and 1:1 atrial retroactivation is present.

The R-AD/AD-R ratio is 2.68 (2.25–3.08) in sinus tachycardia, 1.45 (0.92–1.67) in focal atrial tachycardia, 0.54 (0.45–0.64) in orthodromic atrioventricular reciprocating tachycardia, 0.81 (0.63–1.13) in atrial flutter, with a significant statistical difference between the different types of supraventricular tachycardias (Fig. 4.11).[3]

An R-AD interval greater than 100 ms differentiates focal atrial tachycardia from orthodromic atrioventricular reciprocating tachycardia with a sensitivity of 89%, a specificity of 95%, an area under the curve (AUC) of 0.93, a positive predictive value of 85%, and a negative predictive value of 96%. An R-AD/AD-R ratio greater than 0.85 differentiates focal atrial tachycardia from orthodromic atrioventricular reciprocating tachycardia with a sensitivity of 95%, a specificity of 79%, an AUC of 0.89, a positive predictive value of 93%, and negative predictive value of 84%. It should be noted that, in the study in which these data were obtained, to differentiate between sinus tachycardia and focal atrial tachycardia, the R-AD interval had to be greater than 201 ms (sensitivity, 70%; specificity, 90%; AUC, 0.85) and the R-AD/AD-R ratio greater than 2.01 (sensitivity, 86%; specificity, 96%; AUC, 0.96) (Fig. 4.11).[3]

All cases of orthodromic atrioventricular reciprocating tachycardia are characterized by a short R-AD interval because of the fast nondecremental retroconduction along the accessory pathway. The position of atrial depolarizations is variable in most cases of atrial flutter because of different atrioventricular conduction ratios. A long R-AD interval is present in most cases of focal atrial tachycardia, but a short R-AD interval is seen in 12% of cases, mainly those originating from the pulmonary veins.[3]

The third step to differentiate between the different types of narrow QRS complex supraventricular tachycardia is to analyze the QRS complex. The median QRS duration during an episode of narrow QRS complex tachycardia is 52 ms (48–60 ms) for sinus tachycardia, 60 ms (52–60 ms) for focal atrial tachycardia, 60 ms (50–63) for orthodromic atrioventricular reciprocating tachycardia, 56 ms (50–60 ms) for atrial flutter, with no statistical difference between the types of supraventricular tachycardia. QRS alternans is mainly present in dogs with orthodromic atrioventricular reciprocating tachycardia (46% of cases) and is mainly visible in the left precordial leads (V2-V6). Twelve percent of dogs with focal atrial

tachycardia also show QRS alternans, which is mainly visible in the inferior leads (II, III, and aVF) and V3. QRS alternans is defined as variations in the QRS amplitude of more than 0.1 mV on a beat-to-beat basis, which may be originated by subtle beat-to-beat variations in the His–Purkinje system refractoriness.[3]

The median QT interval was 167 ms (159–178 ms) in sinus tachycardia, 198 ms (180–200 ms) in focal atrial tachycardia, 180 ms (160–194 ms) in orthodromic atrioventricular reciprocating tachycardia, and 200 ms (170–220 ms) in atrial flutter.[3] To differentiate atrial depolarizations from T waves during supraventricular tachycardia, the author and colleagues have proposed using the "QT rule". In case of supraventricular tachycardia, the QT interval duration should range between 160 and 220 ms; if this interval is longer or shorter, then it is likely that an atrial depolarization has erroneously been identified as a T wave.

Functional or rate-related bundle branch block can be observed for several beats at the beginning of a supraventricular tachycardia if the refractory period of one of the intraventricular bundles fails to adapt to the abrupt increase in rate, resulting in a conduction delay or block within the bundle. This aberration may resolve after the accommodation of the rate-related shortening of the refractory period of the His–Purkinje system. This phenomenon occurs more frequently in orthodromic atrioventricular reciprocating tachycardia than in the other types of supraventricular tachycardia because of its paroxysmal behavior.

One type of supraventricular tachycardia can be related with a wide QRS complex. In preexcited supraventricular tachycardia, the atrial depolarization is conducted to the ventricle through both the accessory pathway and the atrioventricular node, producing a preexcited QRS complex characterized by a prolonged duration.

Finally, the recording of an electrocardiogram or Holter monitoring during initiation and termination of a supraventricular tachycardia can provide critical information about the mechanism of the tachycardia. Supraventricular tachycardia due to a macroreentrant circuit usually starts and ends abruptly, presenting a paroxysmal behavior. Abrupt initiation of supraventricular tachycardia with a prolonged AD-R interval suggests the presence of a dual atrioventricular physiology, and the arrhythmia is most likely an orthodromic atrioventricular reciprocating tachycardia using a slow atrioventricular nodal pathway as an antegrade limb. The gradual

initiation and termination of a supraventricular tachycardia is termed warm-up and cool-down and is typical of an enhanced abnormal automaticity of focal atrial tachycardia. Usually, the termination of a supraventricular tachycardia with an atrioventricular block (atrial depolarization not followed by a QRS complex) suggests, but does not prove, that the underlying mechanism of the supraventricular tachycardia is not focal atrial tachycardia and that the atrioventricular node is a part of the reentrant circuit, with the block occurring in the antegrade limb of the atrioventricular node.

DIAGNOSIS AND EVALUATION OF WIDE QRS COMPLEX TACHYCARDIAS

The differential diagnosis of wide QRS complex tachycardia is clinically relevant for different reasons.[83] In the presence of an underlying myocardial disease, the prognosis of a patient with ventricular tachycardia is worse than the prognosis of a patient with supraventricular tachycardia. Furthermore, the drugs usually used for the treatment of supraventricular tachycardia can cause severe hemodynamic deterioration in patients with ventricular tachycardia, resulting in hypotension and ischemia, which will consequently render the arrhythmia impossible to treat with electrical cardioversion and may degenerate into ventricular fibrillation.[83] The differential diagnosis of a wide QRS complex tachycardia (QRS complex duration >80 ms in dogs and >50 ms in cats) includes ventricular tachycardia, supraventricular tachycardia with intraventricular conduction disturbances (anatomical or functional), and preexcited tachycardia. The cause of a wide QRS complex tachycardia can be determined based on the information obtained from the history, the physical examination findings, and the 12-lead electrocardiogram. Perhaps the most important medical history finding suggesting ventricular tachycardia is the presence of an underlying myocardial disease, such as dilated cardiomyopathy, arrhythmogenic cardiomyopathy, hypertrophic cardiomyopathy, or chronic myocarditis. The signalment is also an important consideration, since familiar ventricular arrhythmias are described in different breeds such as the

German Shepherd, the Springer Spaniel, the Rhodesian Ridgeback, and the Belgian Shepherd (see pp. 341–343).

Usually, the clinical signs associated with ventricular tachycardia are not related to the underlying mechanism but are caused by a rapid heart rate, which commonly results from the heart disease and decreased right and/or left ventricular systolic function. The severity of the clinical signs is also related to the site of origin of the ventricular tachycardia, which affects the right and left ventricular activation sequence and intraventricular and interventricular synchrony.

The first step in the analysis of an electrocardiogram showing a wide QRS complex tachycardia is the comparison, when possible, with an electrocardiogram during sinus rhythm. A significant shift of the QRS axis and a marked change in morphology, when compared with the sinus rhythm, suggests a diagnosis of ventricular tachycardia,[83] while the presence of QRS complexes during tachycardia similar to those during sinus rhythm is suggestive of supraventricular tachycardia.

Furthermore, ventricular tachycardia is often associated with slightly irregular RR intervals, a subtle or marked variation in the morphology of the QRS complexes, and changes in the ST segment and T wave. These abnormalities can be associated with changes in the direction of the ventricular activation wavefront as it exits from the reentrant circuit or with variability in the depolarization and repolarization patterns of the ventricular myocardium.

Conversely, uniform RR intervals, QRS morphology, ST segment, and T wave suggest the presence of a supraventricular tachycardia, because ventricular myocardial activation always follows the same pathway (e.g., the atrioventricular node, the His–Purkinje system, and eventually the accessory pathway).

The second step in the analysis of a wide QRS complex tachycardia is the evaluation of the atrioventricular relationship. In human medicine, atrioventricular dissociation is present in 60–75% of cases of ventricular tachycardia.[83] Evidence of atrioventricular dissociation usually establishes ventricular tachycardia as the underlying mechanism, but the absence of atrioventricular dissociation is less helpful. The presence of atrioventricular dissociation can be identified by a close analysis of the electrocardiogram in each of the 12 leads. Atrioventricular dissociation can manifest as obvious P waves dissociated from the QRS complex, fusion beats, and intermittent

capture beats. Fusion beats have an intermediate morphology between a normal conducted beat and a wide QRS complex and result from simultaneous activation of the ventricular myocardium from the normal conduction system and from the abnormal ventricular focus. Intermittent capture beats are intermittent sinus beats during ventricular tachycardia caused by impulse conduction along the normal conduction system. These beats have a similar morphology to sinus, normally conducted, beats. Both fusion and intermittent capture beats are more evident during slower ventricular tachycardia and usually do not alter the ventricular tachycardia rate and RR interval duration.

If signs of atrioventricular dissociation are not obvious, other electrocardiographic features should be considered: the morphological characteristics of the QRS complex on the 12 leads, and the mean electrical axis of the QRS complex in the frontal plane.[83]

Based on the morphology of the QRS complex in the standard limb and precordial leads, it can be determined that a patient is suffering from:

- Supraventricular tachycardia associated with a complete left bundle branch block if QRS complexes are positive in leads I, II, III, and aVF; have a normal mean electrical axis in the frontal plane; and are negative in V1 and positive in V2 to V6.
- Supraventricular tachycardia associated with a complete right bundle branch block if QRS complexes are negative in leads I, II, III, and aVF with a right axis shift in the frontal plane, positive in V1 and negative in V2 to V6. Usually, the morphology of the QRS complex in case of complete right bundle branch block presents an Rr', rr', or rR' pattern in leads V1 (Fig. 4.12).

In ventricular tachycardia, intraventricular conduction does not follow the rules that apply to anatomical or functional block of the normal intraventricular conduction system. Ventricular tachycardia is therefore diagnosed in the presence of QRS complexes with different morphologies to those described for complete left or complete right bundle branch block. The only exception is ventricular tachycardia arising from the inferior part of the right ventricular outflow tract, which has a positive QRS polarity in leads I, II, III, and aVF with a normal mean electrical axis in the frontal plane, negative in V1 and positive from V2 to V6.

Another diagnostic parameter to be considered is the mean electrical axis of the QRS complexes in the frontal plane. A superior or leftward shift in the mean electrical axis, especially in the first portion of the QRS complex when compared with sinus rhythm, is suggestive of ventricular tachycardia.

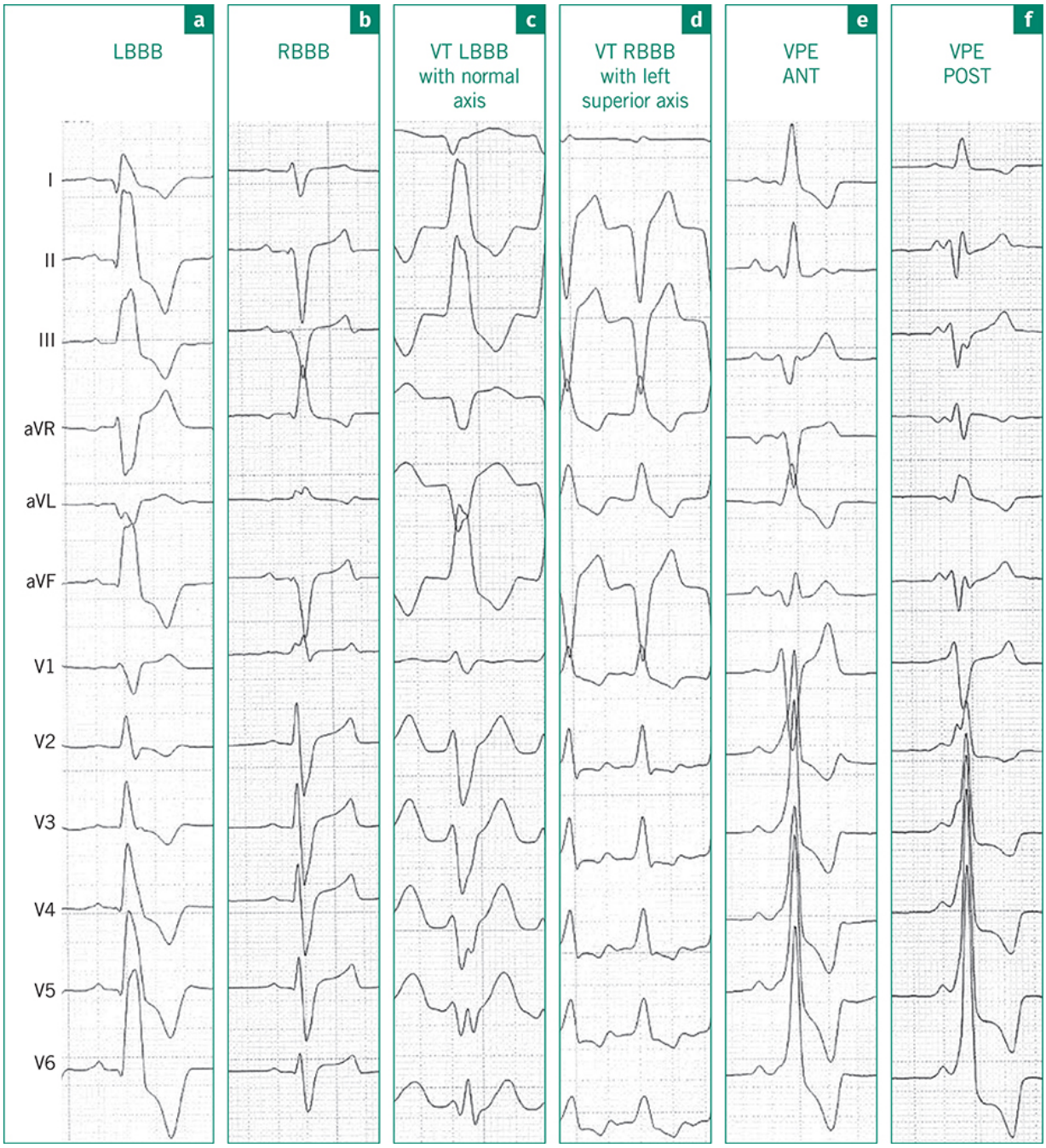


FIGURE 4.12. Different wide QRS complex appearances in 12-lead electrocardiograms (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6). Speed, 50 mm/s; calibration, 10 mm/1 mV. a) Sinus beat conducted with a complete left bundle branch block (LBBB). b) Sinus beat conducted with a

complete right bundle branch block (RBBB). c) Ventricular ectopic beat conducted with a left bundle branch block morphology and a normal axis in the frontal plane. d) Ventricular ectopic beat conducted with a right bundle branch block morphology and left superior (bifascicular) axis in the frontal plane. e) Sinus beat conducted with ventricular preexcitation along an anterior accessory pathway (VPE ANT). f) Sinus beat conducted with ventricular preexcitation along a posterior accessory pathway (VPE POST). VT, ventricular tachycardia.

APPROACH TO BRADYARRHYTHMIAS

Bradyarrhythmias are commonly encountered in clinical practice and are defined as a heart rate <60 bpm in dogs and <140 bpm in cats. While several electrocardiographic criteria can be used to diagnose supraventricular tachycardias and ventricular tachycardias, data about bradycardias are lacking. The proposed algorithm to approach bradyarrhytmias is based on the following steps: evaluation of the presence of P waves and, if present, of their relationship with QRS complexes; evaluation of the QRS complex duration (narrow or wide QRS complex); and evaluation of the regularity of the time intervals (PP, PQ, and RR intervals).

The first step requires the identification of signs of atrial depolarization compatible with P waves.[84] If there are no P waves and QRS complexes are narrow, the differential diagnosis includes sinus standstill associated with a junctional escape rhythm (Fig. 4.13), temporary atrial standstill or sinoventricular conduction, persistent atrial standstill, and slow ventricular response atrial fibrillation characterized by very fine atrial fibrillation waves. If RR intervals are regular, the last option can be ruled out. If there are no P waves and QRS complexes are wide, the differential diagnosis includes sinus standstill with a ventricular escape rhythm, permanent atrial standstill (Fig. 4.14), and third-degree atrioventricular block associated with atrial fibrillation.[84] In the latter case, fine oscillations of the isoelectric line compatible with f waves can be visualized. Endocardial mapping is needed to definitively differentiate between permanent atrial standstill and third-degree atrioventricular block associated with atrial fibrillation (see p. 294).

If P waves are present, the next step is to determine the relationship between P waves and QRS complexes. If P waves are always associated with a narrow QRS complex and no blocked P waves are visible, the diagnosis is sinus bradycardia. If atrial deflections are not compatible with

impulse initiation at the sinus node and are consistent with P' waves, an atrial escape rhythm should be suspected.[84]

If P waves are present, and more P waves are present than QRS complexes, the diagnosis is either second-degree atrioventricular block or third-degree atrioventricular block. If the nonconducted atrial deflection is a premature P' wave, the diagnosis is a nonconducted premature atrial ectopic beat. To differentiate between different atrioventricular conduction disturbances, the regularity of the PP, PQ, and RR intervals should be checked. If the PQ interval is regular and constant, a second-degree atrioventricular block should be considered: Wenckebach or Mobitz type 1, Mobitz type 2, 2:1, or advanced. Mobitz type 2 atrioventricular block is characterized by a nonconducted P wave flanked by at least two normally conducted P waves, while 2:1 atrioventricular block is characterized by alternately conducted P waves and advanced second-degree atrioventricular block is characterized by more than one nonconducted P wave with a more than 3:1 atrioventricular ratio. In second-degree atrioventricular block, the QRS complexes are narrow. If the PQ interval is variable, atrioventricular dissociation is present, and the diagnosis is third-degree or complete atrioventricular block (Fig. 4.15). In this case, the QRS complexes are usually wide.[84]

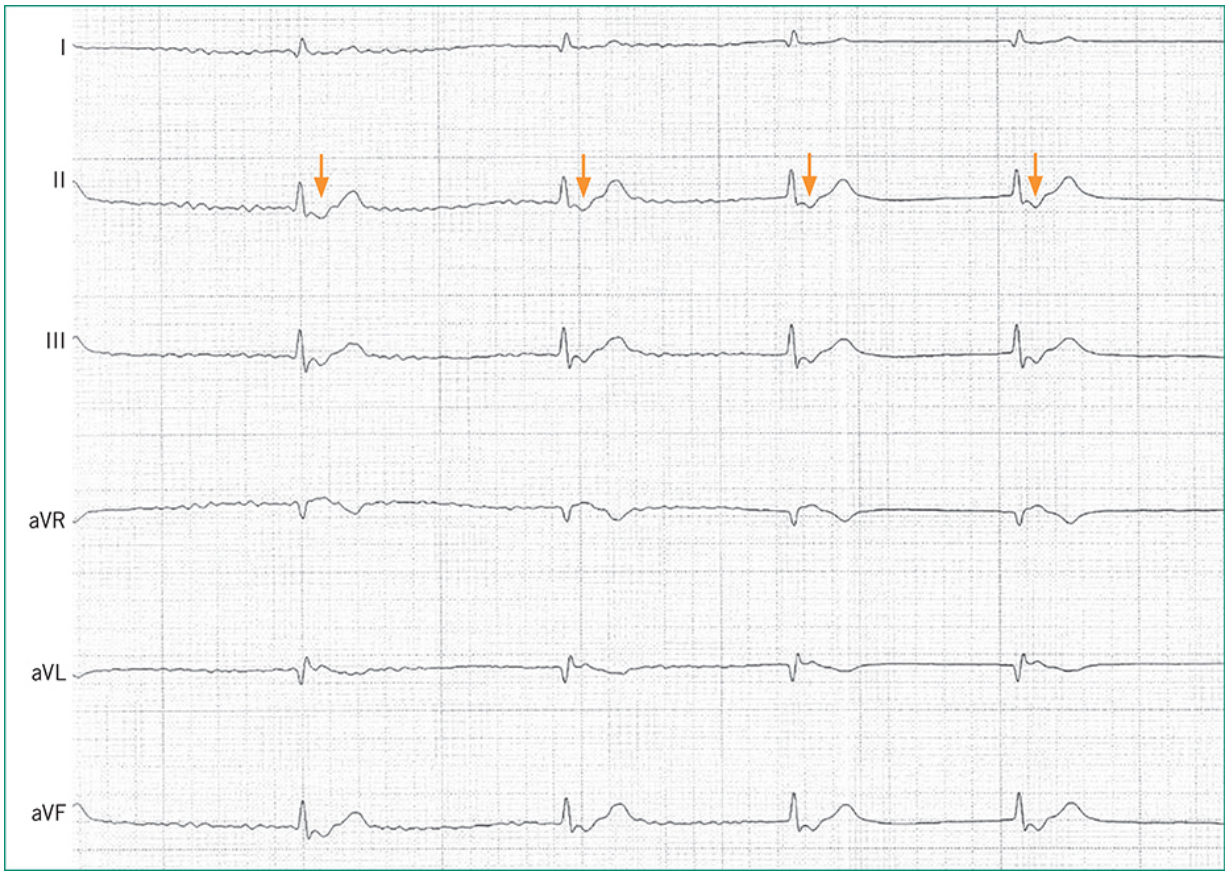


FIGURE 4.13. Sinus standstill with a junctional escape rhythm in a 13-year-old male West Highland White Terrier. Notice the presence of a narrow QRS complex (45 ms) bradycardia. No P waves are visible. After each narrow QRS complex, a negative atrial deflection is present in the ST segment (arrows). The atrial deflection shows a concentric inferior-to-superior axis and is compatible with an atrial retroconduction. Six limb leads (I, II, III, aVR, aVL, aVF); speed, 50 mm/s; calibration, 5 mm/1 mV.

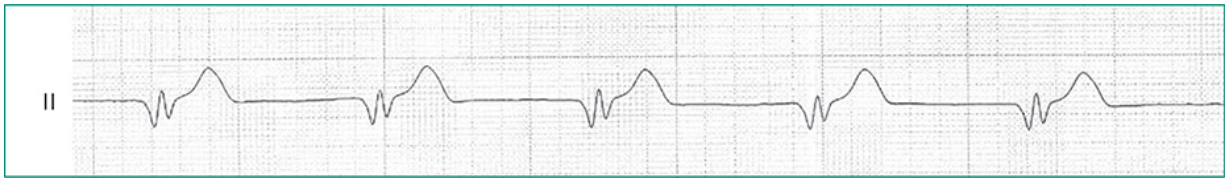


FIGURE 4.14. Permanent atrial standstill with monomorphic idioventricular rhythm in a 4-year-old male Labrador Retriever. Notice the presence of a wide QRS complex (95 ms) bradycardia. No P waves and no f waves are visible. Lead II; speed, 50 mm/s; calibration, 5 mm/1 mV.

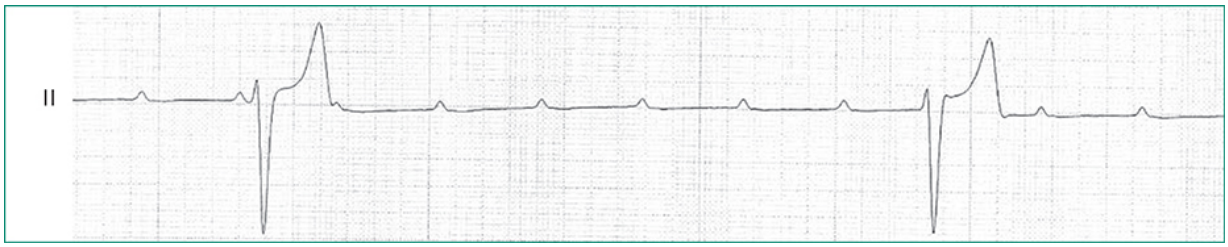


FIGURE 4.15. Complete or third-degree atrioventricular block with monomorphic idioventricular rhythm in a 14-year-old female mixed-breed dog. Notice the presence of a wide QRS complex (80 ms) bradycardia. P waves are visible with a variable PQ interval (atrioventricular dissociation). Lead II; speed, 50 mm/s; calibration, 10 mm/1 mV.

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CHAPTER 5

Holter monitoring for assessment and management of arrhythmias

Roberto Santilli, Stefano Battaia

DEFINITION

Holter monitoring provides a continuous recording of cardiac electrical activity during normal daily activities, exercise, and sleep. This diagnostic tool is extremely useful in veterinary cardiology as a patient's heart rate and rhythm recorded in the consulting room is not representative of their heart rate and rhythm at home. Holter monitoring can therefore provide useful information for the diagnosis and treatment of cardiac disease.

INDICATIONS FOR HOLTER MONITORING

Holter monitoring is indicated in the following situations:[1–7]

- In animals with episodes of transient loss of posture or consciousness with a history suggestive of a paroxysmal arrhythmia.
- In cases of exercise intolerance with a history suggestive of a paroxysmal arrhythmia.
- For the dynamic characterization of arrhythmias and heart rate variability, by determining the influence of and relationship with states of wakefulness and sleep. This is particularly useful both for supraventricular and ventricular arrhythmias.
- For the characterization and diagnosis of certain types of bradyarrhythmias.

- For screening for diseases in breeds at risk of arrhythmias, such as dilated cardiomyopathy in Doberman Pinschers, arrhythmogenic cardiomyopathy in Boxers and English Bulldogs, and familiar ventricular arrhythmias in German Shepherds, Rhodesian Ridgebacks and Leonbergers.
- To assess the efficacy of an antiarrhythmic treatment.
- To evaluate pacemaker function.

TECHNICAL ASPECTS

RECORDING

Optimal positioning of the electrodes is crucial to obtain a clean recording free of artifacts for the entire run, especially during periods of daily activity but also during sleep. The most commonly used lead system in veterinary medicine is the noncorrected orthogonal bipolar system, which is based on three channels called X, Y, and Z. These channels analyze the three vectors of cardiac activation in the frontal (channel X, similar to lead I), sagittal (channel Y, similar to lead aVF), and horizontal planes (channel Z, similar to lead V10) (Fig. 5.1).[8] The skin should be prepared methodically. The chest hair must be clipped, and the skin should be degreased (normal alcohol is an option, but specific commercial products are also available). Even though the electrodes are self-adhesive, additional fixation with hypoallergenic tape is suggested to fix the cables to the thorax. Placement of a cotton bandage and, subsequently, of a self-adhesive elastic band is a good option to fix the cables and the recorder; alternatively, specific Holter vests of different sizes are available on the market. After placing the electrodes on the skin, it is advisable to control the signal of each channel. Recording devices have undergone rapid evolution; digital recorders using memory chips have become increasingly smaller and can be easily carried by the patient during daily activities. It is important to choose a recorder with a minimum sampling capacity of 250 samples per second. In addition, in some cases (patients with sporadic episodes of transient loss of consciousness), the possibility of recording for long periods of time (48 hours and up to 7 days) can be of great help. The increasing availability of these recorders has supplanted the use of loop recorders, in which the storage of the areas of interest depended on manual activation by the owner

or automatic activation. With these devices, activation stores a short section of the trace around the time of the event, which may be detected automatically or predefined by the operator.[9] Implantable loop recorders allow a longer monitoring period of months to years, which may be useful in patients who have infrequent syncopal episodes.[10–13] With these devices, only short sections of the trace are stored in response to automatic or manual activation of the owners. When setting the criteria for automatically detected events, it is important to account for the marked sinus arrhythmia and sinus pauses often seen in resting dogs. Disadvantages of these devices are the need to anesthetize the animal for implantation; the risk of infection, seroma formation, skin erosion, and device migration; and costs.

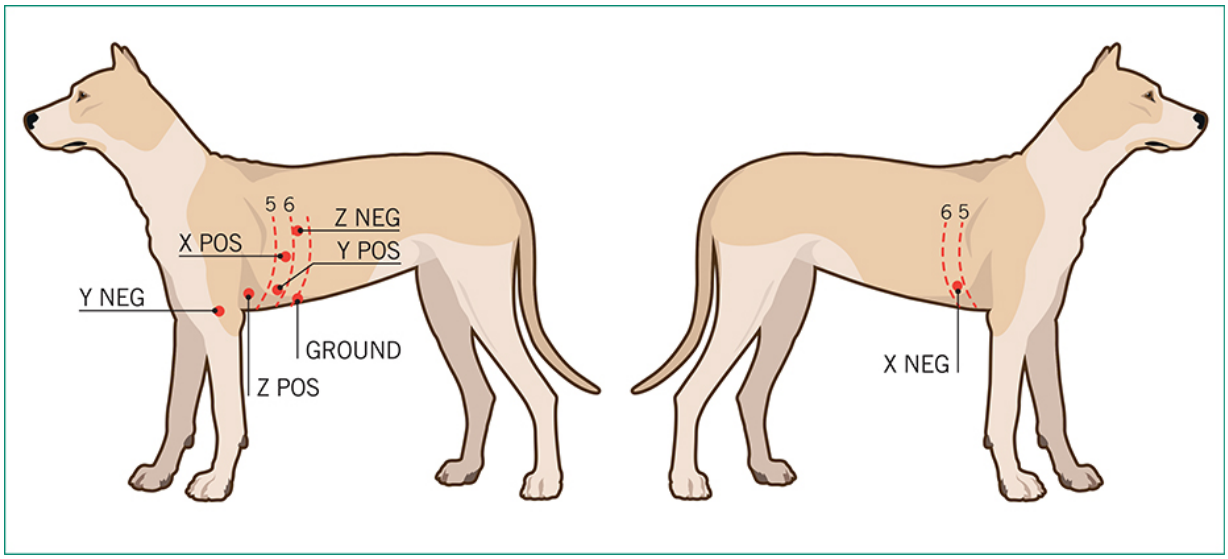


FIGURE 5.1. Recommended position of the seven electrodes for the noncorrected orthogonal bipolar system to record Holter tracings. 5, 6: Ribs.

ARTIFACTS

Artifacts complicate the reading of the recording, increase the duration of the reading and editing processes, and sometimes confound the correct diagnosis. Most artifacts are better recognized by an experienced eye than by the automatic analysis.

Recording artifacts

The most common artifacts are related to poor contact between the electrodes and the skin or to detachment of some of the electrodes.

Movement and intense exercise are another common cause of artifacts in veterinary patients; however, they are commonly requested during Holter monitoring in order to record the cardiac activity of normal daily life and exclude the presence of arrhythmias triggered by sympathetic activation or to evaluate the chronotropic competence in patients affected by bradycardia. Movement artifacts that make reading impossible are much less frequent today owing to the three leads, and rarely will an artifact affect all three leads at once or affect them with the same intensity. Usually, one of the leads can still provide sufficient information for a correct diagnosis.

Artifacts associated with interpretation

The main artifacts causing problems with automatic reading are described below.

Horizontal resolution artifacts are related to a failure to recognize beats due to a fast heart rate. This can happen with fast ventricular or supraventricular tachycardia, especially with older devices with a sampling rate <250 samples/second (Fig. 5.2). These artifacts are particularly important to identify in dogs with atrial fibrillation, because they can lead to an inadequate calculation of the average heart rate over 24 hours, resulting in incorrect treatment decisions.[14] Furthermore, such artifacts can in turn create artifactual tachograms that can erroneously lead to the suspicion of exit blocks, typical of sinus node dysfunction or atrioventricular blocks. Vertical resolution artifacts are related to the detected QRS amplitude and can be avoided by changing the reading settings of the software (noise level and minimum amplitude of the QRS, which should be set at a lower level). They occur more particularly in cats, in which the QRS amplitude is particularly low (Fig. 5.3).

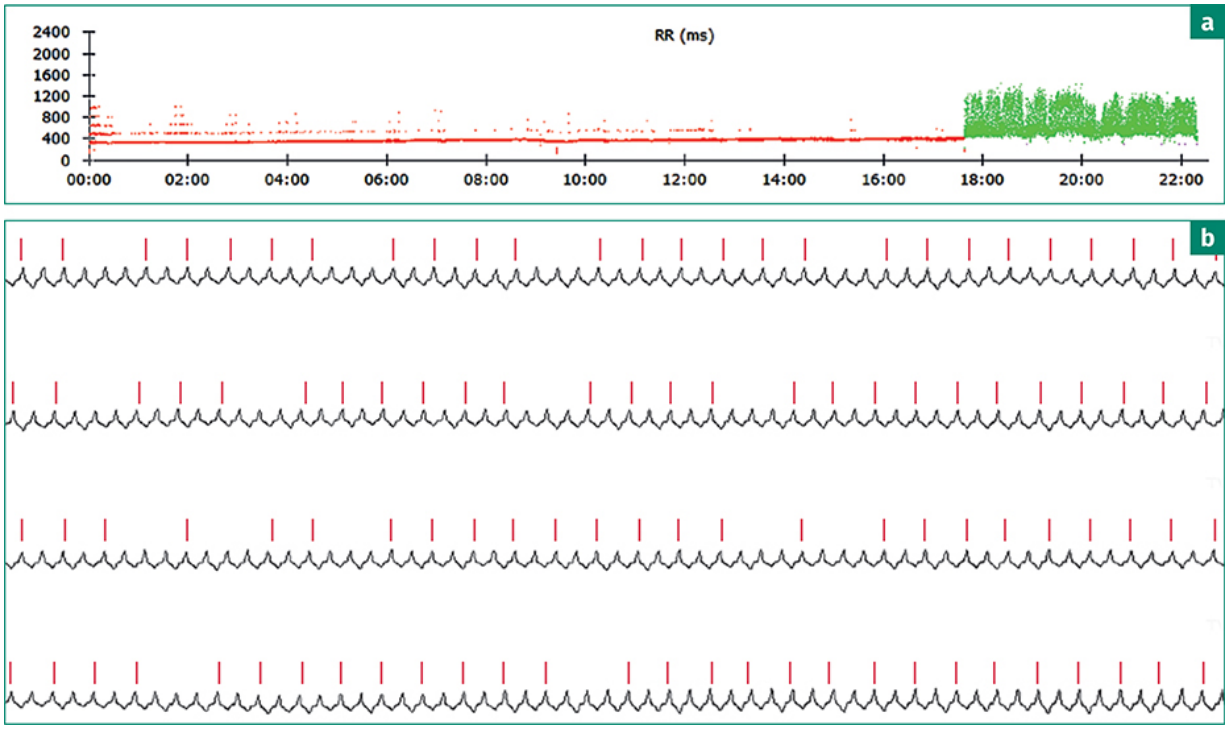


FIGURE 5.2. Holter recording of a 10-year-old male Boxer with arrhythmogenic cardiomyopathy, with a horizontal resolution artifact due to incessant monomorphic ventricular tachycardia. a) Twenty-four-hour tachogram showing the distribution of RR intervals during sinus rhythm (green) and ventricular tachycardia (red). The second part of the tracing shows a decrease in the ventricular tachycardia rate after continuous rate infusion of lidocaine; the horizontal lines progressively disappear, and sinus rhythm returns. Y-axis, RR interval duration; x-axis, hours of day and night. b) Electrocardiographic recording showing monomorphic ventricular tachycardia as the dominant rhythm. The horizontal resolution artifact occurred due to the fast heart rate during ventricular tachycardia. Mostly every other beat is recognized by the software (vertical red lines), forming multiple horizontal lines on the tachogram, particularly during the first part of the tracing, mimicking the presence of exit blocks from the sinus node or variations in the atrioventricular conduction ratio. Lead Y, each line corresponds to 10 seconds. Speed, 20.6 mm/s; calibration, 1 mm/mV.

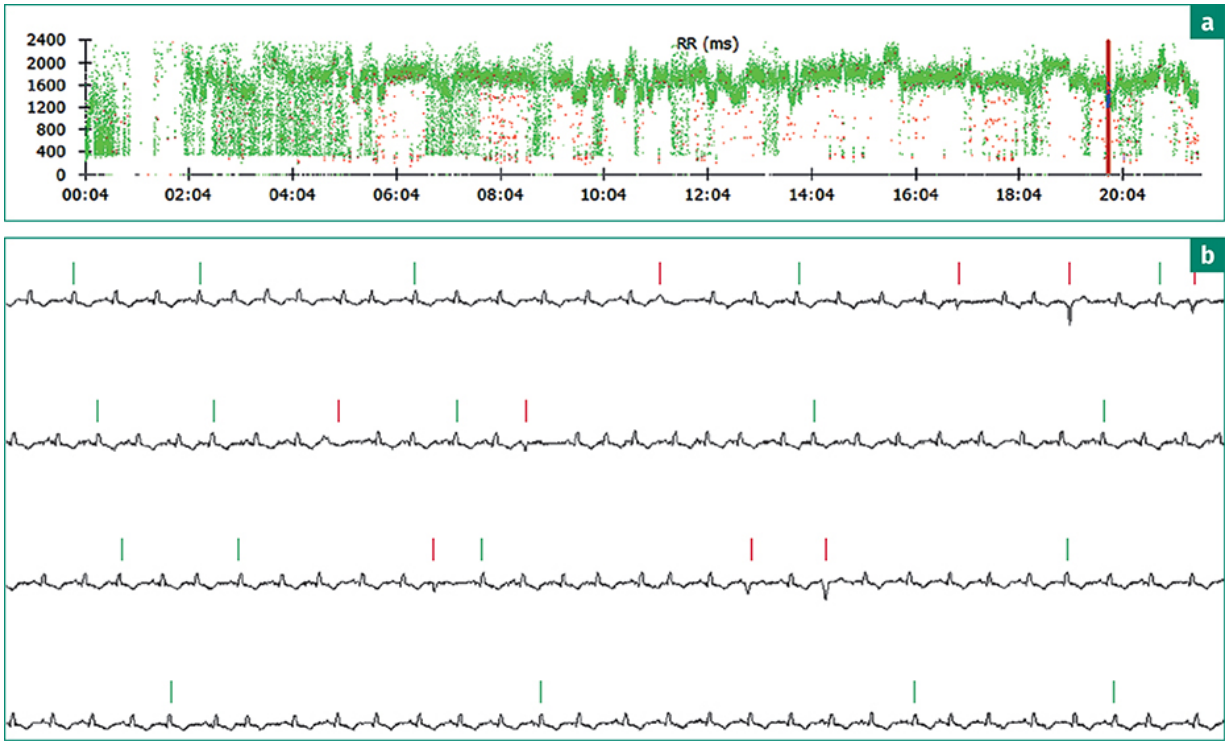


FIGURE 5.3. Holter recording of an 8-year-old female Main Coon with hypertrophic cardiomyopathy with ventricular ectopies and a vertical resolution artifact. a) Twenty-four-hour tachogram showing the distribution of RR intervals during sinus rhythm (green) and during ventricular ectopies (red). Y-axis, RR interval duration; x-axis, hours of day and night. b) Electrocardiographic recording showing sinus rhythm as the dominant rhythm, interrupted by multiform ventricular ectopies. The vertical resolution artifact occurred due to low amplitude QRS complexes. The software recognized few of the normal QRS complexes (vertical green lines) and all ventricular ectopies (vertical red lines), thus leading on the tachogram to an abnormal bradycardic RR distribution, which is frequently present in cases of sinus node dysfunction. This artifact can be avoided by changing the noise level and minimum amplitude of the QRS, which should be set at a lower level. Lead Y, each line corresponds to 10 seconds. Speed, 20.6 mm/s; calibration, 5 mm/mV.

READING PROCEDURE

All three channels are used by the software for automatic reading of the recordings, but it is often useful to identify two preferential channels, i.e., those that present fewer motion artifacts and the greatest amplitude of the QRS complexes and show a morphology of ventricular premature complexes as different as possible from normal beats.

Based on the criteria of normal morphology and duration of the QRS complexes, the software organizes similar beats into groups (families) of normal or atypical beats. Beat grouping into families saves the clinician from having to review every QRS complex, but a careful check of all these

families is fundamental, as normal beats may be classified by the software as atypical, and atypical beats may be classified as normal. This frequently occurs in dogs with intraventricular conduction disturbances (and therefore QRS complexes with increased duration) and ventricular complexes that look similar to normal QRS complexes. If atrial fibrillation is present, things become even more complicated, because it is not possible to rely on the presence of a P wave before the beat to classify it as normal. Furthermore, some P waves, T waves, or oscillations of the isoelectric line may be incorrectly read as QRS complexes and classified into normal or abnormal families. If these families are small, they can simply be classified as artifacts, but if they are not, it is better to change the reading setting.

Supraventricular arrhythmias can be even more difficult to identify for the software, because recognition is based exclusively on the degree of prematurity of the QRS complexes compared to the previous RR cycles. In humans, a value of 20% is usually set; in dogs, given the presence of marked sinus arrhythmia, a reasonable setting is 30/35%.

All RR intervals of the normal QRS complexes, supraventricular and ventricular beats with their coupling intervals, and supraventricular and ventricular tachycardias are represented through color codes on the tachogram.

The tachogram is a scatter plot that presents the hours of recording on the x-axis and the duration of the RR intervals/heart rate on the y-axis. By analyzing the RR interval distribution, it is possible to obtain an indirect assessment of heart rate variability. Figures 5.4a–5.4c show two tachograms of patients with a normal heart rate variability. Tachograms can look different depending on the reading software used. The tachogram in Figure 5.4a is usually preferred: each RR interval is represented by a point, so the veterinarian can, at a glance, get an idea of the RR interval distribution throughout the 24 hours. In addition, regions displaying a paucity of certain intervals, called zones of avoidance, can be seen as wide bands on these tachograms.[15] Typical patterns of distribution are then useful to suspect sinus node dysfunction.[7] Other programs create different tachograms with two lines (Fig. 5.4c), one for the heart rate and one for RR intervals, but these are less helpful in providing an immediate idea of a patient's heart rate variability.

Figure 5.5 shows a tachogram from a patient with reduced heart rate variability. Reduced heart rate variability is related to high sympathetic

tone, which can be normal during the first hour of monitoring but is suggestive of high sympathetic tone, for example due to heart failure, if it persists.

Most tachograms also show supraventricular and ventricular ectopic beats using different colors. By analyzing their localization on the tachogram, it is possible to identify them as premature or escape beats and to evaluate their frequency during the 24-hour monitoring period as well as any correlations with the patient's autonomic state resulting from sympathetic and parasympathetic influences.

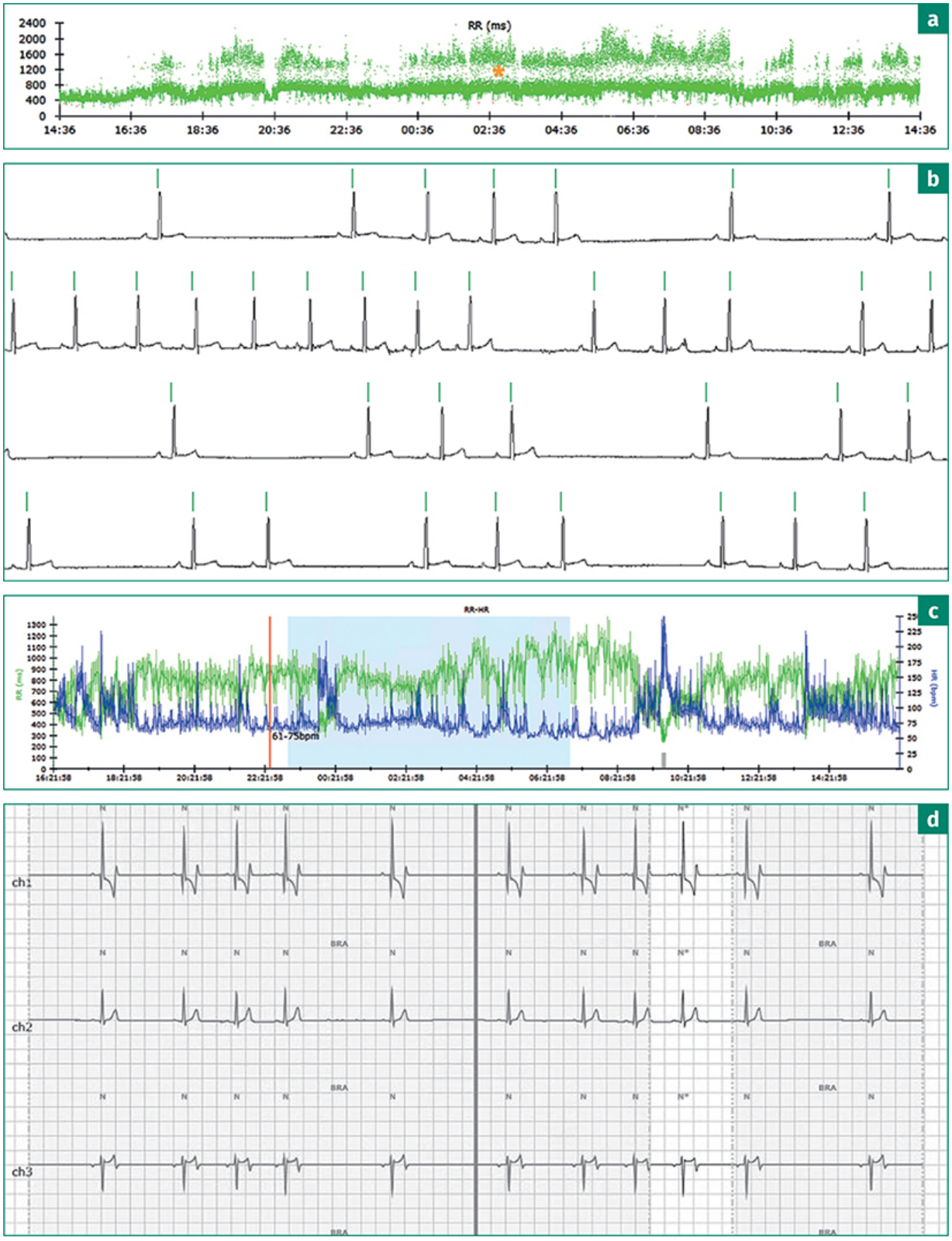


FIGURE 5.4. Holter recording of a 5-year-old female Poodle. a) Twenty-four-hour tachogram showing the distribution of RR intervals during sinus rhythm (green). Y-axis, RR interval duration; x-axis, hours of day and night. b) Electrocardiographic recording showing a sinus arrhythmia with

normal QRS complexes (vertical green lines) as the dominant rhythm. Lead Y; each line corresponds to 30 seconds. Speed, 20.6 mm/s; calibration, 5 mm/mV. c) Twenty-four-hour tachogram in a 6-year-old male Golden Retriever showing a normal duration of RR intervals (green) and normal heart rate (HR) (blue). Y-axis, RR interval duration (green) and HR (blue); x-axis, hours of day and night. d) Electrocardiographic recording showing sinus arrhythmia with normal QRS complexes (N) as the dominant rhythm. Three channels (X, Y, Z); speed, 25 mm/s; calibration, 10 mm/mV. The heart rate variability is normal in both dogs, but the first tachogram shows bands wherein beats of a certain RR interval duration are less frequent, called zones of avoidance (*). Note that in both patients, there is a reduced heart rate variability with a higher mean heart rate during the first hours of the recording, due to high sympathetic tone after leaving the hospital.

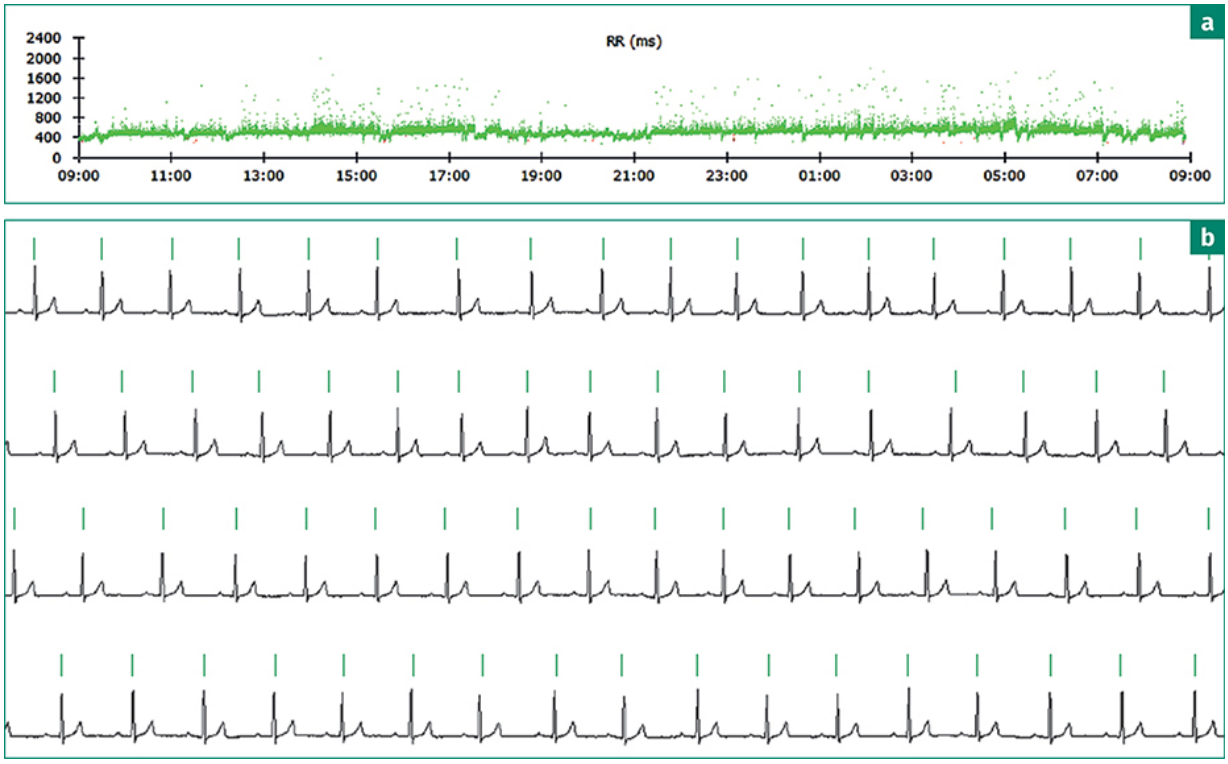


FIGURE 5.5. Holter monitoring of a 12-year-old male Yorkshire Terrier with chronic degenerative mitral valve disease and reduced heart rate variability. a) Twenty-four-hour tachogram showing the distribution of RR intervals during sinus rhythm (green). Y-axis, RR interval duration; x-axis, hours of day and night. b) Electrocardiographic recording showing sinus rhythm with normal QRS complexes (green vertical lines) as the dominant rhythm. The tachogram shows a regular distribution of RR intervals throughout the recording with a reduced heart rate variability and no zone of avoidance. Lead Y, each line corresponds to 10 seconds. Speed, 20.6 mm/s; calibration, 5 mm/mV.

A rapid initial inspection of the tachogram can also help identify prolonged periods of artifacts/noise that could influence the final diagnosis and can be excluded as a first step from the analysis, by directly not taking account of this part of the tachogram.

The average heart rate can be calculated based on the Holter recording using different methods: instantaneous beat-to-beat assessment (based on

the RR interval), rolling beat average (e.g., repeated averages of 8-beat intervals, calculated advancing forward one beat at a time and reaveraging), and simple average (number of beats/numbers of minutes of the recording).[6]

Because sinus arrhythmia is a common observation in the dog, the average heart rate may vary greatly between calculations made based on short or long heart rate segments.[16] Rolling averages may be reported as an absolute value (minimum or maximum value) or may designate bradycardia or tachycardia if the defined rate exceeds 10 seconds (e.g., amount of time the rate exceeds 150 bpm).[6]

The last part of a Holter analysis is the inspection of the automatic reading of the events: couplets, triplets, ventricular tachycardia, accelerated idioventricular rhythm, idioventricular rhythm, allorhythmia (bigeminy, trigeminy, quadrigeminy), supraventricular tachycardia, bradycardia, delays, and pauses. If the different beat families have been checked adequately, this part can be very quick and easy.

Particular attention must be given to delays and pauses, because they could hide the presence of atrioventricular blocks, since P waves are not recognized by Holter reading systems; for pauses, a cutoff value of 3,000 ms for dogs and 2,000 ms for cats is suggested.

HEART RATE VARIABILITY ANALYSIS

Heart rate variability analysis is a useful noninvasive diagnostic tool to study the effect of the autonomic nervous system on the heart. Although the P wave is a closer graphic representation of sinus node activity and the PP interval would be preferred, most software do not reliably detect P waves and the RR interval is used as a substitute for the PP interval. The presence of ventricular or supraventricular arrhythmias and of atrioventricular blocks or artifacts can invalidate heart rate variability calculations; these beats must therefore be removed from the analysis, and calculations should include at least 85% of normal beats.

Different methods can be used to calculate heart rate variability:

- The *time domain method* compares normal-to-normal (NN) intervals (i.e., all intervals between adjacent QRS complexes resulting from sinus node

depolarizations) at various points in time, and the indices are expressed in units of time. Simple time domain variables that can be calculated include the mean NN interval, the mean heart rate, the difference between the longest and shortest NN intervals, and the difference between night and day heart rates. Twenty-four-hour Holter monitoring also allows more complex statistical time-domain measures to be calculated. These can be divided into two classes: those derived from direct measurements of the NN intervals or instantaneous heart rate, and those derived from the differences between NN intervals. The simplest variable is the standard deviation of the NN intervals (SDNN), i.e., the square root of variance. Since variance is mathematically equal to total power spectral density, SDNN reflects all the cyclic components responsible for variability in the period of recording. Because the total variance of heart rate variability increases with the length of recording that is analyzed, the length of recording used to determine SDNN values should be standardized. Other commonly used statistical variables period include the standard deviation of the average NN intervals (SDANN), and the SDNN index (i.e., the mean of the standard deviations of the NN intervals for each 5-min segment calculated over 24 hours, which measures the variability due to cycles shorter than 5 min). The most used measures derived from interval differences include the square root of the mean squared differences of successive NN intervals (RMSSD), the number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording (NN50), and the proportion derived by dividing NN50 by the total number of NN intervals (pNN50). All these measurements of short-term heart rate variability are highly correlated.

- The series of NN intervals can also be converted into a geometric pattern, and a simple formula is used to determine the heart rate variability triangular index measurement, which is the integral of the density distribution (i.e., the number of all NN intervals) divided by the maximum of the density distribution. The major advantage of this geometric method lies in the relative insensitivity to the analytical quality of the series of NN intervals.
- *Frequency domain method:* Power spectral density analysis provides the basic information of how power (i.e., variance) distributes as a function of frequency. Frequency domain indices are expressed in Hertz (number of cycles per second). Low frequency components of the spectrum are in

general related to sympathetic activity, whereas high frequency components are related to parasympathetic activity. The result of this analysis includes ultra-low frequency, very low frequency, low frequency, and high frequency components.

HOLTER MONITORING IN DOGS: NORMAL FINDINGS

Recent studies have provided new insights into the dog's normal heart rhythm, underlining some interesting differences with humans.[17] The average heart rate of dogs is faster than that of humans (mean of 81 bpm and range of 64–119 bpm in dogs; mean of 74.5 bpm and range of 59–103 bpm in humans), and dogs have skewed nonsingular beat distributions, wide interval bands corresponding with regions displaying a paucity of intervals (zones of avoidance), and linear plus nonlinear rate changes.[15,17] In particular, changes seem to be linear with a dominant sympathetic modulation and nonlinear with a dominant parasympathetic modulation. Poincaré plots (plots of RR intervals where the duration of the current cardiac beat is shown on the x-axis and the duration of the following beat on the y-axis[18]) seem to show linear rate changes as intervals prolong until a point of divergence from the line of identity at a mean interval of 598.5 ms (95% CI: 583.5–613.5 ms) (bifurcation interval).[17] Figure 5.6 shows the nonlinear changes in heart rate typical of dogs.[17]

A large study evaluating 5,000 healthy dogs found that the mean difference in heart rate measured during the physical examination between dogs weighing 5 kg and 55 kg was only 10.5 bpm, which was considered unlikely to be clinically significant.[19] The same study showed that differences in heart rate were anyway detected among a variety of breeds; specifically, Chihuahuas, Cavalier King Charles Spaniels, Staffordshire Bull Terriers, and Yorkshire Terriers had higher heart rates, and Border Collies, Golden Retrievers, Labrador Retrievers, Springer Spaniels and West Highland White Terriers had lower heart rates.[19] Another study demonstrated higher values of heart rate variability in Cavalier King Charles Spaniels than in other breeds.[20]

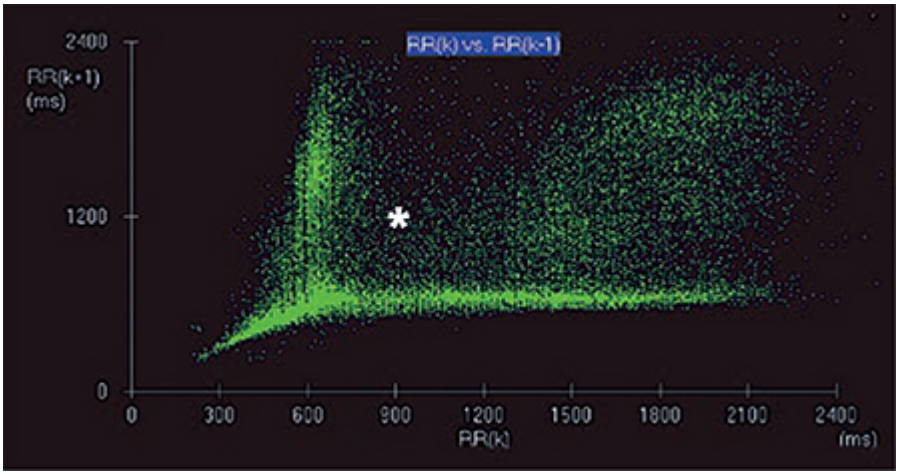


FIGURE 5.6. Poincaré plots of a normal dog with sinus arrhythmia. In dogs, as the beat-to-beat intervals increase, they do so along the line of identity (diagonal line from lower left corner to upper right corner) until approximately 600 ms when a bifurcation develops resulting in two "branches" or "clusters" along the x- and y- axes. A paucity of beats is noted for certain beat-to-beat intervals forming the zone of avoidance (*). Additionally, some dogs develop a "cloud" of long–long RR intervals with an upper border along the line of identity.[17] X-axis, RR interval duration (k); y-axis, RR+1 interval duration (k+1).

The effect of age, body weight, and temperament on heart rate was investigated in a study involving around 400 dogs, and it was reported that dogs <1 year old had faster heart rates than older individuals,[21] but young adults can have, however, slower heart rates.[18] A large variability has been reported in geriatric dogs, depending on other factors such as temperament and comorbidities.[16] Larger dogs have modestly slower heart rates, but temperament has a greater influence on heart rate than body weight.[21,22]

Mental stress is also known to increase heart rate and has been reported to be the dominant factor affecting heart rate in dogs with normal sinus node function.[22]

Holter monitoring in normal dogs can reveal the presence of sinus pauses with a duration of up to 6 seconds, occasional second-degree atrioventricular block during periods of slow heart rate, and sinus tachycardia with rates above 240 bpm during periods of exercise, and the instantaneous heart rate may reach values greater than 300 bpm for short periods.[23]

The frequency of ventricular ectopy on 24-hour ambulatory electrocardiographic recordings has been published for normal dogs of

several breeds (<91 in Boxers,[24] <50 in Dobermans,[25] <9 in Beagles,[23] <2 in Salukis,[26] <24 in large breed dogs[27]).

HOLTER MONITORING IN CATS: NORMAL FINDINGS

Holter parameters in normal cats have been described.[28] Cats can have intermittent sinus arrhythmia and heart rate variability can be appreciated on the tachogram[29] (Fig. 5.7). In a study involving 23 healthy cats, it was present in 78% of cats. In this study, the median heart rate was 165 bpm (range, 70–303 bpm). The mean heart rate varied significantly with age and gender: entire male cats were reported to have significantly higher heart rates than female cats and neutered male cats, and cats younger than 6 years had a lower heart rate than cats older than 6 years.[29]

Ventricular arrhythmias can be present during the 24 hours in normal cats: the median number of ventricular premature complexes per cat has been reported to be 3 complexes/24 hours (range, 0–146 complexes) and, interestingly, cats between 7 and 15 years of age have significantly more ventricular premature complexes than those between 1 and 6 years of age.

The heart rate over 24 hours has not been proved to be useful to differentiate between normal cats and cats affected by asymptomatic hypertrophic cardiomyopathy, but the latter have more frequent and complex ventricular and supraventricular arrhythmias.[29,30]

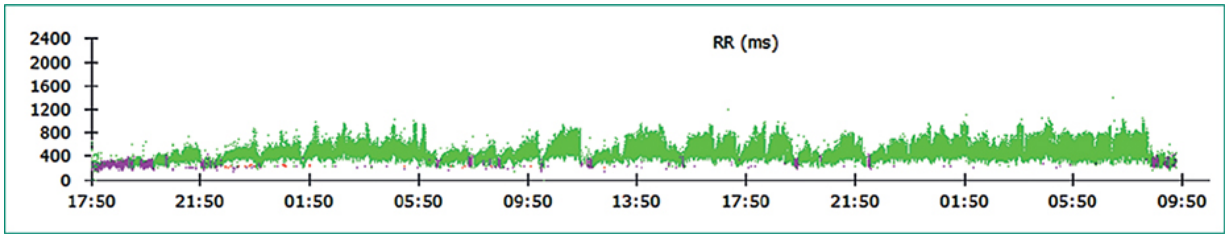


FIGURE 5.7. Holter recording of a 4-year-old male domestic shorthair cat. Twenty-four-hour tachogram showing the distribution of RR intervals during sinus rhythm (green) and supraventricular tachycardia (purple). Y-axis, RR interval duration; x-axis, hours of day and night. In cats, the tachogram shows a regular distribution of RR intervals throughout the recording, with minimal heart rate variability and no zone of avoidance.

HOLTER MONITORING OF DIFFERENT ARRHYTHMIAS

SUPRAVENTRICULAR ARRHYTHMIAS

As stated before, supraventricular ectopic beats are recognized by the software based on their prematurity compared to the previous RR interval. Therefore, in dogs with marked sinus arrhythmia, it is fundamental to check rapidly all the beats that have been classified as supraventricular ectopic beats, because normal sinus beats are often included in this category. If a lot of false positive supraventricular ectopic beats are found, the cutoff value for prematurity can be gradually increased by a value of 2%.

An additional criterion for the identification of supraventricular ectopic beats is the analysis of the P wave morphology, which usually tends to diverge at least a little from that of a sinus P wave. This difference is not always evident; therefore, a good advice is to observe the trace in the three channels and to look for variations in polarity, a small notch, or atrial deflections in the previous T wave or even ST segments (mainly in cases of focal atrial tachycardia originating from the pulmonary veins).[31]

The investigation of paroxysmal supraventricular tachycardia is one of the most common reasons why Holter monitoring is performed. When runs of supraventricular tachycardia are documented, some crucial points have to be described: how the supraventricular tachycardia starts and stops, heart rate and morphology of the QRS, relationship between the atria and ventricles (together with quantification of the RP' and P'R intervals), and any possible associations with clinical signs reported by the owner in the diary. Supraventricular tachycardia caused by enhanced automaticity is usually characterized by a gradual onset, while reentrant tachycardia is characterized by a sudden onset and cessation (Figs. 5.8 and 5.9). In addition, the possible presence of a trigger could aid in the diagnosis.

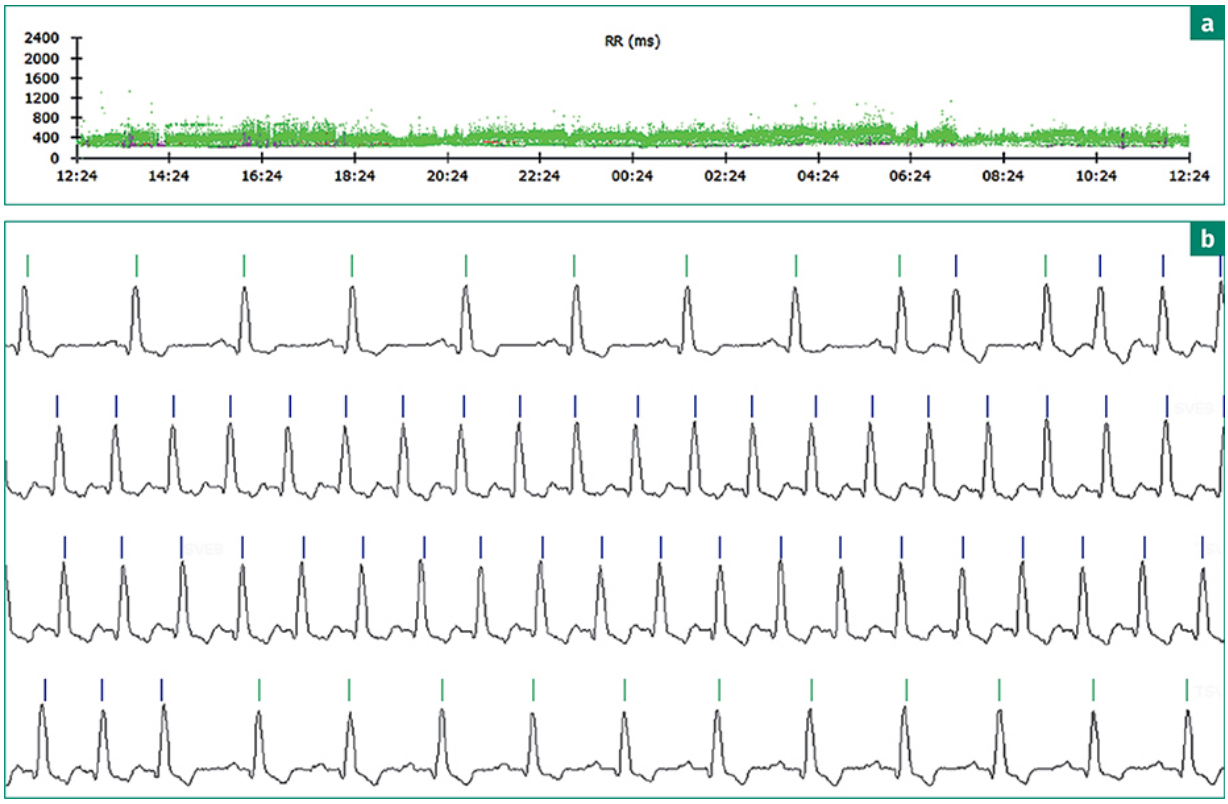


FIGURE 5.8. Holter recording from a 7-year-old female Australian Shepherd with chronic myocarditis and frequent self-limiting runs of focal atrial tachycardia. a) Twenty-four-hour tachogram showing the distribution of RR intervals during normal sinus rhythm (green) and atrial ectopic activity (purple). Y-axis, RR interval duration; x-axis, hours of day and night. b) Electrocardiographic recording showing sinus rhythm (green vertical lines) as the dominant rhythm, interrupted by a run of focal atrial tachycardia (purple vertical lines) caused by abnormal enhanced automaticity and characterized by a gradual onset and cessation with normal QRS complexes (green vertical lines). Lead Y, each line corresponds to 30 seconds. Speed, 41.2 mm/s; calibration, 5 mm/mV.

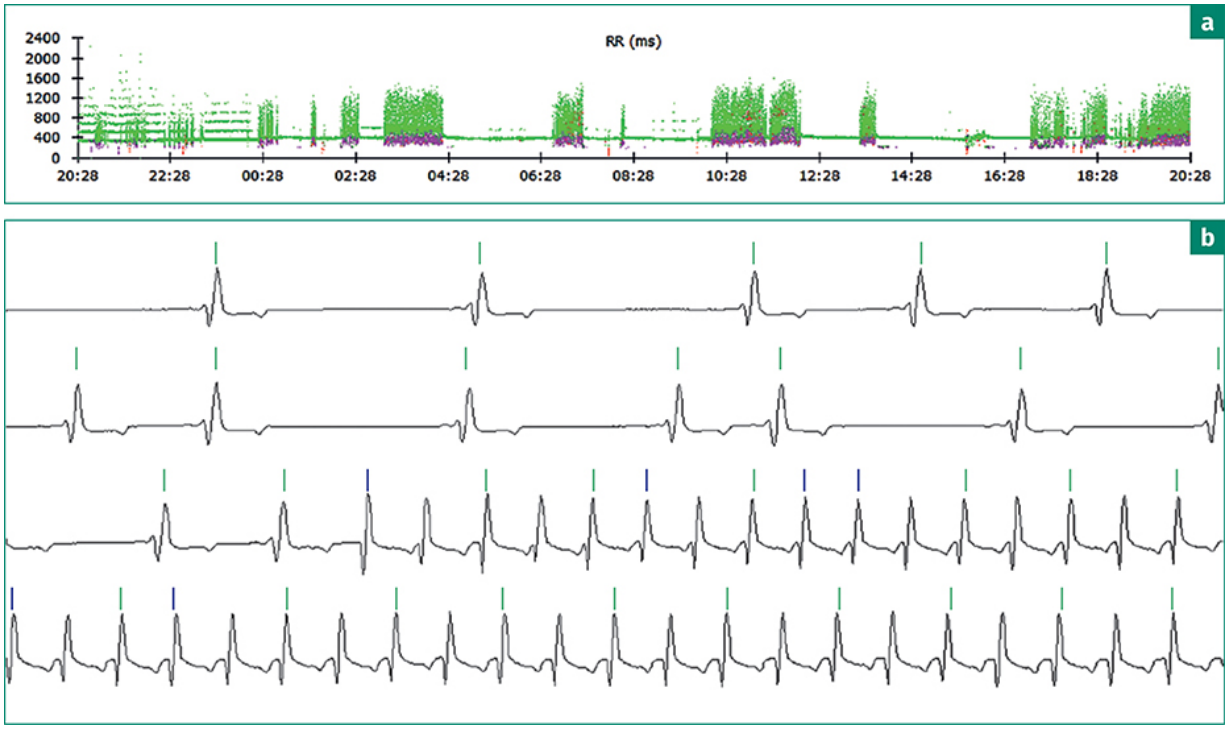


FIGURE 5.9. Holter recording from a 1-year-old male Labrador Retriever with an atrioventricular accessory pathway. a) Twenty-four-hour tachogram showing the distribution of RR intervals during sinus rhythm (green) and supraventricular ectopic activity (purple). The initial part of the recording shows a horizontal resolution artifact with multiple lines due to the fast ventricular rate during reciprocating tachycardia. Y-axis, RR interval duration; x-axis, hours of day and night. b) Electrocardiographic recording showing sinus rhythm with ventricular preexcitation (vertical green lines) as the dominant rhythm, interrupted by runs of orthodromic atrioventricular reciprocating tachycardia (vertical purple and green lines). Lead Y; each line corresponds to 5 seconds. Speed, 41.2 mm/s; calibration, 5 mm/mV.

Atrial fibrillation is the most frequent supraventricular arrhythmias that is routinely investigated in dogs with Holter monitoring (Fig. 5.10). The reason is that the average heart rate over 24 hours recorded in a home environment cannot be predicted based on a brief electrocardiogram. A Holter recording may also provide additional valuable information about concurrent ventricular arrhythmias, and dogs diagnosed with atrial fibrillation, structural heart disease, and congestive heart failure can occasionally show a spontaneous cardioversion after starting treatment for congestive heart failure (Fig. 15.11).[32] Therefore, a baseline Holter recording before starting treatment is a good practice and provides information on heart rate distribution beyond the mean 24-hour rate (minimum and maximum heart rates, number of hours when the heart rate is below a predetermined rate, and number and duration of pauses), which is

helpful for the management of the arrhythmia. A multicenter prospective observational study evaluating the optimal rate control in dogs with atrial fibrillation has determined that rate control affects survival, and an optimal target average heart rate <125 bpm should be sought. The main problem of this target is that some dogs could potentially have an average heart rate >125 bpm during the 24 hours, but the tachograms may show that these dogs have very a high heart rate during activity and in conditions of high sympathetic tone, for example, but an adequate heart rate during most of the remaining hours. Therefore, it is also useful to determine how long the mean heart rate is above 125 bpm, although data to make treatment decisions based on this consideration are lacking.

Another paper has translated the concept of *mesor* (midline estimating statistic of rhythm) from human medicine to dogs.[33] Parameters such as heart rate have been shown to vary with circadian rhythm in a sinusoidal manner around a central tendency or mesor, a rhythm-adjusted mean. When sinusoidal variation is present and data are not equidistant, the mesor is the most accurate reflection of the average heart rate, and the authors demonstrated that the heart rate varies in a circadian manner in dogs with atrial fibrillation.[34] Unfortunately, there is currently no software that can easily calculate the mesor, but they may become available in the future.

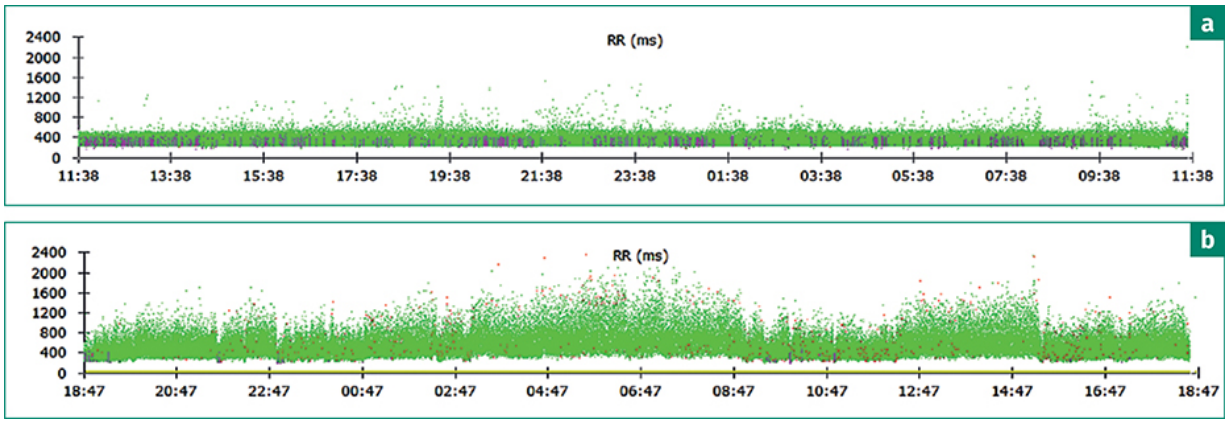


FIGURE 5.10. Holter recording from a 7-year-old male Dogue de Bordeaux with long-standing persistent atrial fibrillation. a) Twenty-four-hour tachogram before treatment showing the distribution of RR intervals during normal heart rate (green) and tachycardia (purple). b) Twenty-four-hour tachogram after treatment with digoxin (0.003 mg/kg PO twice a day) and diltiazem R (2 mg/kg PO twice a day) showing the distribution of RR intervals during normal heart rate (green) and tachycardia >180 bpm (purple). Notice the variation in the RR intervals in b), with an increased amount of green dots for durations above 500 ms (<120 bpm). Y-axis, RR interval duration; x-axis, hours of day and night.

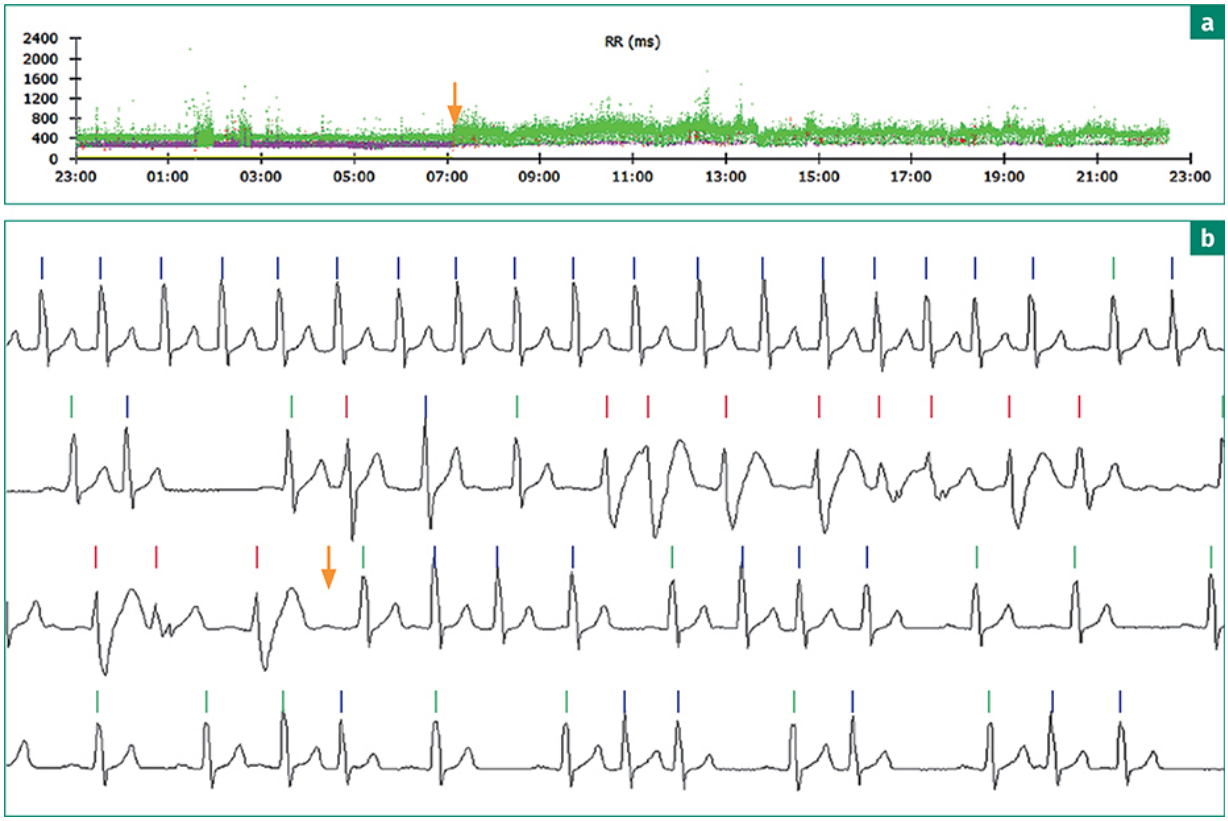


FIGURE 5.11. Holter recording from a 5-year-old male Doberman with dilated cardiomyopathy and spontaneous cardioversion of paroxysmal atrial fibrillation after monomorphic ventricular tachycardia. a) Twenty-four-hour tachogram showing the distribution of RR intervals during either sinus rhythm or normal ventricular rate during atrial fibrillation (green), fast ventricular rate during atrial fibrillation (purple), and ventricular ectopy (red). Y-axis, RR interval duration; x-axis, hours of day and night. b) Electrocardiographic recording showing atrial fibrillation as the initial rhythm; at around 07:10 a.m. (arrow in b), a monomorphic ventricular tachycardia occurred (vertical red lines), followed by sinus rhythm (vertical green lines) interrupted by atrial ectopies, couplets, and self-limiting runs of focal atrial tachycardia (vertical purple lines). Lead Y; each line corresponds to 5 seconds. Speed, 41.2 mm/s; calibration, 5 mm/mV.

VENTRICULAR ARRHYTHMIAS

As stated before, rare single ventricular ectopic beats may be a normal finding in dogs, and the general conclusion of the previously reported studies is that in normal dogs, up to 50 single ventricular premature beats over 24 hours can generally be considered within acceptable limits. However, if less than 50 ventricular beats are found, but these have a high grade (e.g., R-on-T phenomenon, presence of couplets or triplets, or a fast run of ventricular tachycardia), a complete cardiac or possibly a systemic workup should be strongly suggested.

In addition to the total number of ventricular premature complexes, the assessment of ventricular arrhythmias on Holter recordings should include other parameters, such as arrhythmia distribution over the 24 hours: a greater concentration of ventricular arrhythmias at night may suggest bradycardia-dependent ventricular arrhythmias (Fig. 5.12a), while conversely, a prevalence of these arrhythmias during the day could depend on the adrenergic tone or other triggers (Fig. 5.12b).

Polarity of ventricular arrhythmias is not usually assessed in dogs, as this can be influenced by positioning and recumbency of the patient. Ventricular complexes arising from different regions of the heart may be more likely to induce arrhythmia-induced cardiomyopathy than a singular focus. However, there is no data to support this hypothesis in the dog.

The minimum coupling interval is a useful parameter that can be easily calculated and reported. Ventricular premature complexes are usually presented in terms of degree of prematurity; the interval between the R wave of the beat preceding the most premature ectopic beat and the largest deflection of the ectopic QRS complex should be measured. Very short coupling intervals result in the onset of the premature ectopic beat occurring close to the peak of the T wave of the previous beat (R-on-T phenomenon); as a result, a premature beat occurring during this window of time could initiate ventricular fibrillation in the presence of an underlying structural or electrical cardiac disease. The identification and definition of an R-on-T phenomenon is difficult and imprecise in dogs and cats, and the minimum coupling interval is therefore a more objective and quantitative parameter, although there is still no cutoff value to stage the risk of ventricular fibrillation. Another important point is the variability of the coupling interval: ventricular premature beats have a fixed or relatively fixed coupling interval when the arrhythmogenic mechanism is a reentry, while this is rarer when triggered activity or enhanced automaticity are the underlying mechanisms.[35]

Another important parameter that should be evaluated is the ventricular burden: large numbers of premature ventricular complexes can lead to development of systolic dysfunction. In human beings, the likelihood of developing arrhythmia-induced cardiomyopathy increases when the ventricular burden (defined as the percentage of any form of ventricular premature complex) exceeds 24% of all QRS complexes in a 24-hour period.[36] However, other factors have been considered crucial for the

development of this myocardial disorder in humans, such as a QRS duration >150 ms, an epicardial localization of ventricular beats, and the absence of premature ventricular complex variability throughout the day and night in patients with frequent ventricular ectopies.[37,38] The ventricular burden in the dog has not been determined; however, this approximate number provides at least some guidelines. It should be emphasized that the decision to treat based on the number of ventricular ectopic beats should be made on a case-by-case basis because of the multiple factors that must be considered. In general, more than 25% of ventricular ectopic complexes warrants therapy, while treatment is likely not necessary if ventricular ectopic beats represent less than 10% of all QRS complexes, and they are primarily singlets with only a few multiples. The gray zone for individual care lies between these two cutoffs. When evaluating the number of ventricular ectopies and the efficacy of the antiarrhythmic treatment, it is fundamental to remember that spontaneous variability has been reported to account for as much as 80% of the change in frequency of ventricular premature complexes in Boxers with frequent arrhythmias.[39] A study involving German Shepherd dogs with inherited ventricular arrhythmias showed a similar trend, and changes in the frequency of ventricular ectopy of up to 61% were considered within the limits of spontaneous variability.[3] Furthermore, the frequency of ventricular ectopy has been shown to be positively correlated to increasing age.[24]

Lastly, ventricular arrythmias should be graded to determine their prognostic significance. Historically, the Lown grading scheme has been used, which was modified for veterinary medicine as follows: [40,41]

- Grade 1: single, uniform ventricular ectopic beats
- Grade 2: bigeminy, trigeminy, or multiform ventricular ectopies
- Grade 3: presence of couplets or triplets
- Grade 4: R-on-T phenomenon or ventricular tachycardia

The ventricular tachycardia rate is another important prognostic parameter; in Dobermans, a fastest rate of ventricular premature complexes ≥260 bpm has been related to a risk of sudden cardiac death.[42]

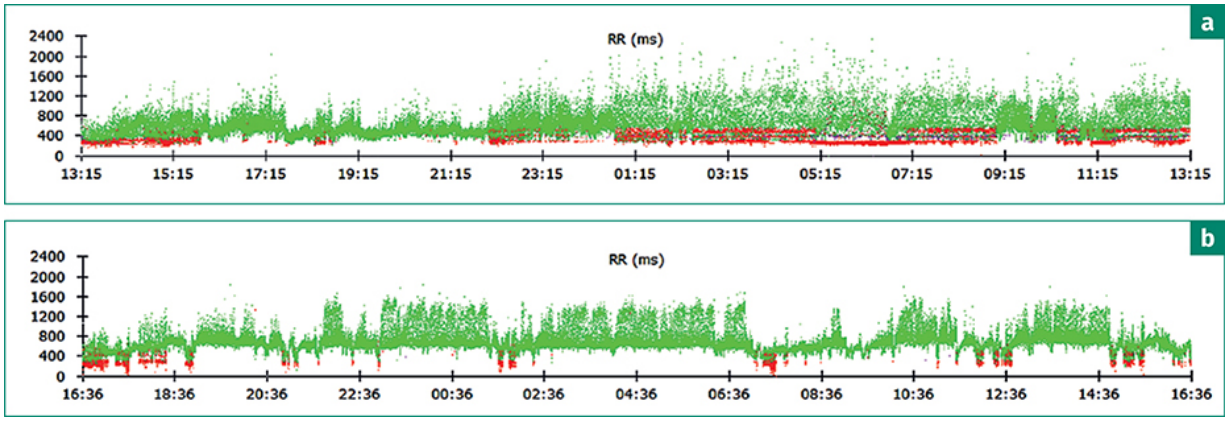


FIGURE 5.12. a) Holter recording from a 7-month-old male German Shepherd with bradycardia-dependent inherited ventricular arrhythmias. Twenty-four-hour tachogram showing the distribution of RR intervals during sinus rhythm (green) and ventricular tachycardia (red). Notice the concentration of ventricular arrhythmias during period of long RR intervals. b) Holter recording from a 6-year-old female Boxer with arrhythmogenic cardiomyopathy and tachycardia-dependent (catecholaminergic) ventricular arrhythmias. Twenty-four-hour tachogram showing the distribution of RR intervals during periods of sinus rhythm (green) and ventricular tachycardia (red). Notice the concentration of ventricular arrhythmias during short RR intervals. Y-axis, RR interval duration; x-axis, hours of day and night.

BRADYARRHYTHMIAS

Sinus node dysfunction is the most common condition in which Holter monitoring is essential to reach or confirm a diagnosis and better characterize the disease (bradycardia variant or tachycardia-bradycardia variant) (Figs. 5.13 and 5.14).

The criteria suggested to diagnose sinus node dysfunction in dogs include an average heart rate of less than 65 bpm (in the tachycardia-bradycardia variant, the heart rate can be more than 65 bpm), a minimum heart rate below 35 bpm, more than 3,000 sinus pauses (consequence of sinus arrest, sinoatrial block, or sinus standstill) exceeding 2 seconds in 24 hours, more than 5 pauses exceeding 4 seconds, and one pause exceeding 5.5 seconds (unless reflex proven). The type and frequency of escape beats and rhythms are very different between dogs.[43]

The tachogram of most dogs with sinus node dysfunction usually reveals a characteristic beat-to-beat pattern, with multiple clusters of beats over a longer range of RR intervals, while the tachogram of dogs with normal sinus function tends to display a double band of RR intervals (as substitutes for the PP intervals) with a very small number of RR intervals in between these two bands.[15] Poincaré plots can display typical patterns that do not

seem to depend on sympathetic and parasympathetic tone, as clustering of the RR intervals is caused by supraventricular tachycardia and atrioventricular block.[7]

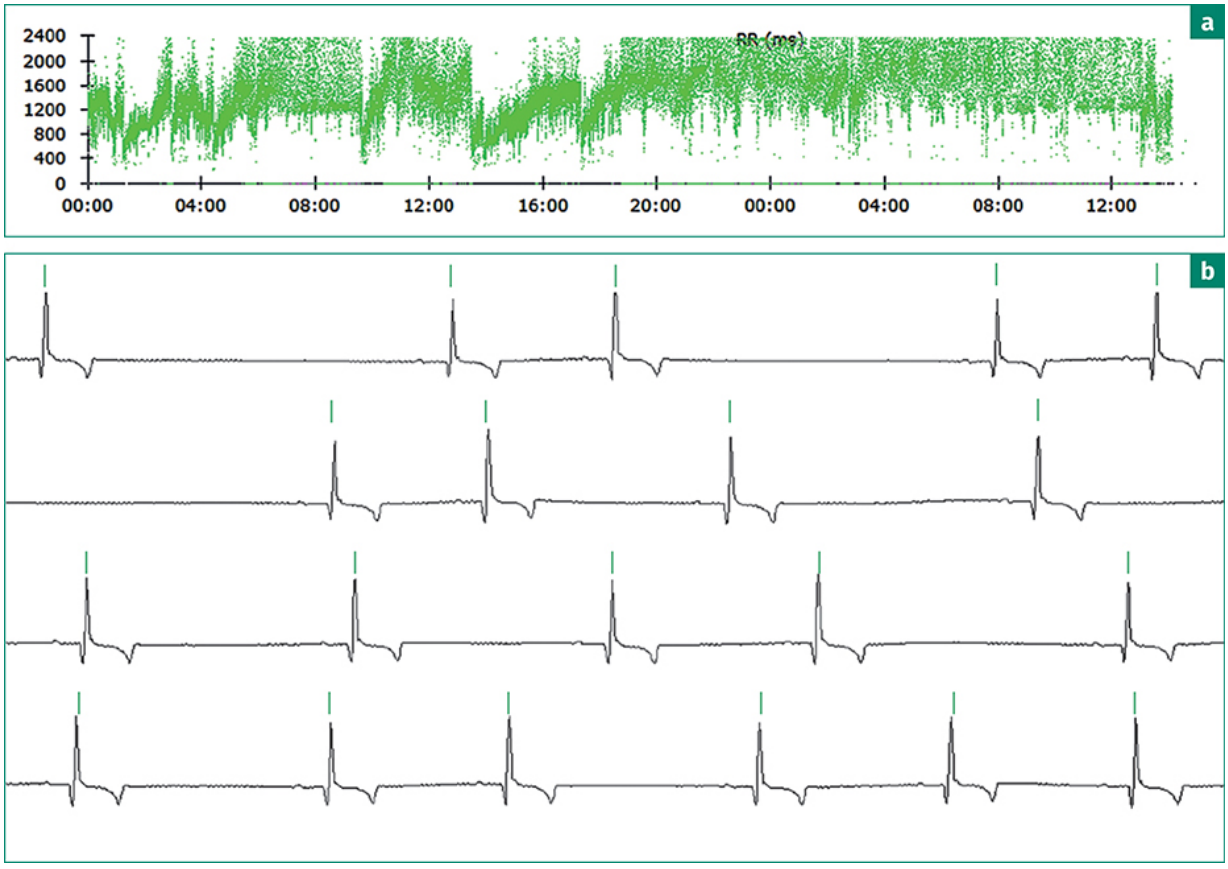


FIGURE 5.13. Holter recording from a 14-year-old female West Highland White Terrier with sinus node dysfunction. a) Twenty-four-hour tachogram showing the distribution of RR intervals during sinus bradyarrhythmia (green). Y-axis, RR interval duration; x-axis, hours of day and night. b) Electrocardiographic recording showing sinus bradyarrhythmia (green vertical lines) with frequent sinus arrest as the dominant rhythm. Note the concentration of green dots in the area of long RR intervals (above 1200 ms). Lead Y; each line corresponds to 10 seconds. Speed, 9.2 mm/s; calibration, 5 mm/mV.

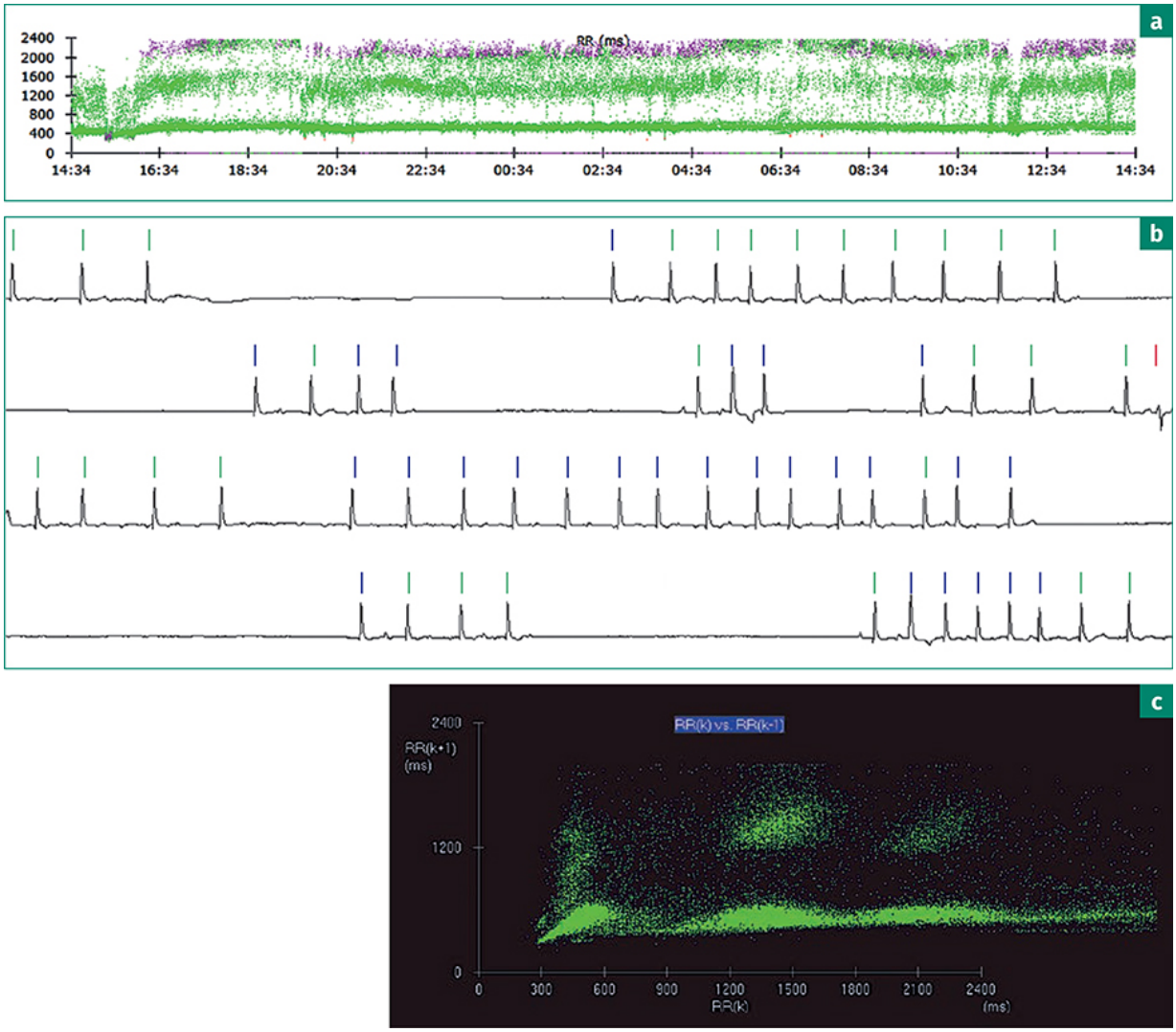


FIGURE 5.14. Holter monitoring of a 12-year-old female Miniature Schnauzer with sinus node dysfunction tachycardia-bradycardia variant. a) Twenty-four-hour tachogram showing the distribution of RR intervals during sinus rhythm (green), atrial and junctional ectopic activity (purple), and ventricular ectopic activity (red). Y-axis, RR interval duration; X-axis, hours of day and night. b) Electrocardiographic recording showing sinus rhythm (green vertical lines) as the dominant rhythm, interrupted by frequent focal atrial tachycardia (purple vertical lines) followed by sinus and ventricular arrest and junctional (purple vertical lines) or sinus beats. Notice the distribution of the RR intervals, with multiple parallel lines suggestive of sinus node exit block. Lead Y, each line corresponds to 10 seconds. Speed, 9.2 mm/s; calibration, 5 mm/mV. c) Poincaré plot in the same dog. Notice the presence of clustering of the RR intervals suggestive of sinus node exit block. X-axis, RR interval duration (k); y-axis, RR+1 interval duration (k+1).

CONDUCTION DISORDERS

For first-degree atrioventricular blocks, it is important to remember that the duration of the PQ interval in dogs is normally inferior to 130 ms, although longer PQ intervals are frequently found at night and during rest. There is

no range that establishes when this increase can be considered as a marker of an atrioventricular conduction disorder. It is therefore important to specify in the report whether the presence of a first-degree atrioventricular block is constant or intermittent together with the range of the PQ interval (the minimum PQ interval can be measured in the strip with the highest heart rate and the maximum PQ interval in the strip with the lowest heart rate).

For second-degree atrioventricular blocks, it is important to specify their number (rare/frequent) and to indicate whether they are Wenckebach or Mobitz type II blocks; this is not always easy, and both types can often be found in a Holter recording. The easiest method to determine the type of second-degree atrioventricular block is to compare the PQ interval of the last conducted beat with the first PQ interval following the block: in Mobitz type I blocks, the PQ interval following the block will be always shorter than the previous one. For advanced second-degree atrioventricular block, the key point to understand the underlying mechanism is to evaluate the sinus rate. An advanced atrioventricular block with a concomitant and progressive decrease in the sinus rate is usually suggestive of a reflex or neurally-mediated syncope characterized by inappropriate vagal reflex affecting either the sinus or the atrioventricular node (type 1B syncope). Conversely, a sudden onset atrioventricular block with a concomitant increase in the sinus rate is highly suggestive of a conduction system disorder (type 1E syncope).[44] While some cases of persistent block may be diagnosed from a resting electrocardiogram, ambulatory electrocardiographic monitoring may be useful in cases of intermittent block to document the heart rate over a longer period.

Reflex or neurally mediated syncope is a heterogeneous group of conditions characterized by an inappropriate autonomic response to a stimulus that results in bradycardia and hypotension. Cardioinhibitory syncope occurs due to an inappropriate increase in vagal tone that produces sinus bradycardia and/or paroxysmal atrioventricular conduction disorders, while vasodepressor syncope is characterized by a sudden withdrawal of sympathetic tone that results in profound hypotension. As ambulatory blood pressure measurements are difficult in dogs, ambulatory electrocardiograms are helpful to identify dogs with cardioinhibitory syncope. Cardioinhibition is likely to be the predominant mechanism if there are long sinus pauses; shorter sinus pauses suggest a vasodepressor component with vasodilation.

Other findings can however increase the suspicion of a vasodepressor component with vasodilation, such as ST segment depression (Fig. 5.15).

The finding of intraventricular conduction blocks on the surface electrocardiogram is another common reason for performing a Holter test, as it can help identify the presence of a major conduction disorder after a diagnosis of complete or troncular left bundle branch block, bifascicular or trifascicular block. However, there is no obvious rationale to suggest a Holter monitor after diagnosis of a complete right bundle branch block in the absence of cardiac-related signs.

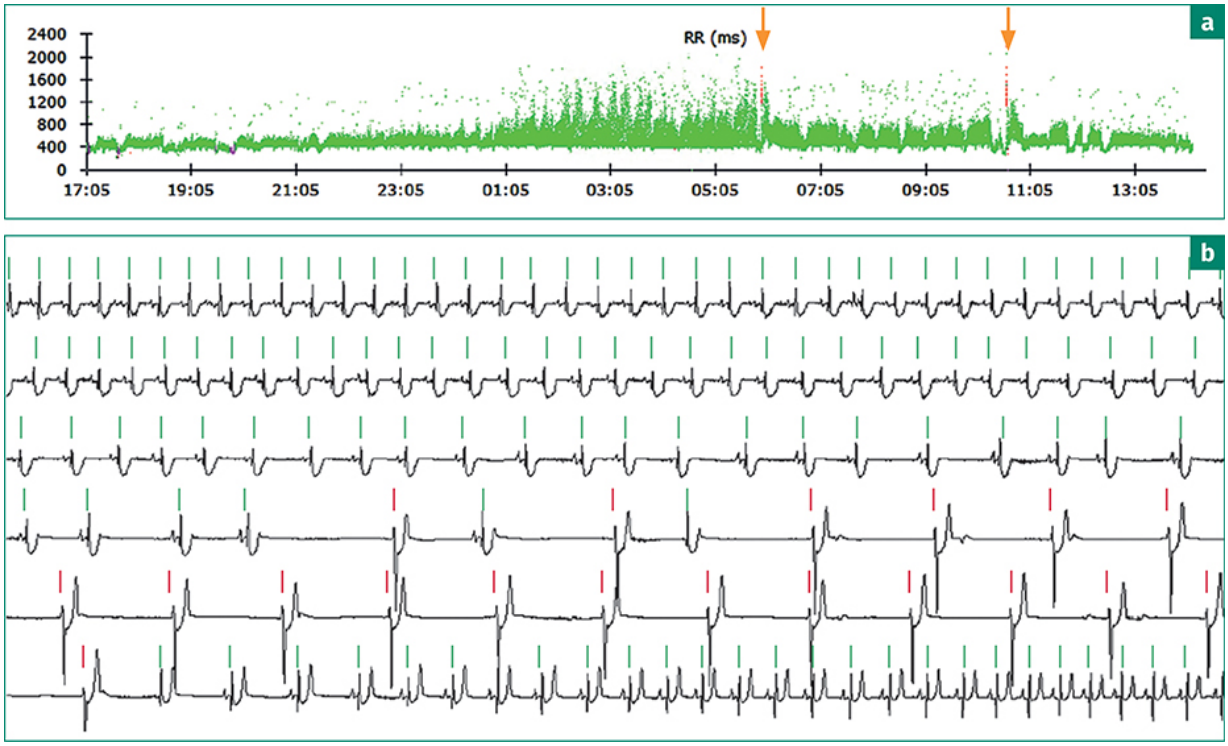


FIGURE 5.15. Holter recording from a 12-year-old male Cavalier King Charles Spaniel with chronic degenerative mitral valve disease and frequent episodes of transient loss of consciousness after cough (arrows). a) Twenty-four-hour tachogram showing the distribution of RR intervals during sinus rhythm (green) and ventricular ectopic activity (red). Y-axis, RR interval duration; x-axis, hours of day and night. b) Electrocardiographic recording showing an initial sinus rhythm, followed by progressive sinus bradycardia (green vertical lines) and a sinus arrest, which is interrupted by a ventricular escape rhythm (red vertical lines). Finally, sinus rhythm is restored with a progressive increase in heart rate. The electrocardiographic feature is suggestive of a situational reflex syncope (type 1A[43]) due to an inappropriate vagal reflex. The concomitant presence of ST segment depression increases the suspicion of an associated vasodepressor component with profound vasodilation and myocardial hypoperfusion. Lead Y; each line corresponds to 15 seconds. Speed, 13.7 mm/s; calibration, 5 mm/mV.

HOLTER MONITORING IN THE DIFFERENT DISEASE STATES

DILATED CARDIOMYOPATHY

Holter monitoring is recommended for screening in Doberman Pinschers and might be indicated in other breeds such as Great Danes. A 24-hour Holter test is currently recommended, although seven-day Holter monitoring seems to improve the sensitivity of detecting the disease.[45]

Holter monitoring is a fundamental tool in dogs with a dilated cardiomyopathy phenotype, as some of these dogs may suffer from an arrhythmia-induced cardiomyopathy rather than from a familial dilated cardiomyopathy. Because this condition is potentially reversible, it is important to consider it in the differential diagnosis. Arrhythmia-induced cardiomyopathy is demonstrated if chronic tachycardia >200 bpm on the Holter recording.[46] A young age of the patient, specific breeds (e.g., Labrador Retriever), and reversal of the dilated cardiomyopathy phenotype after antiarrhythmic treatment makes the diagnosis of arrhythmia-induced cardiomyopathy likely.

The reported recommendations of the European Society of Veterinary Cardiology for screening of dilated cardiomyopathy in Doberman Pinschers are as follows:[1]

- From 0 to 50 single ventricular premature complexes per 24 hours: considered normal in Dobermans, although detection of any number of ventricular premature complexes is cause for concern. Complex ventricular premature complexes that have a short coupling interval (>250/min) should also be considered as an additional diagnostic criterion, as couplets, triplets, or single short runs of ventricular premature complexes with a fast instantaneous rate (>260/min) are potentially dangerous and are less likely to be caused by myocardial damage secondary to other systemic diseases. In these cases, dilated cardiomyopathy cannot be ruled out and a follow-up Holter examination should be performed within 3-6 months.
- More than 300 ventricular premature complexes per 24 hours or two consecutive recordings within a year showing between 50 and 300 ventricular premature complexes per 24 hours: diagnostic of occult

dilated cardiomyopathy in Dobermans regardless of the concurrent echocardiographic findings.

- Between 50 and 300 ventricular premature complexes in 24 hours and a follow-up Holter within the following 12 months showing <50 ventricular premature complexes: dilated cardiomyopathy cannot be definitively ruled out and ongoing screening is strongly recommended.

It is important to underline that ventricular escape complexes and accelerated idioventricular rhythms (ventricular rate <160 bpm) are not considered to be diagnostic for dilated cardiomyopathy, and in these cases systemic diseases that could potentially cause ventricular arrhythmias should always be excluded.[1]

The significance of atrial premature complexes and atrial tachycardia in the diagnosis of dilated cardiomyopathies in Dobermans has been recently reviewed: atrial premature complexes were present with no obvious cardiac disease and were not identified until after ventricular premature complexes were present. They therefore could not be used as a marker for the development of dilated cardiomyopathy. In addition, extracardiac diseases, especially gastrointestinal diseases, influenced the occurrence of atrial premature complexes.[47]

Conversely, the finding of persistent atrial fibrillation on Holter monitoring has been linked to shorter survival times and significantly higher mean heart rates in Dobermans affected by dilated cardiomyopathy.[48]

ARRHYTHMOGENIC CARDIOMYOPATHY

Holter monitoring is a fundamental part of the diagnosis, screening, management, and prognosis evaluation of canine arrhythmogenic cardiomyopathy. An annual Holter study is therefore recommended for breeding Boxers, English Bulldogs, and dogs with a family history of arrhythmogenic cardiomyopathy. The proposed Holter criteria for identifying arrhythmogenic cardiomyopathy in an asymptomatic dog are:[2]

- From 0 to 20 single ventricular premature complexes per 24 hours: within normal limits.
- From 20 to 100 ventricular premature complexes per 24 hours: indeterminate, a follow-up Holter study should be suggested after 6 to 12

months.

- From 100 to 300 single ventricular premature complexes per 24 hours: suspicious of arrhythmogenic cardiomyopathy.
- From 100 to 300 ventricular premature complexes per 24 hours with increased complexity (frequent couplets, triplets, ventricular tachycardia), or 300 to 1,000 single ventricular premature complexes per 24 hours: dog likely affected by arrhythmogenic cardiomyopathy.
- More than 1,000 ventricular premature complexes per 24 hours: dog affected by arrhythmogenic cardiomyopathy.

These criteria are based on the prevalence of the arrhythmias in the asymptomatic population, and it is strongly advised to consider all issues for each individual dog, including their genetic status, family history, evidence of ongoing systemic disease, and repeated Holter studies before making strict recommendations.

Holter findings also have an important prognostic significance in Boxers with suspected arrhythmogenic cardiomyopathy and structurally normal hearts: the presence of more than 50 ventricular premature complexes per 24 hours, polymorphic ventricular premature complexes, and ventricular tachycardia have all been associated with a shorter survival time (Fig. 5.16).[49]

While supraventricular arrhythmias do not occur in dogs with familiar dilated cardiomyopathy, they may be observed in those with arrhythmogenic cardiomyopathy (in particular atrial flutter and sustained focal atrial tachycardia). Indeed, fibrofatty infiltration may predominantly affect tissues other than the ventricular myocardium, and this can occur both in Boxers and English Bulldogs.

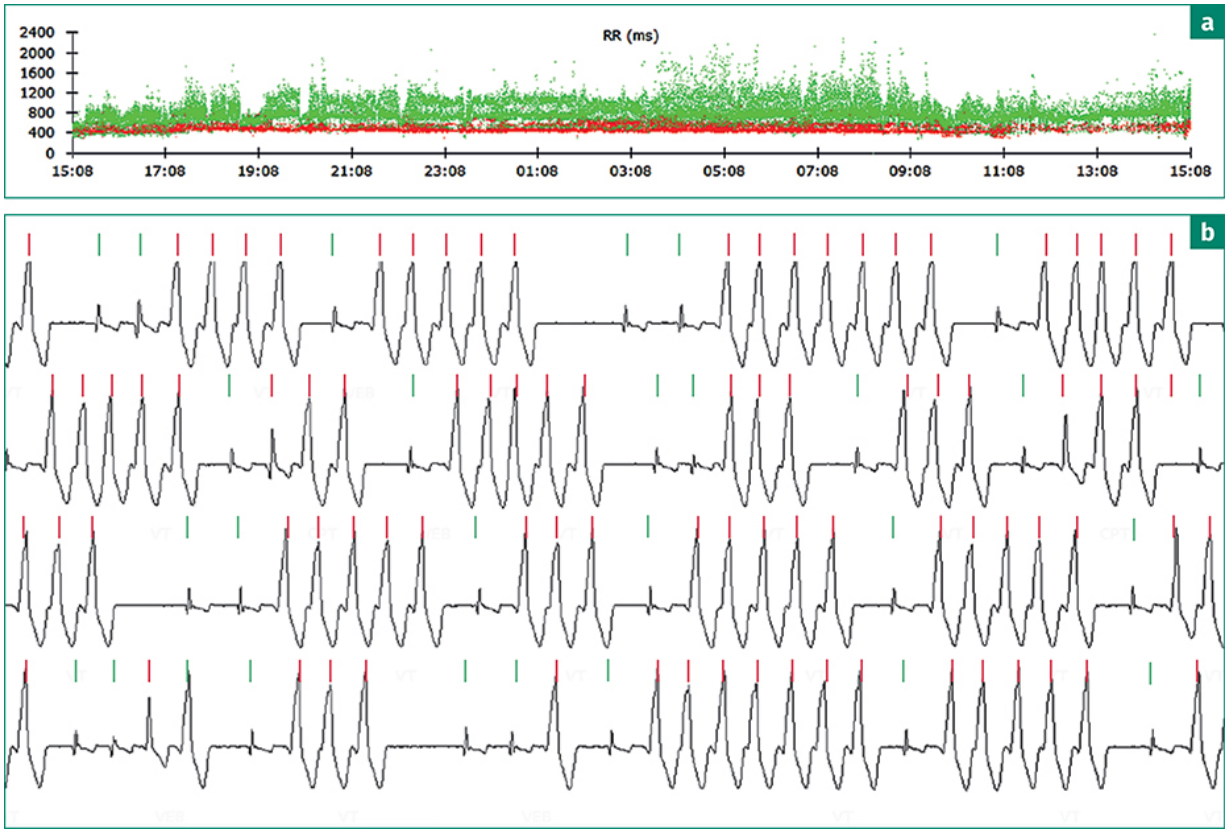


FIGURE 5.16. Holter recording from an 8-year-old female Boxer with arrhythmogenic cardiomyopathy, and frequent couplets, triplets, and runs of repetitive monomorphic ventricular tachycardia throughout the 24 hours. a) Twenty-four-hour tachogram showing the distribution of RR intervals during sinus rhythm (green) and ventricular ectopic activity (red). Y-axis, RR interval duration; x-axis, hours of day and night. b) Electrocardiographic recording showing sinus rhythm as the dominant rhythm (green vertical lines) and couplets, triplets, and runs of repetitive monomorphic ventricular tachycardia (vertical red lines). Lead Y; each line corresponds to 10 seconds. Speed, 20.6 mm/s; calibration, 5 mm/mV.

FELINE CARDIOMYOPATHIES

Factors contributing to ventricular arrhythmias in feline cardiomyopathies include the disorganized architecture of the left ventricular myocardium and the presence of ischemic areas. These arrhythmias are triggered by a combination of ischemia, fibrosis, decrease in the number and function of gap junctions, a mismatch between blood supply and muscle volume, and increased sympathetic tone. Arrhythmias caused by abnormal automaticity originate from ischemic cells, which have low resting membrane potential values, and reentrant arrhythmias are promoted by the presence of fibrosis, areas of slow conduction, and the increased dispersion of the refractory periods within the myocardium. Ventricular tachycardias occurring with

hypertrophic cardiomyopathy may therefore be nonsustained, repetitive, and monomorphic.[50]

A recent study evaluating Holter monitoring in cats with decompensated and compensated hypertrophic cardiomyopathy showed that ventricular arrhythmias were common in both groups, but neither the presence nor the complexity of the arrhythmias could be linked to the disease prognosis. The median number of ventricular premature complexes over 24 hours was 867 in cats with decompensated hypertrophic cardiomyopathy, 431 in cats with compensated hypertrophic cardiomyopathy and 2 in healthy control cats, thus highlighting the fact that the finding of ventricular arrhythmias in cats should always raise the concern for preclinical hypertrophic cardiomyopathy.[51] Unfortunately, no cutoff values are yet available to use Holter monitoring as a screening test in adjunction to echocardiography.

A study evaluating cats with asymptomatic hypertrophic cardiomyopathy showed that an obstructive form did not influence the number of ventricular arrhythmias; additionally, there was no correlation between the severity of the obstruction and the presence of arrhythmias.[30,51]

INHERITED VENTRICULAR ARRHYTHMIAS

Holter findings characteristic of familial arrhythmias include frequent single polymorphic beats, couplets, allorhythmias, and repetitive nonsustained episodes of polymorphic ventricular tachycardia, which all occur mainly during rest or sleep and are abolished by a fast heart rate.[52–54]

These arrhythmias should be considered in young German Shepherd dogs, Rhodesian Ridgebacks, and Leonbergers, although dogs of other breeds such as Labradors and Golden Retrievers have also been found to have similar electrocardiographic phenotypes.[52–54] The problem of these primary arrhythmic disorders is that affected dogs are often asymptomatic but also have a high risk of sudden cardiac death. There are currently no guidelines regarding screening of these breeds and no consensus on whether an annual Holter study should be recommended until adulthood; however, cardiology specialists should encourage general practitioners to always perform a 5-minute electrocardiogram before general anesthesia and a Holter study if an arrhythmia is detected in these dogs.

MYXOMATOUS MITRAL VALVE DISEASE

In dogs with myxomatous mitral valve disease, ventricular arrhythmias may occur but are usually benign and do not require treatment. They are most likely triggered by a change in the mechanical forces between the valve apparatus and the ventricles that causes prolongation of the refractory period in the cells of the papillary muscles.[55] In case of severe high grade ventricular arrhythmias, an additional cause should be sought (e.g., electrolyte disorders such as hypomagnesemia secondary to diuretic treatment, associated myocardial disorders, or extracardiac diseases such as splenic neoplasia).

Furthermore, an enlarged left atrium is associated with a higher number of supraventricular arrhythmias due to atrial stretching.[55] Although not yet proven, supraventricular arrhythmias could also be related to the risk of developing atrial fibrillation, which is the most common supraventricular tachycardia and most common indication for Holter monitoring in dogs with myxomatous mitral valve disease.

A study evaluating dogs with myxomatous mitral valve disease and a history of syncope revealed they did not have a higher occurrence of arrhythmias but were less affected by sinus arrhythmia. They also had changes in heart rate variability parameters, representing decreased overall heart rate variability, decreased parasympathetic, and increased sympathetic modulation of heart rate.[56]

Evaluation of heart rate variability is particularly useful to assess the sympathovagal balance, which can change due to parasympathetic withdrawal during the development of heart failure.[57]

SUBAORTIC STENOSIS

Ventricular arrhythmias are also reported with ventricular hypertrophy secondary to pressure overload. In these cases, as occurs in cats, arrhythmias are triggered by a combination of ischemia, fibrosis, decrease in the number and function of gap junctions, a mismatch between blood supply and muscle volume, and increased sympathetic tone.[58,59]

Therefore, in case of moderate to severe subaortic stenosis, annual Holter monitoring should be always suggested.

PACEMAKER FUNCTION EVALUATION

If the Holter monitoring software has a pacemaker-induced beat recognition system, it is advisable to activate it, as periods of stimulated rhythm may otherwise be considered as ventricular beats. Some software can also consider the pacing mode and the programmed basal rate.[6]

Another advice in case of pacemaker malfunction and if an intrinsic rhythm is present together with the paced beats is to set the pacemaker as the unipolar lead before starting the Holter recording, so that the spikes are more visible and paced beats are more easily recognized. In case of suspected pacemaker malfunction, it is also advisable to switch off the rate-responsive mode to simplify the analysis of the RR intervals.[6]

When evaluating pacemaker malfunction, a correct interpretation of a Holter recording must answer three main questions: is there a failure to pace, a failure to capture, or a failure to sense?

- Failure to pace: A spike is missing in the fixed stimulation period, following the last stimulated complex or spontaneous complex, and the consequence is a pause that is longer than the programmed stimulation period, but that is a multiple of this period.
- Failure to capture: This condition is manifested by a spike that is not followed by a capture response (falling in a period out of the refractory period for the paced chamber). Even if this is intermittent, this is a very serious complication because it means we cannot be certain that stimulation takes place in all circumstances.
- Failure to sense: To stimulate on demand, the pacemaker must sense spontaneous activity in each cavity. The failure to sense may manifest in two ways: 1) the pacemaker cannot sense the electrical potential of the spontaneous activity, and in this case the spike is triggered without taking account of the spontaneous activity (undersensing); 2) the pacemaker senses an inadequate cardiac electrical potential (e.g., the T wave) or an extracardiac potential (e.g., a potential provoked by the contraction of peripheral muscles) and interprets it as spontaneous activity (oversensing), and in this case, it may result in a pause without any cardiac activity as long as the extracardiac potential lasts.

Apart from pacemaker malfunction, Holter monitoring can be useful to evaluate the hysteresis rate in non-pacemaker-dependent patients.[6]

Hysteresis is a programmable operation that encourages additional intrinsic cardiac beats. When examining the effectiveness of hysteresis, the frequency of intrinsic complexes in the hysteresis zone should be determined, as this assists in adjusting the hysteresis rate and frequency of scanning for intrinsic rhythm. In some situations, activating hysteresis may result in excessively slow pacing rates.

Beats paced at the shorter RR intervals are paced at the “lower rate”, while those paced at the longer RR intervals are paced at the “hysteresis rate”. The intrinsic beats between these two paced intervals are those beats with a rate slower than the lower pacing rate that followed an intrinsic beat but were permitted to depolarize the heart because hysteresis was activated. This operation can decrease right ventricular pacing, optimizing atrioventricular association.[6]

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CHAPTER 6

Electrophysiological mapping

Roberto Santilli, Manuela Perego, Weihow Hsue

INTRODUCTION

An electrophysiological study consists of a systematic analysis of rhythm disturbances by recording and measuring a variety of electrophysiological events with the dog in the basal state, and by evaluating the response to programmed electrical stimulation.[1]

Intracardiac electrophysiological studies have led to considerable advances in the understanding of canine cardiac arrhythmias. While most bradyarrhythmias can be diagnosed with a standard electrocardiogram in the dog and cat, during supraventricular tachycardia or ventricular tachycardia, P waves are often hidden in the QRS complex, ST segment, or T wave. Without an accurate identification of the P waves and of their correlation with the QRS-T complexes, it is often difficult to determine the underlying mechanism of the arrhythmia. Intracardiac recordings can magnify P waves, and atrial deflections that were previously obscured can be identified.[2–17]

An electrophysiological study is now considered the method of choice to analyze cardiac arrhythmias, recognize their origin and underlying mechanisms, and possibly cure them with radiofrequency catheter ablation. Since the early 2000s, several studies have reported the use of this technique in dogs with supraventricular and ventricular arrhythmias.[2–5,7–17]

TECHNIQUE

In dogs, electrophysiological investigations are performed under general anesthesia induced with propofol (4 mg/kg in a bolus intravenously [IV]) after preanesthetic medication with midazolam (0.2 mg/kg intramuscularly [IM]) and maintained with a mixture of isoflurane or sevoflurane (1–2%) and oxygen (100%). The animals are placed in right lateral recumbency. Antiarrhythmic drugs should be discontinued for at least 5 half-lives before the procedure.[4] For standard endocardial mapping, three multipolar electrode catheters are inserted percutaneously in the venous system using a modified Seldinger technique and under fluoroscopic and intracardiac electrocardiographic guidance. A decapolar catheter is inserted along the right external jugular vein into the coronary sinus (CS), a quadripolar catheter is inserted along the right femoral vein and positioned at the anterior tricuspid valve annulus to record the His bundle potentials, and an ablation catheter with a deflectable curve is inserted via the right or left femoral vein, depending on the animal's size, into the right atrium, right ventricle, or at the tricuspid valve annulus to perform atrial or ventricular programmed electrical stimulation and unipolar or bipolar endocardial mapping (Fig. 6.1).[4]

To map focal atrial tachycardias or typical and atypical atrial flutters, a second decapolar catheter is inserted into the right femoral vein and positioned along the right atrial lateral wall to record the potentials from the anterolateral aspect of the crista terminalis (high right atrium, HRA) with the proximal pair of electrodes, the mid-lateral right atrial (MRA) potentials with the middle pair, and the low posterolateral right atrial (LRA) potentials with the distal pair (Fig. 6.2).[7,8,12,15]

To map the left atrial chamber or pulmonary veins ostia in the absence of a patent foramen ovale, a transseptal puncture should be performed using the technique described here.[8] From the right femoral vein, under fluoroscopic guidance, a specially designed guidewire is first inserted into a transseptal Brockenbrough curved needle and pushed across the fossa ovalis into the left chamber. To locate the area, a rapid movement of the tip of the needle from the thicker muscular septum to the thin wall of the fossa ovalis is generally used. Marked tenting of the interatrial septum, which can be seen with transesophageal echocardiography, is then obtained and the septum is perforated using the transseptal wire. Transesophageal echocardiography and fluoroscopy are used to confirm that the guidewire is

in the left atrial lumen, and the Brockenbrough needle is pushed to perforate the septum. A contrast medium is then used for confirmation if necessary. An introducer is placed into the left atrium along the wire and used to move the mapping and ablation catheters (Fig. 6.3). Transseptal puncture using three-dimensional (3D) electroanatomical mapping has been also described.[18] A particular type of electrode catheter, composed by multiple electrodes positioned in a circular fashion, called Lasso catheter, is used to map the pulmonary vein ostia during ablation procedures.[8]

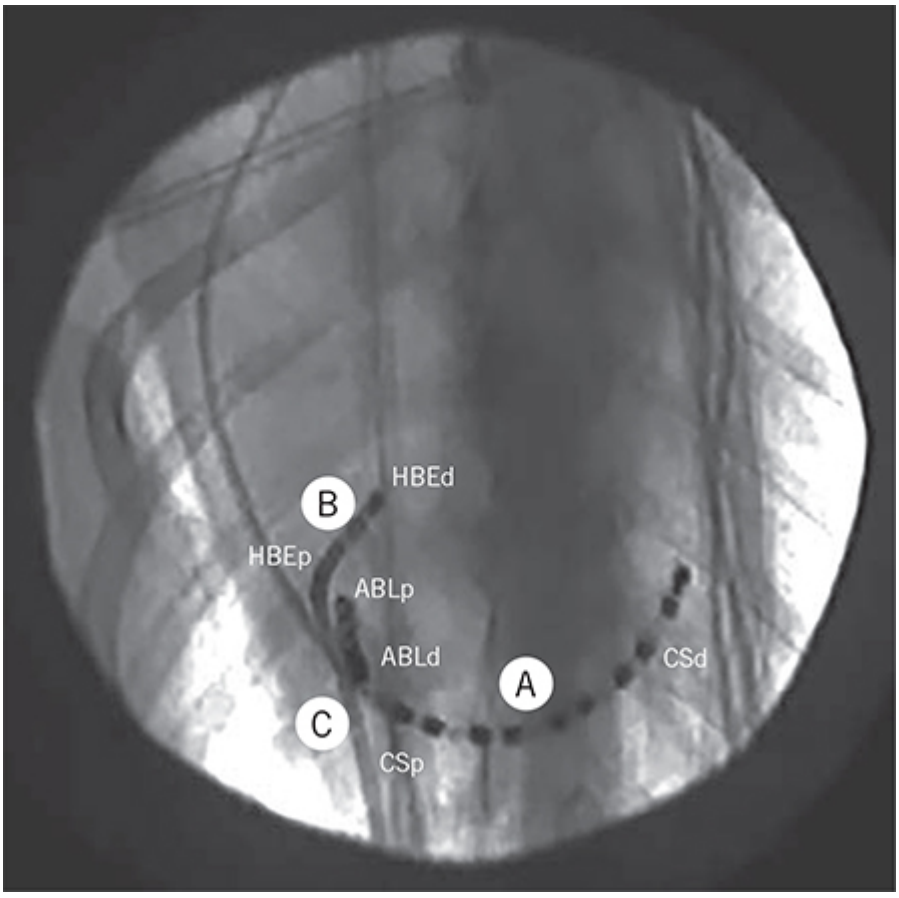


FIGURE 6.1. Dorsoventral fluoroscopic view showing the standard position of the electrodes to perform an electrophysiological study. A decapolar catheter (A) is introduced along the right jugular vein into the coronary sinus to record the left atrial potentials with the distal pair (CSd) and the coronary sinus ostium potentials with the proximal pair (CSp); a quadripolar catheter (B) is placed along the femoral vein at the anteroseptal aspect of the tricuspid valve annulus to record the His potentials (HBEp, HBEd); and an ablation catheter (C) is positioned via the femoral vein at the tricuspid valve annulus or in the right atrium or right ventricle (ABLp, ABLd).

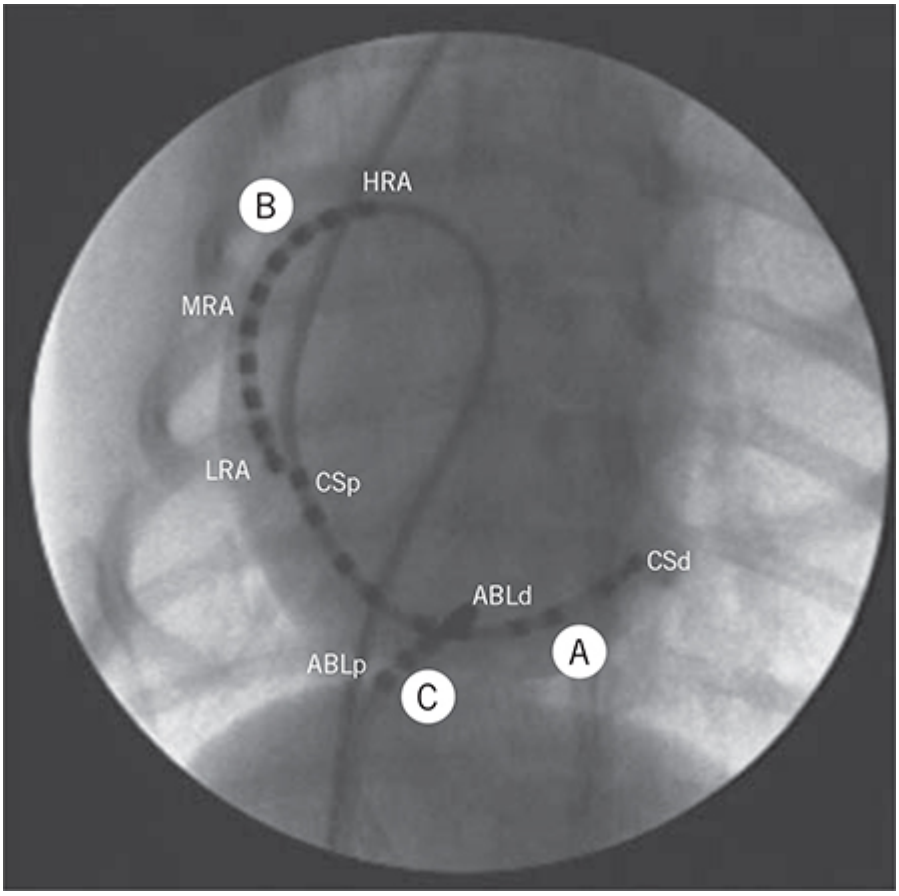


FIGURE 6.2. Dorsoventral fluoroscopic view showing the position of the electrodes to map atrial flutters or focal atrial tachycardias. A decapolar catheter (A) is introduced along the right jugular vein into the coronary sinus to record the left atrial potentials with the distal pair of electrodes (CSd) and the coronary sinus ostium potentials with the proximal pair (CSp); a second decapolar catheter (B) is introduced along the femoral vein and positioned along the right atrial lateral wall to record potentials form the anterolateral aspect of the crista terminalis (high right atrium, HRA) with the proximal pair of electrodes, the mid-lateral right atrial potentials (MRA) with the middle pair, and the low posterolateral right atrial potentials (LRA) with the distal pair; an ablation catheter (C) is placed along the femoral vein at different levels of the right atrium and tributary veins (ABLp, ABLd).

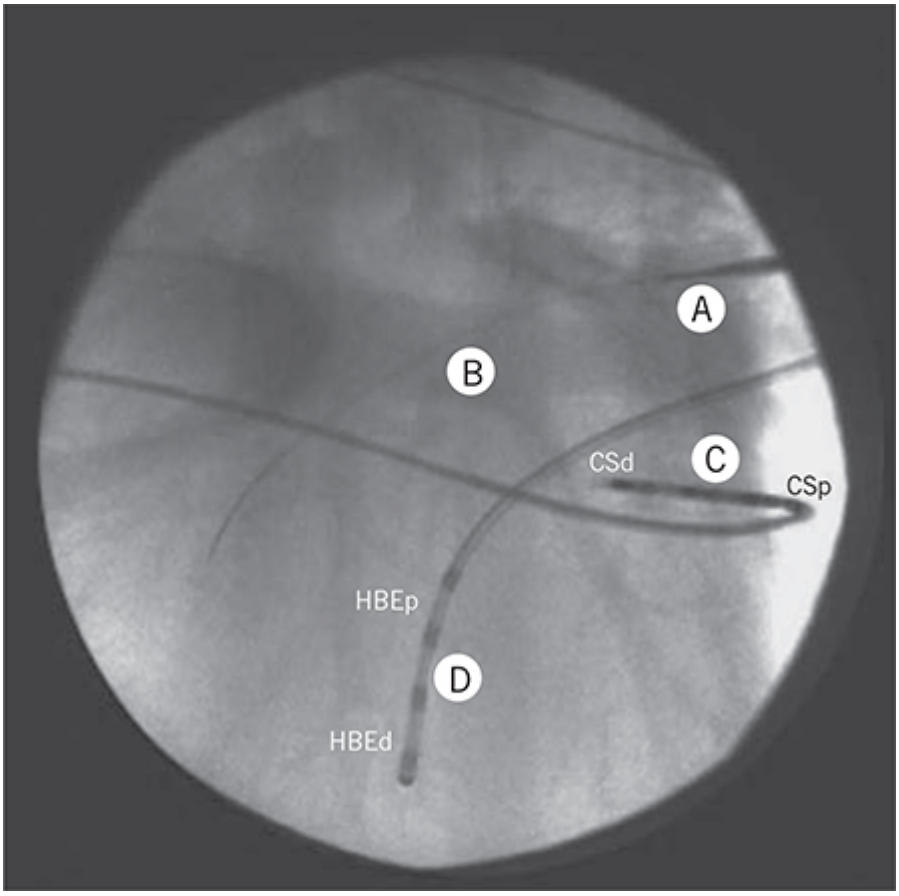


FIGURE 6.3. Right lateral fluoroscopic view during a transseptal puncture. From the right femoral vein under fluoroscopic and transesophageal echocardiographic guidance, a Brockenbrough curved needle (A) is placed at the fossa ovalis, and a specially designed wire (B) is pushed into the left atrium to allow positioning of a long introducer in the chamber. A decapolar catheter (C) is introduced along the right jugular vein into the coronary sinus to record the left atrial potentials with the distal pair of electrodes (CSd) and the coronary sinus ostium potentials with the proximal pair (CSp); a quadripolar catheter (D) is placed via the femoral vein at the anteroseptal aspect of the tricuspid valve annulus to record the His potentials (HBEp, HBEd).

To map ventricular tachycardias, both an endocardial approach, with the ablation catheter positioned in the right or left ventricular lumen, or a transpericardial epicardial approach can be used. With the latter technique, epicardial mapping is performed through an echoguided pericardial puncture by advancing an epidural introducer needle into the pericardial space. A contrast medium is then injected to verify the exact position of the needle tip before introducing a guidewire. Finally, an introducer sheath is placed over the wire to allow passage of the ablation catheter into the pericardial space to map the right and left ventricular epicardium (Fig. 6.4).[9]

Once all the intracardiac electrodes have been placed, surface and intracardiac electrocardiographic signals are displayed on a recorder at a paper speed of 150–300 mm/s. Intracardiac electrograms are recorded at filter settings of 50–500 Hz. Pacing is performed with stimuli that are twice the diastolic threshold and 2 ms in duration.

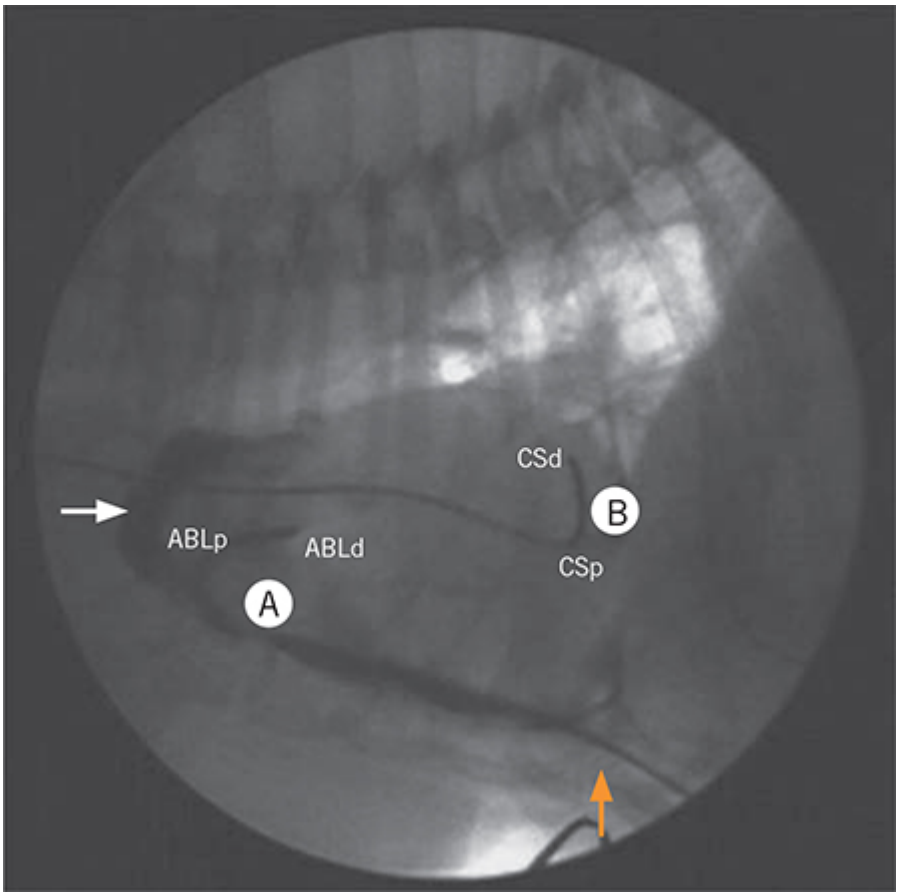


FIGURE 6.4. Right lateral fluoroscopic view during epicardial mapping of a right ventricular outflow tract aneurysm (white arrow) using a transpericardial approach in an English Bulldog with segmental arrhythmogenic right ventricular cardiomyopathy. Through an echoguided pericardial puncture, an epidural needle is introduced into the pericardial space (orange arrow). A contrast medium is then injected to verify the exact position of the needle. A guidewire is then positioned over the needle to allow passage of an ablation catheter that is used to perform mapping, pacing, and ablation of the epicardial side of the aneurysm (ABLp, ABLd) (A). A decapolar catheter (B) is introduced through the right jugular vein into the coronary sinus to record the left atrial potentials with the distal pair of electrodes (CSd) and the coronary sinus ostium potentials with the proximal pair (CSp).

BASAL ELECTROPHYSIOLOGICAL STUDY

Most measurements obtained in the basal state are performed with the animal in sinus rhythm and acquired using the electrocardiogram displayed by the catheter placed at the His bundle area. The His bundle electrogram (H) is recognized as a small biphasic or triphasic deflection between the atrial (A) and ventricular (V) electrograms (Fig. 6.5). The His bundle electrogram divides the PQ interval into three components defined as the PA, AH, and HV intervals. The PA interval is an approximate measurement of the intra-atrial conduction time from the area around the sinus node to the low right atrium. The AH interval is the conduction time from the low right atrium near the atrioventricular node to the His bundle. This interval is an approximation of the atrioventricular nodal conduction time. The HV interval measures the conduction time from the proximal His bundle to depolarization of the ventricular myocardium.

During the basal study, the conduction intervals (AH and HV), effective antegrade and retrograde refractory periods (ERPs), and Wenckebach point of the atrioventricular node are first obtained. Normal values have been described in 15 adult dogs before and after administration of atropine and propranolol (Table 6.1).[19] The antegrade and retrograde ERPs of the atrioventricular node can be measured using a programmed stimulation technique. A paced train of eight extra stimuli (S_1) are delivered with a current of 2 mA and a duration of 2 ms to the ventral septal right atrium for the antegrade ERP and to the right ventricular apex for the retrograde ERP. The S_1S_1 interval (or drive cycle length) set is slightly shorter than that of the native sinus rhythm, and after the eighth stimulus a premature extrastimulus (S_2) is introduced with a progressively shorter S_1-S_2 interval (from 300 to 180 ms), until S_2 is not conducted through the atrioventricular node. The ERP of the atrioventricular node is defined as the longest S_1-S_2 interval at which S_2 failed to reach the His Bundle (antegrade) or ventral right atrium (retrograde). Similarly to what is observed in human beings, 46% of dogs present ventriculoatrial conduction during the basal state, which is enhanced by high sympathetic tone (Fig. 6.6).[5,7,8] The antegrade and retrograde atrioventricular node Wenckebach points are obtained with incremental atrial and ventricular pacing, respectively. The pacing cycle length at which a second-degree atrioventricular or ventriculoatrial block occurs is considered the Wenckebach point (Fig. 6.7).

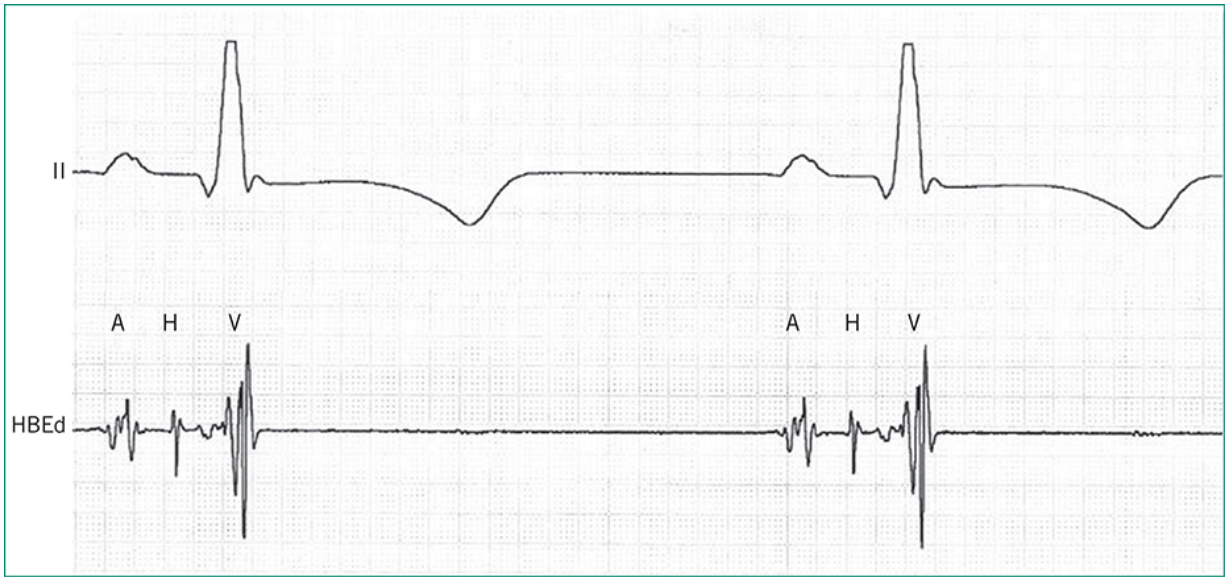


FIGURE 6.5. His bundle electrogram recorded by the distal pair of electrodes (HBEd) of the quadripolar catheter placed at the anteromedial portion of the ventricular side of the tricuspid valve annulus and its correlation with lead II of the surface electrocardiogram. Note the atrial potential (A), triphasic His potential (H) and ventricular potential (V). The His electrogram is useful to assess the atrial–His and His–ventricular conduction times. Speed, 150 mm/s; calibration, 22.8 mV/cm.

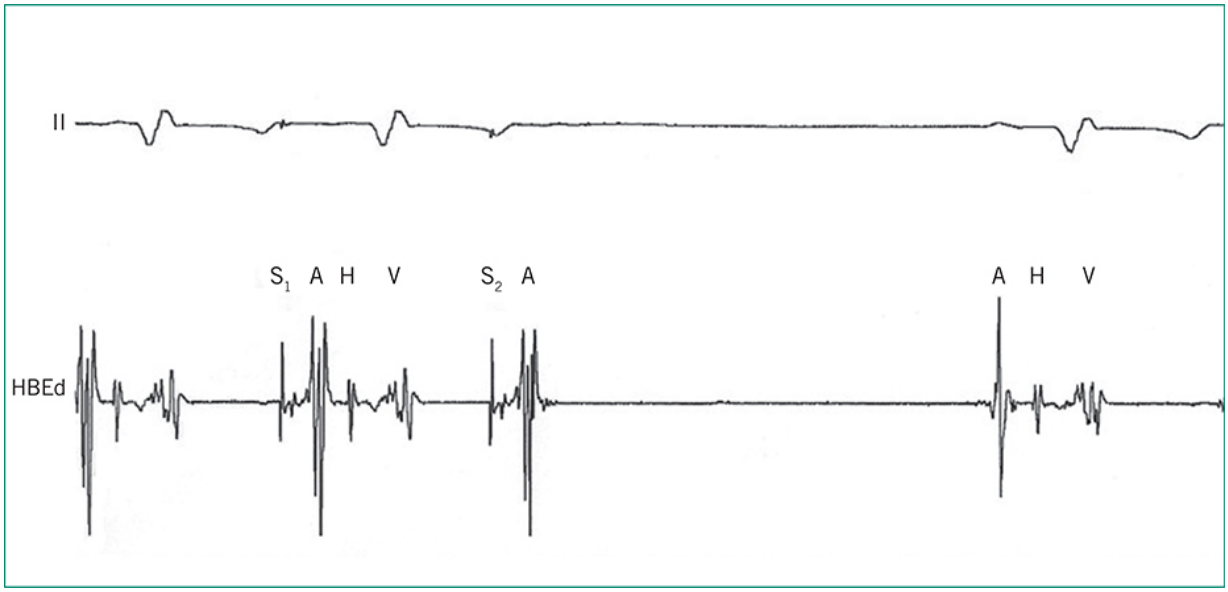


FIGURE 6.6. His bundle electrogram (HBEd) and simultaneous lead II recorded during programmed atrial stimulation to assess the antegrade atrioventricular node effective refractory period. After a train of eight paced stimuli (S_1) with a cycle length faster than the native rhythm that depolarizes the atria (A), the His bundle region (H), and the ventricle (V), an extrastimulus (S_2) is introduced that depolarizes only the atria and induces an atrioventricular block. The pacing cycle length at which the extrastimulus is not conducted to the ventricle is considered the effective refractory period. Speed, 100 mm/s; calibration, 22.8 mV/cm.

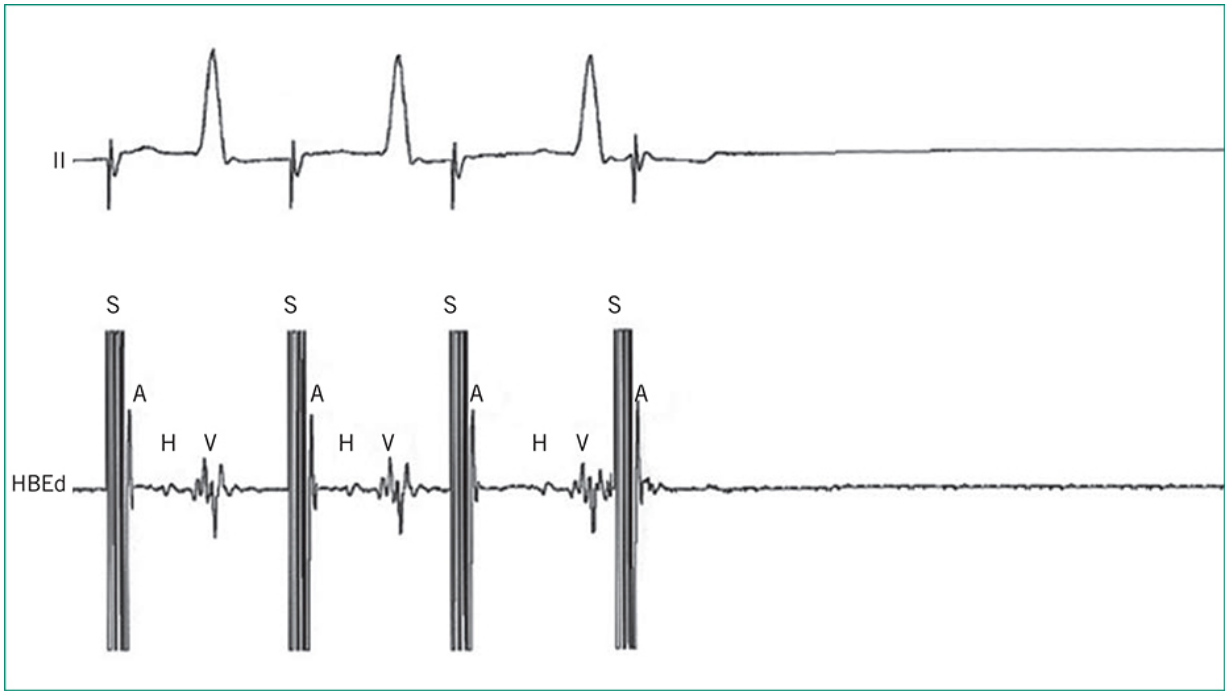


FIGURE 6.7. His bundle electrogram (HBEd) and simultaneous lead II recorded during incremental atrial pacing (S) to assess the antegrade atrioventricular node Wenckebach point. Pacing the atria with a progressive shorter cycle length (S followed by A, H, and V), a second-degree atrioventricular block is induced (S followed by A without V). The shortest cycle length at which atrial depolarization fails to reach the ventricle is considered the atrioventricular node Wenckebach point. Speed, 100 mm/s; calibration, 22.8 mV/cm.

TABLE 6.1. Electrophysiological measurements in the dog.[19]

Measurements	Baseline (range) ms
WP-A	230 (180–540)
ERP-A	190 (150–300)
WP-R	330 (280–510)
ERP-R	270 (220–470)
A-ERP	140 (110–210)
V-ERP	170 (150–240)
AH	76 (54–116)
HV	36 (30–44)

PA	16 (0–30)

WP-A, antegrade atrioventricular (AV) node Wenckebach point; ERP-A, antegrade AV node effective refractory period; WP-R retrograde AV node Wenckebach point; ERP-R, retrograde AV node effective refractory period; A-ERP, atrial effective refractory period; V-ERP, ventricular effective refractory period; AH, atrial–His interval; HV, His–ventricular interval; PA, P wave–atrial interval.

MAPPING SUPRAVENTRICULAR TACHYCARDIAS

Based on the underlying electrogenic mechanism, supraventricular tachycardias are classified into sinus tachyarrhythmia, focal atrial tachycardia, multifocal atrial tachycardia, macroreentrant atrial tachycardia or atrial flutter, atrioventricular nodal reciprocating tachycardia, atrioventricular reciprocating tachycardia, and focal and nonparoxysmal junctional tachycardia.[20,21] The electrocardiographic and electrophysiological features of focal atrial tachycardia, atrioventricular reciprocating tachycardia, macroreentrant atrial tachycardia, and focal junctional tachycardia have been described in the dog.[2–8,11,12,15–17]

To define the type of tachycardia during an electrophysiological study, the following pacing techniques should be used: programmed atrial stimulation with single or double extrastimuli, rapid incremental atrial pacing, atrial bursts, resetting, and entrainment.[2–5,7,8,10]

Programmed atrial stimulation is used to induce tachycardia and to study its location, type, and mechanism. Tachycardia induction is considered reproducible if initiated with the same S_1S_2 interval. Reentrant or nonautomatic tachycardias (e.g., microreentrant focal atrial tachycardia, orthodromic atrioventricular reciprocating tachycardia, or macroreentrant atrial tachycardia) can be initiated and terminated as soon as the S_1S_2 interval encounters the refractory period of one of the two limbs of the circuit. Automatic tachycardias (e.g., focal atrial tachycardia or focal junctional tachycardia), since there is no effect of programmed stimulation on initiation or termination of these arrhythmias, can be initiated with rapid atrial bursts (the atrium is paced with a very short cycle length of 200–250 ms using a train of 10–15 beats) or with isoproterenol hydrochloride (0.02–0.04 μg/kg/min IV in a constant rate infusion [CRI]).[8,10] If the suspected

mechanism for focal atrial tachycardia is early afterdepolarization, bradycardia can be induced with short-acting opioids (e.g., remifentanil, 10 μg/kg/hour IV CRI).[22]

Automatic focal atrial tachycardia can be differentiated from reentrant tachycardias such as orthodromic atrioventricular reciprocating tachycardia by first measuring the ventriculoatrial interval after cessation of overdrive atrial pacing. In cases of orthodromic atrioventricular reciprocating tachycardia, the ventriculoatrial interval is fixed, which confirms the presence of a predetermined anatomical circuit, while in cases of focal atrial tachycardia it is variable (more than 10 ms from baseline).[4,5,8]

Resetting corresponds to the interaction of a single extrastimulus with the tachycardia circuit resulting in a less than compensatory pause (S_1S_2 interval + pause = double of tachycardia cycle length). Resetting is used to prove that the accessory pathway is part of the supraventricular tachycardia circuit and to differentiate the types of atrioventricular nodal–dependent tachycardias (atrioventricular nodal reciprocating tachycardia from orthodromic atrioventricular reciprocating tachycardias). A single ventricular extrastimulus during tachycardia is given while the His bundle is refractory, looking for preexcitation of the atrium with an identical activation sequence or for tachycardia termination to testify the presence of an extranodal path for reaching the atria (Fig. 6.8).[2–5,11,14]

The entrainment technique is useful when studying anatomical reentry, as in the case of typical and atypical atrial flutters[7,12,15] or reentrant ventricular tachycardia[9]. Entrainment is defined as a stable conduction, which derives from the interaction of two rhythms. The degree of interaction depends on the distance between the site of stimulation and the circuit, the electrophysiological properties of tissues, and the presence of an excitable gap. Pacing the atrium or the ventricle with a cycle length shorter than the tachycardia cycle length accelerates the tachycardia with the same activation sequence and, as the activation sequence changes, a different degree of fusion of the wavefronts that will depend on the distance between the site of stimulation and the circuit. If the site of stimulation is within the circuit (e.g., the isthmus), no fusion appears (concealed entrainment). If there is apparent entrainment, the first postpacing interval can be used to assess the location of the tachycardia circuit. The length of this interval is proportional to this distance. Concealed entrainment with a first postpacing

interval shorter than 30 ms is crucial to identify the critical isthmus of atrial and ventricular anatomical reentry. The reported isthmuses in dogs include: the cavotricuspid isthmus, responsible for typical and reverse typical atrial flutter;[7] the right atrial free wall and interatrial septum, responsible for atypical atrial flutter[12] and cranial vena cava flutter;[15] and the right ventricular outflow tract in English Bulldogs with segmental arrhythmogenic right ventricular cardiomyopathy (Fig. 6.9).[9]

When the tachycardia is already present during mapping or once it is induced, the first step in the analysis of the arrhythmia is to measure the tachycardia cycle length. The mean atrial cycle lengths reported in dogs are 270 ± 38 ms for focal atrial tachycardia, 213 ± 30 ms for orthodromic atrioventricular reciprocating tachycardia, 260 ms for permanent junctional reciprocating tachycardia, 199 ± 57 ms for macroreentrant atrial tachycardias, and 420 ms (interquartile range [IQR], 32.5) for focal junctional tachycardia.[10,11,17]

The following step consists in the analysis of the sequence of atrial and ventricular activation during tachycardia and of the response to atrial and ventricular stimulation protocols. These parameters are crucial to define the type of tachycardia, its location, and the targets of ablation.

Focal atrial tachycardia is defined as an atrial activation that starts rhythmically from a small area (focus) and then spreads out centrifugally. Even though focal atrial tachycardias exhibit three different electrogenic mechanisms (abnormal automaticity, microreentry, and triggered activity), all of them are grouped in the same category. Endocardial mapping performed during focal atrial tachycardia allows localization of the site of origin of the tachycardia. The site of origin is defined as the site of earliest presystolic activity relative to the onset of the P wave during tachycardia (–39.9 ± 17.7 ms), where a sharp and negative unipolar recording with a QS pattern appears (Fig. 6.10).[8] Other tools to determine the location of atrial ectopic foci are mechanical interruption of the tachycardia by application of pressure to the area and the presence of fractionated, long-duration, low-amplitude electrograms. Fractionated potentials consist of three or more consecutive negative deflections with a low peak-to-peak amplitude (Fig. 6.10). In the dog, 57% of atrial potentials in the focus area are fractionated and 31% are low amplitude. Detailed endocardial mapping in a group of 16 dogs revealed 63% of those with focal atrial tachycardia had right-side foci

(crista terminalis, 41%; Koch's triangle, 25%; tricuspid valve annulus, 16 %; right interatrial septum, 9%; and right auricle, 9%) and 37% had focal atrial tachycardia arising from the pulmonary veins (right cranial pulmonary veins, 57%; left cranial pulmonary veins, 28%; right caudal pulmonary veins, 15%). Twelve percent of the dogs presented multiple ectopic foci.[8] During focal atrial tachycardias, endocardial mapping shows a significant portion of the cycle length with no recorded activity even when the entire right and left atrial chambers and the coronary sinus are recorded. In some cases, intra-atrial conduction disturbances prolong the atrial activation over a large portion of the cycle length, and conduction spread can follow a circular pattern. In these cases, entrainment of the tachycardia is used to differentiate reciprocating tachycardia from focal atrial tachycardia. After overdrive atrial pacing from the coronary sinus area during tachycardia, the presence of a variable (more than 10 ms from baseline) ventriculoatrial interval is considered diagnostic for focal atrial tachycardia.[4,5,23] In some cases, left atrial tachycardias arising from the right cranial pulmonary vein can be identified by mapping the high posterior right atrium. The analysis of double potentials in this area can help to establish the location of the ectopic foci. If the amplitude of the first potential is greater than that of the second potential, this indicates a right posterior atrial focus, while in the opposite case a right cranial pulmonary vein focus should be suspected.

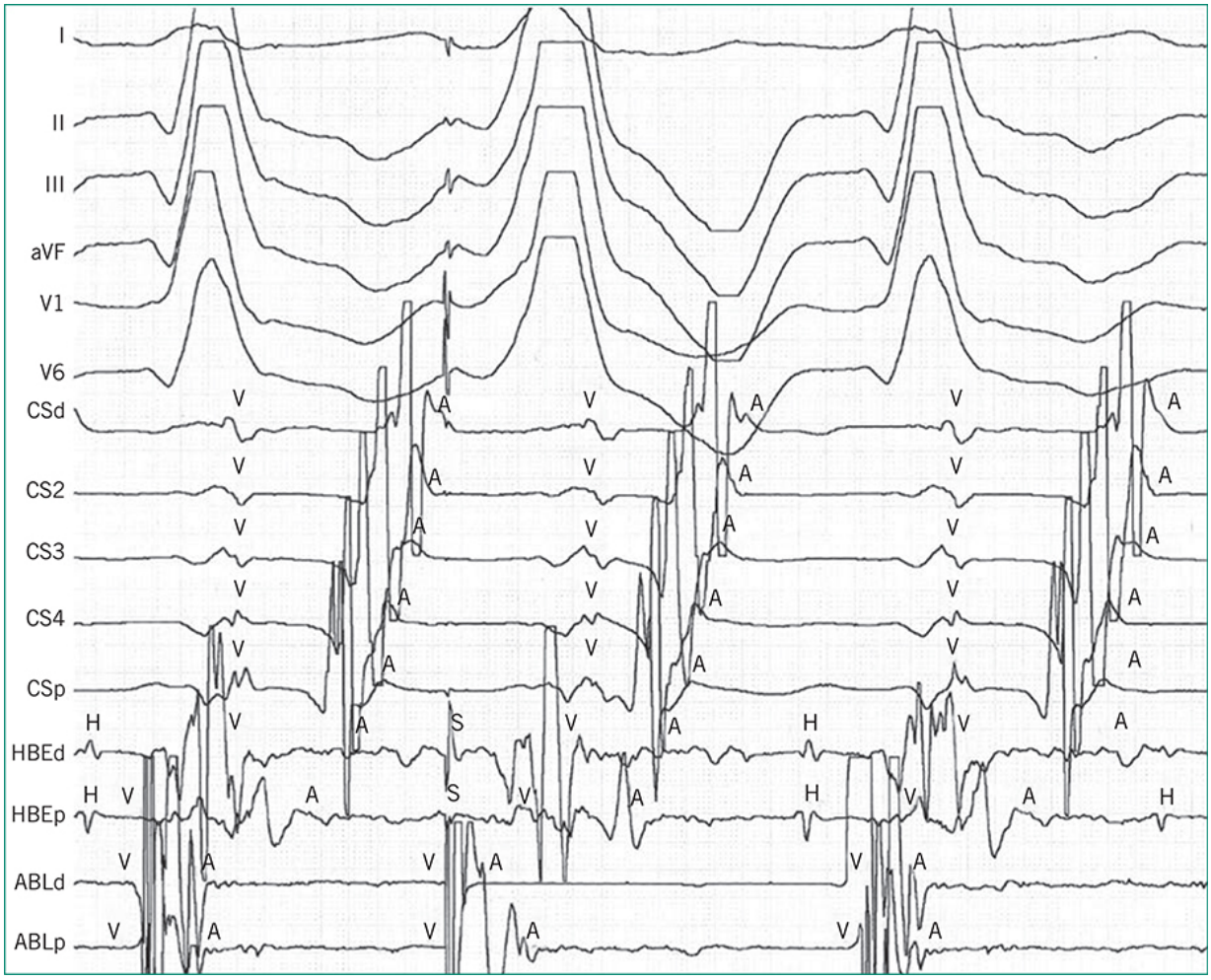


FIGURE 6.8. Tachycardia resetting to differentiate between the types of atrioventricular node–dependent circuits (e.g., atrioventricular nodal reciprocating tachycardia from orthodromic atrioventricular reciprocating tachycardia). The tracings include the six lead-surface electrocardiogram (I, II, III, aVF, V1, V6) and the intracardiac electrograms from the proximal (CSp) to the distal (CSd) coronary sinus, the proximal (HBEp) and distal (HBEd) His bundle, and the proximal and distal tips of the ablation catheter (ABLp, ABLd) placed at the atrial insertion of the accessory pathway. During tachycardia, a single ventricular extrastimulus (S) is given while the His bundle (H) is refractory (50 ms within the HH interval), looking for an acceleration of the tachycardia cycle length with an identical atrial (A) and ventricular (V) activation sequence or for tachycardia termination, to demonstrate the presence of an extranodal path for ventriculoatrial conduction. In this case, resetting occurs, which is diagnostic for orthodromic atrioventricular reciprocating tachycardia. Speed, 300 mm/s; calibration, 22.8 mV/cm.

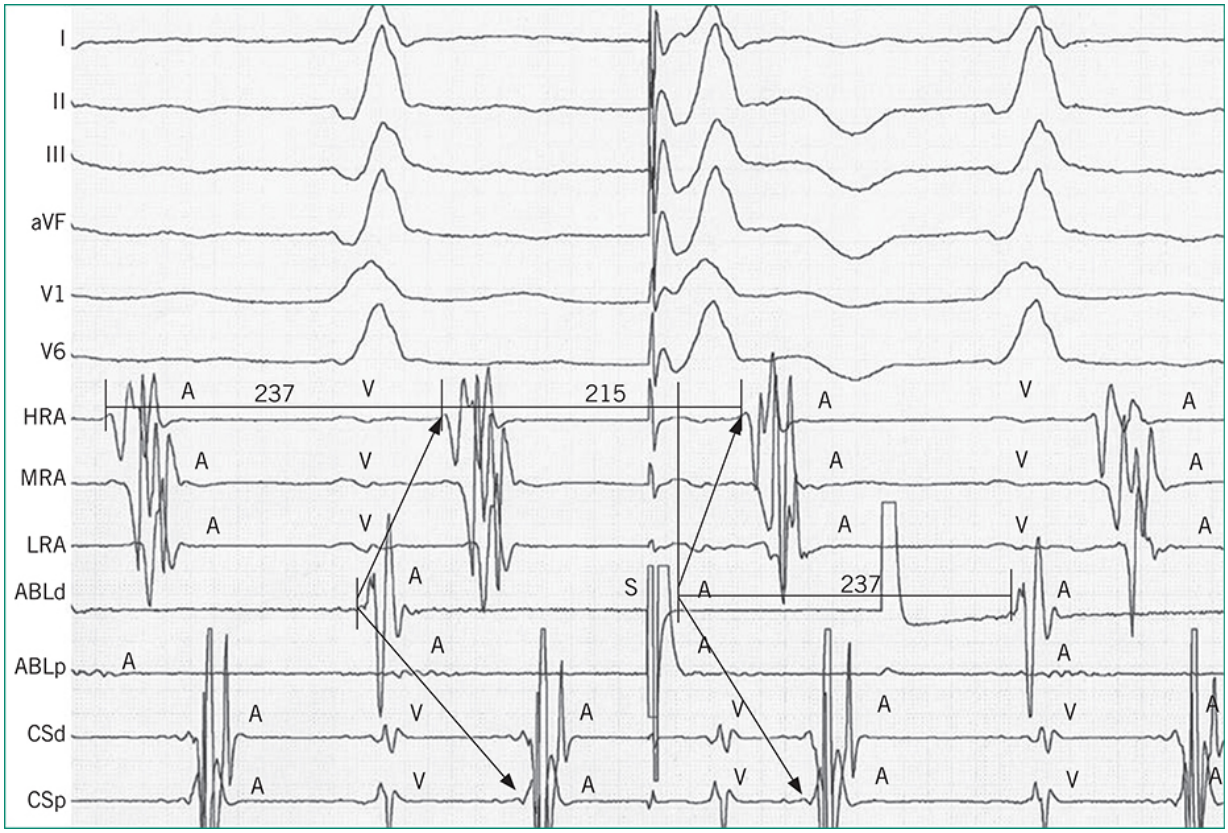


FIGURE 6.9. Concealed entrainment during right septal atrial flutter. The tracings include the six lead-surface electrocardiogram (I, II, III, aVF, V1, V6) and seven intracardiac electrograms from the high, medium, and low posterior right atrial wall (HRA, MRA, LRA), the distal and proximal portions of the right septal isthmus area (ABLd and ABLp), and the distal and proximal portions of the coronary sinus (CSd and CSp). Note the counterclockwise activation pattern moving from the isthmus area (ABLd), where mid-diastolic electrograms were recorded, to the HRA, MRA, LRA and CSd. The atrial cycle length during atrial flutter was 237 ms; an atrial extrastimulus (S) was introduced from the ABLd and accelerated the tachycardia cycle length (215 ms), with the same sequence of activation on intracardiac recording and no change of atrial morphology on the surface electrocardiogram. After pacing, the tachycardia cycle length returned to its original value. Speed, 300 mm/s; calibration, 22.8 mV/cm. From Santilli R. et al.,[12] with permission.

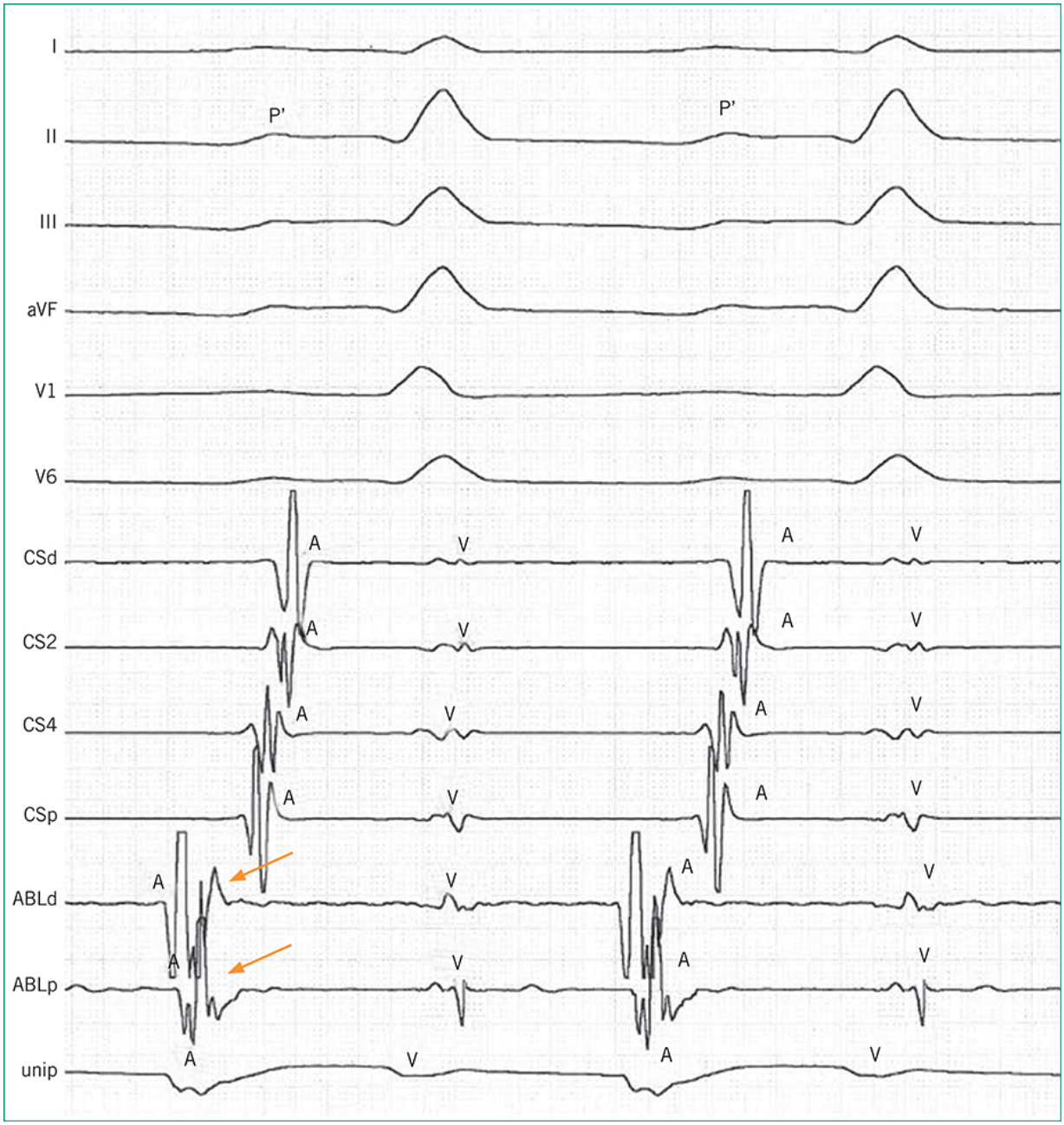


FIGURE 6.10. Endocardial mapping during focal atrial tachycardia arising from the crista terminalis. The tracings include: the six lead-surface electrocardiogram (I, II, III, aVF, V1, V6); seven intracardiac electrograms from the proximal (CSp) to the distal (CSd) coronary sinus and from the proximal and distal tips of the ablation catheter (ABLp, ABLd) placed at the ectopic focus; and the unipolar recording (unip). Note how the atrial potentials (A) recorded by the ablation catheter are fractionated (arrows) and presystolic (–43 ms) relative to the onset of the P' wave of the surface electrocardiogram, where a sharp and negative unipolar recording is observed. Speed, 300 mm/s; calibration, 22.8 mV/cm.

The anatomical distribution and electrophysiological properties of action potentials can be assessed with programmed atrial and ventricular

stimulation and the analysis of the sequence of activation during ventricular preexcitation of reciprocating tachycardia. Antegrade conduction is considered present in case of ventricular preexcitation (either abnormally short or negative HV interval) during normal sinus rhythm or during atrial pacing at progressively shorter cycle lengths (Fig. 6.11).[5,14,16,23] The presence of retrograde conduction along the accessory pathway is demonstrated by the evidence of eccentric ventriculoatrial activation during tachycardia or programmed ventricular stimulation.[2–5,11,14,23] Retrograde atrial activation during orthodromic atrioventricular reciprocating tachycardia starts at the atrial insertion of the accessory pathway. It could be defined as the point of earliest atrial activation of the bipolar signal, with a fusion of V and A and in some cases the presence between the two of a Kent signal (Fig. 6.12) (see p. 215). Except for anteroseptal bypass tracts, atrial retroactivation is eccentric and nondecremental with an all-or-none pattern of conduction.[5,23] Rarely, accessory pathways responsible for permanent junctional reciprocating tachycardia have decremental retrograde ventriculoatrial conduction. In these accessory pathways, a prolongation of the ventriculoatrial interval is observed during ventricular pacing with progressive shortening of the stimulation cycle length.[11,23] Concomitant unipolar recordings are used to optimize the accuracy of accessory pathway localization. A sharp and negative unipolar waveform indicates the exact site of impulse spreading.[5,23] Endocardial mapping in dogs has shown that most accessory pathways are right-sided, located near the coronary sinus ostium in the right posterior and posteromedial tricuspid valve annulus, and 73% have unidirectional retrograde activation with nondecremental properties.[5,14,23]

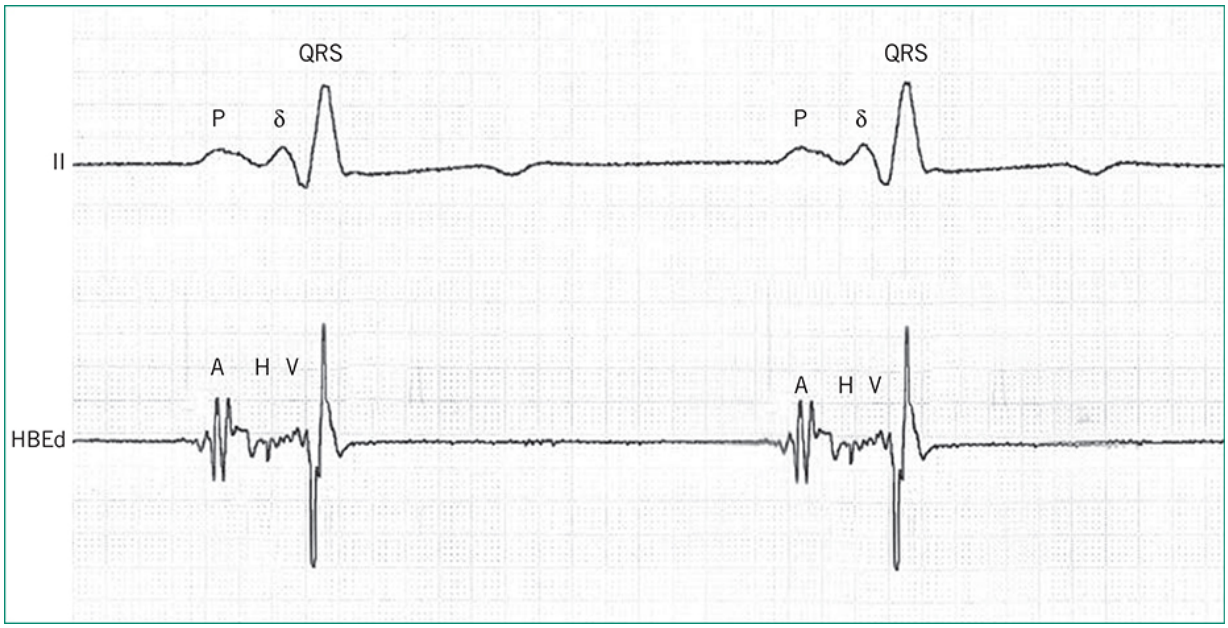


FIGURE 6.11. His bundle electrogram (HBEd) and surface lead II electrocardiogram during ventricular preexcitation. Notice the fusion of the His potential (H) with the ventricular potential (V), which confirms the presence of antegrade conduction along a posteroseptal accessory pathway. The atrial–His (AH) interval is normal. Speed, 150 mm/s; calibration, 22.8 mV/cm.

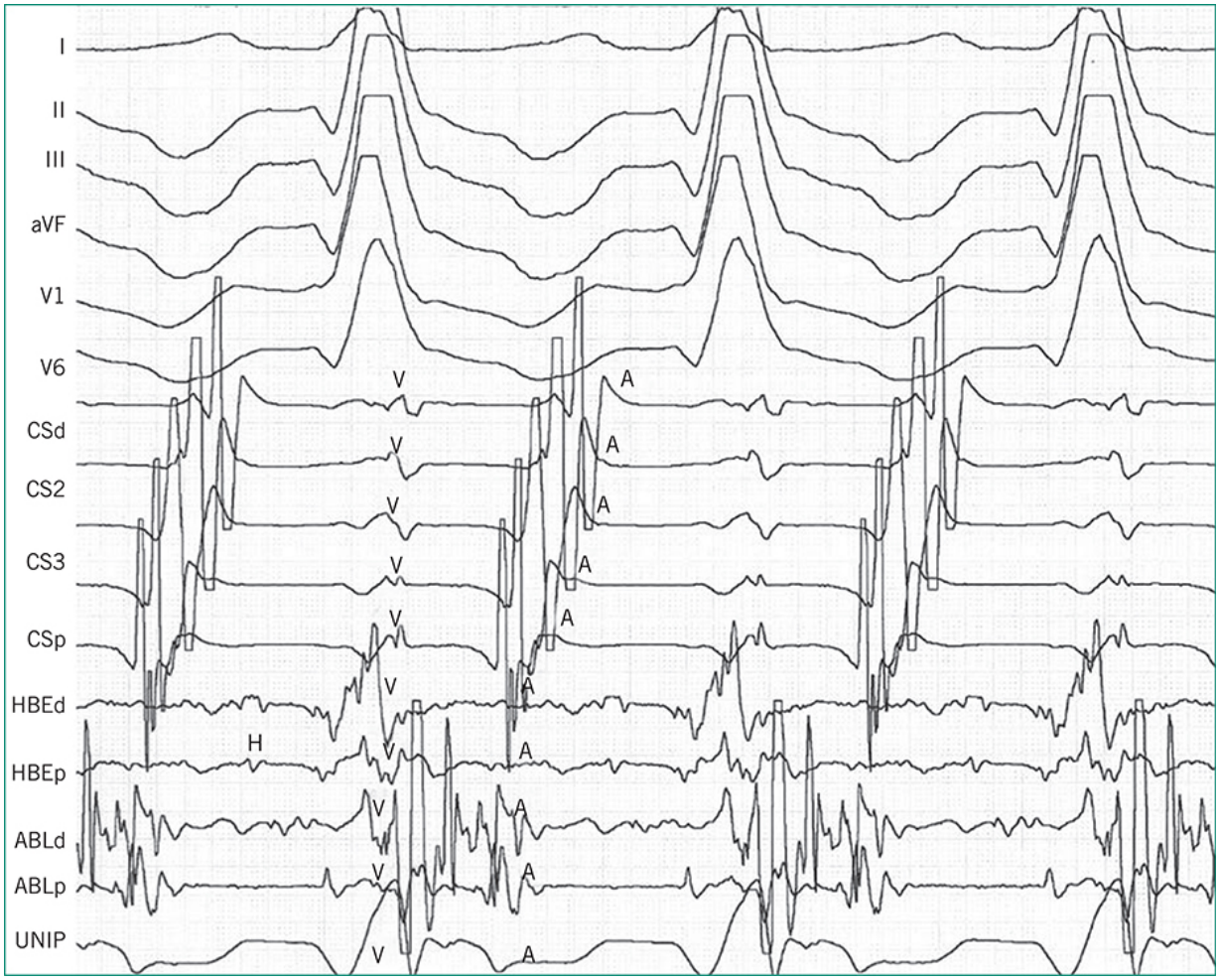


FIGURE 6.12. Endocardial mapping during orthodromic atrioventricular reciprocating tachycardia mediated by a right posterior accessory pathway. The tracings include: the six-lead surface electrocardiogram (I, II, III, aVF, V1, V6); ten intracardiac electrograms from the proximal (CSp) to the distal (CSd) coronary sinus, the proximal and distal His bundle (HBEp, HBEd), and the proximal and distal tips of the ablation catheter (ABLp, ABLd) placed at the atrial insertion of the accessory pathway in the ventricular side of the posterior tricuspid valve annulus; and the unipolar recording (UNIP). Note the sequence of atrial activation (A) from right to left, posterior to anterior, with the earliest site of depolarization at the distal ABLd located at the right posterior tricuspid valve annulus, where a sharp and negative unipolar recording is observed. Speed, 300 mm/s; calibration, 22.8 mV/cm.

Macroreentrant atrial tachycardias are reentrant activations around a large central obstacle (fixed or functional normal or abnormal structures, or a combination) in at least one of its dimensions. Atrial flutter is a macroreentrant atrial tachycardia characterized by an organized atrial rhythm.[20,21] Depending on the location of the protected isthmus (i.e., an area of slow conduction that is part of the anatomical circuit of the arrhythmia), atrial flutters are classified into typical and atypical. The most

common anatomical circuit for atrial flutter includes the cavotricuspid isthmus (CTI), an area of the low posterior right atrium bounded by the inferior vena cava and the Eustachian ridge posteriorly and the tricuspid valve annulus anteriorly.[7,20,21] Based on the rotation pattern around the tricuspid valve annulus, two forms of CTI-dependent atrial flutter have been identified: typical and reverse typical. During typical atrial flutter, the activation wavefront turns counterclockwise around the tricuspid valve annulus, while during reverse typical atrial flutter it turns clockwise (Fig. 6.13).[7] Three forms of atypical atrial flutter have been described in dogs, with the isthmus area located in the interatrial septum, the right atrial free wall, and the entrance of the cranial vena cava into the right atrium.[12,15] Macroreentrant atrial tachycardias are diagnosed based on the presence of entrainment with concealed fusion. Pacing at a site with presystolic activity or a mid-diastolic potential with a cycle length 10–20 ms faster than the atrial tachycardia should entrain a reentrant tachycardia to the pacing rate, without changing the morphology of atrial depolarization or the intracardiac electrogram sequence. The postpacing interval should be less than 30 ms (see Fig. 6.9).[7,12,15]

Focal junctional tachycardia is a rhythm disturbance typical of Labradors Retrievers, which arises from the His bundle area.[10] This arrhythmia is characterized by the presence of isorhythmic atrioventricular dissociation in 90.9% of affected dogs. During focal junctional tachycardia, the ventricles are depolarized starting from the His bundle area, while the atria are depolarized from the sinus node or retrogradely from the atrioventricular junction when the sinus rate falls below the ventricular rate. To diagnose focal junctional tachycardia, detailed endocardial mapping of the His bundle should be performed. The His potentials always precede the ventricular deflection with a normal HV interval (30–48 ms), which demonstrates antegrade conduction. Atrial depolarizations are usually unrelated to the His potentials, showing the classical features of isorhythmic atrioventricular dissociation, and arise from the high right atrium (Fig. 6.14). The AH interval can vary from positive to negative in cases of isorhythmic atrioventricular dissociation with type I synchronization, or it can be shorter than normal and fixed in cases of isorhythmic atrioventricular dissociation with type II synchronization.[10] In most cases, periods of focal junctional tachycardia with 1:1 ventriculoatrial

retroconduction can be recorded. In such a case, the atrial myocardium is activated in a concentric retrograde manner by the impulse originating from the His bundle area.[10]

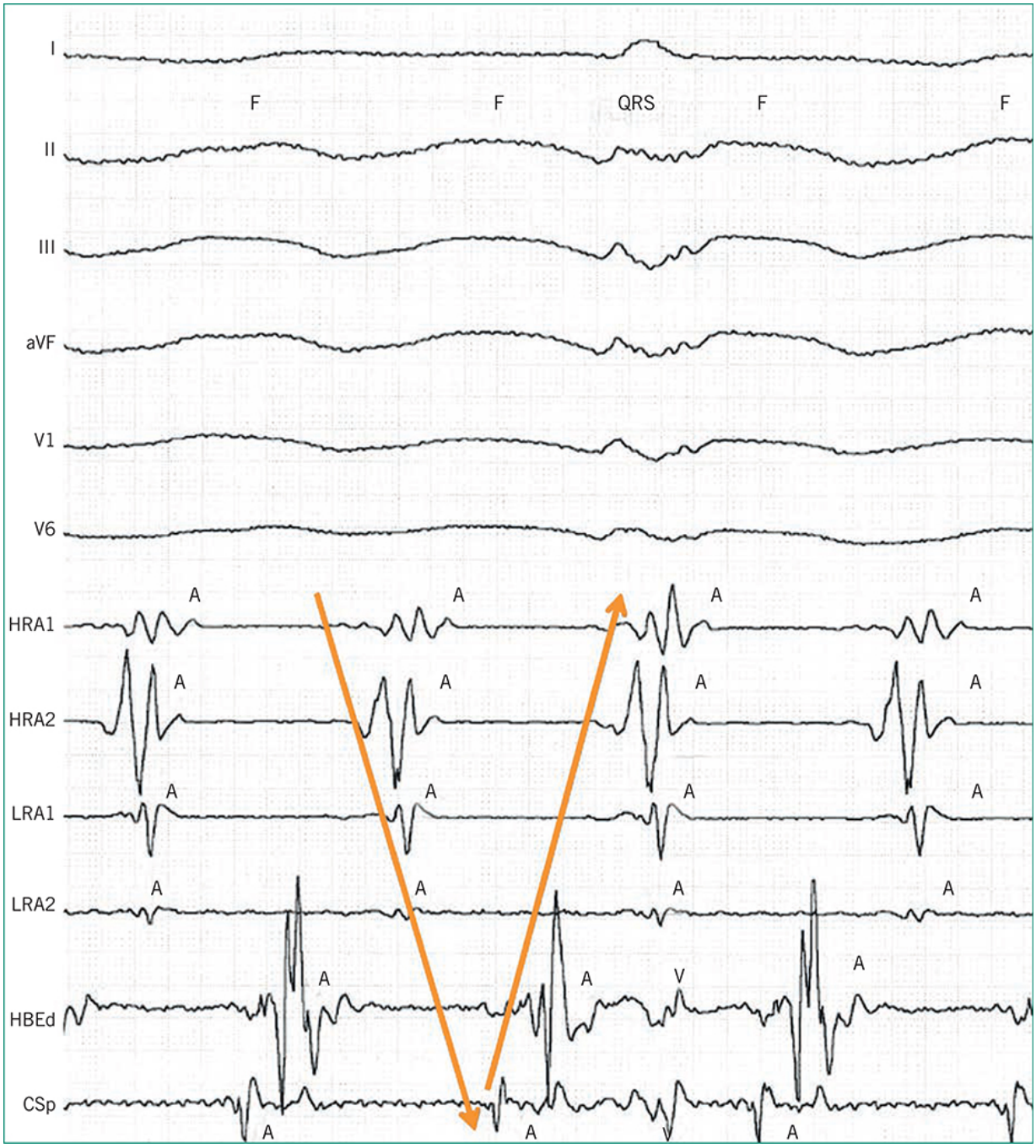


FIGURE 6.13. Endocardial mapping during typical atrial flutter. The tracings include the six lead-surface electrocardiogram (I, II, III, aVF, V1, V6) and six intracardiac electrograms from the high right atrial wall (HRA 1–2), low right atrial wall (LRA1–2), the distal His bundle (HBEd), and the proximal coronary sinus (CSp). Note the sequence of atrial activation (A) defined by the orange

arrows that rotate counterclockwise around the tricuspid valve annulus from the HRA, to the LRA, to the CSp, to the HBEd and back to the HRA. The cavotricuspid isthmus (the area of slow conduction of this anatomical circuit) is located between the LRA2 and the CSp. Speed, 300 mm/s; calibration, 22.8 mV/cm.

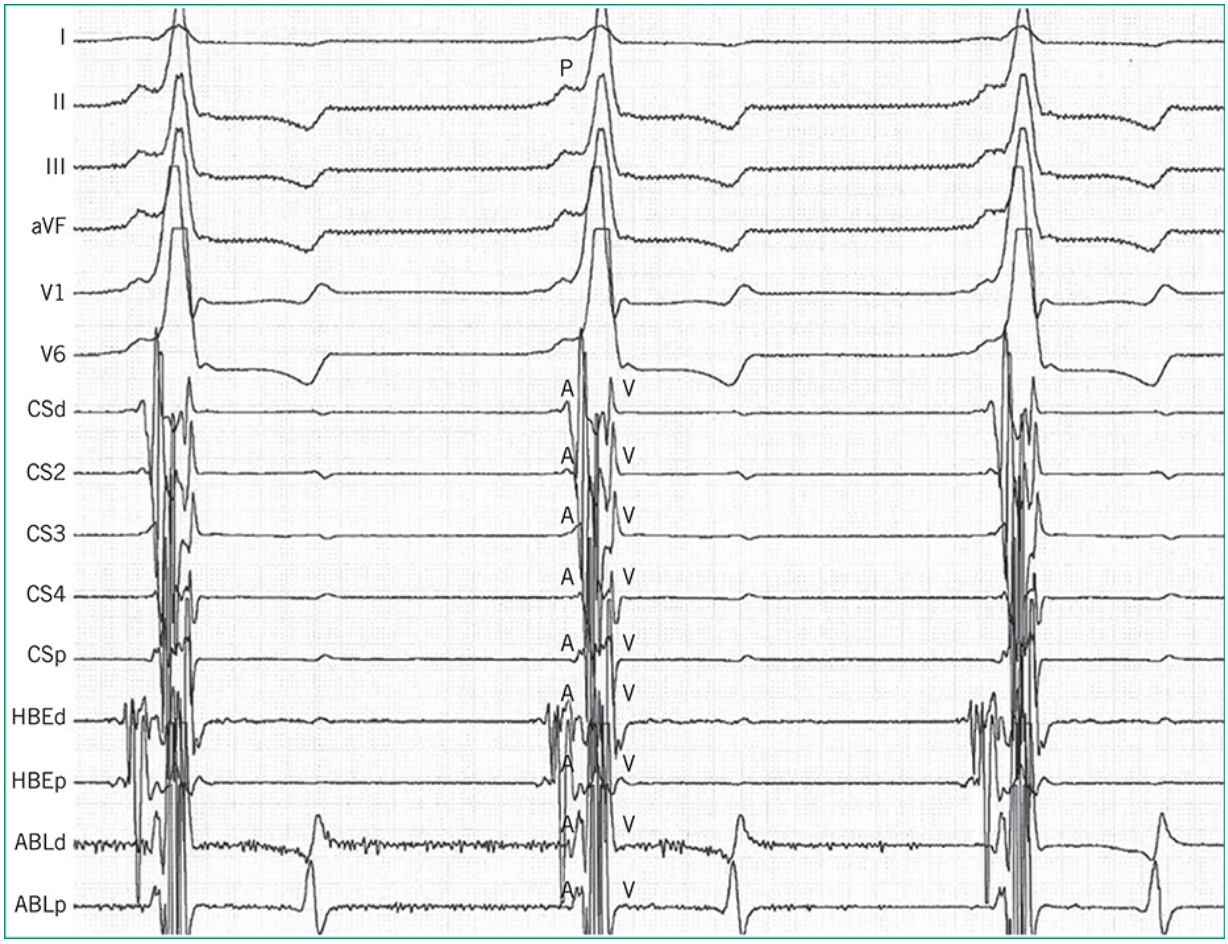


FIGURE 6.14. Endocardial mapping during focal junctional tachycardia with isorhythmic atrioventricular dissociation and type II synchronization. The tracings include the six lead-surface electrocardiogram (I, II, III, aVF, V1, V6) and nine intracardiac electrograms from the proximal (CSp) to the distal (CSd) coronary sinus, the proximal and distal His bundle (HBEp, HBEd), and the proximal and distal tips of the ablation catheter (ABLp, ABLd) placed at the ventricular side of the atrioventricular junction. Note the presence of almost simultaneous atrial (A) and ventricular (V) potentials coming respectively from the sinus node and the junctional area, which are dissociated but synchronized with almost the same discharging rate. Speed, 150 mm/s; calibration, 22.8 mV/cm.

MAPPING VENTRICULAR TACHYCARDIAS

In veterinary medicine, the indications for electrophysiological mapping in case of ventricular arrhythmias are limited to sustained monomorphic ventricular tachycardias or cases of frequent ventricular ectopic beats that

do not respond to antiarrhythmic treatment, especially if there is no obvious underlying heart disease.[9,24,25] The electrocardiographic and electrophysiological features of right ventricular outflow tract monomorphic ventricular tachycardias in the English Bulldog with arrhythmogenic cardiomyopathy were described in a 2009 study. Two different morphologies of wide QRS complex tachycardias (mean duration, 91.6 ± 9.83 ms) with a left bundle block morphology and inferior axis (81 ± 13.73°) and a mean ventricular cycle length of 240 ± 14.14 ms were reported. All tachycardias arose from a right ventricular outflow tract aneurysm and depending on the location of the circuit (caudal free wall and cranial septum), lead I and lead aVL had a different polarity.[9]

Mapping of the arrhythmic substrate in dogs with ventricular tachycardia and right ventricular outflow tract aneurysm can be performed with endocardial mapping or via a transpericardial approach on the epicardial side.[9] After evaluation of the atrioventricular and ventriculoatrial conduction times in the basal state, right ventricular programmed stimulation is started at the endocardial or epicardial side of the right ventricular outflow tract using a train of eight beats with a progressive shorter cycle length (from 300 ms until ventricular refractoriness is reached or ventricular tachycardia is induced) delivered with a 2 ms pulse width at twice the late diastolic threshold. The number of extra stimuli is limited to one or two for each pacing cycle length with a coupling interval from 240 to 180 ms. As soon as ventricular tachycardia is induced, the entrainment mapping technique is performed to characterize the presence of an anatomical reentry and locate the tachycardia circuit. Once a diastolic electrogram is found, to identify the critical isthmus area, overdrive pacing of the tachycardia with a cycle length 10–20 ms shorter than the tachycardia cycle length should be performed to obtain concealed entrainment with a first postpacing interval 30 ms shorter than ventricular tachycardia cycle length. In some cases, due to the diffuse damage of the endocardial and epicardial substrates, concealed entrainment can be obtained from a rather large area. In these cases, the finding of fractionated mid-diastolic potentials during sinus rhythm can help locate the critical isthmus (Fig. 6.15).[9,24]

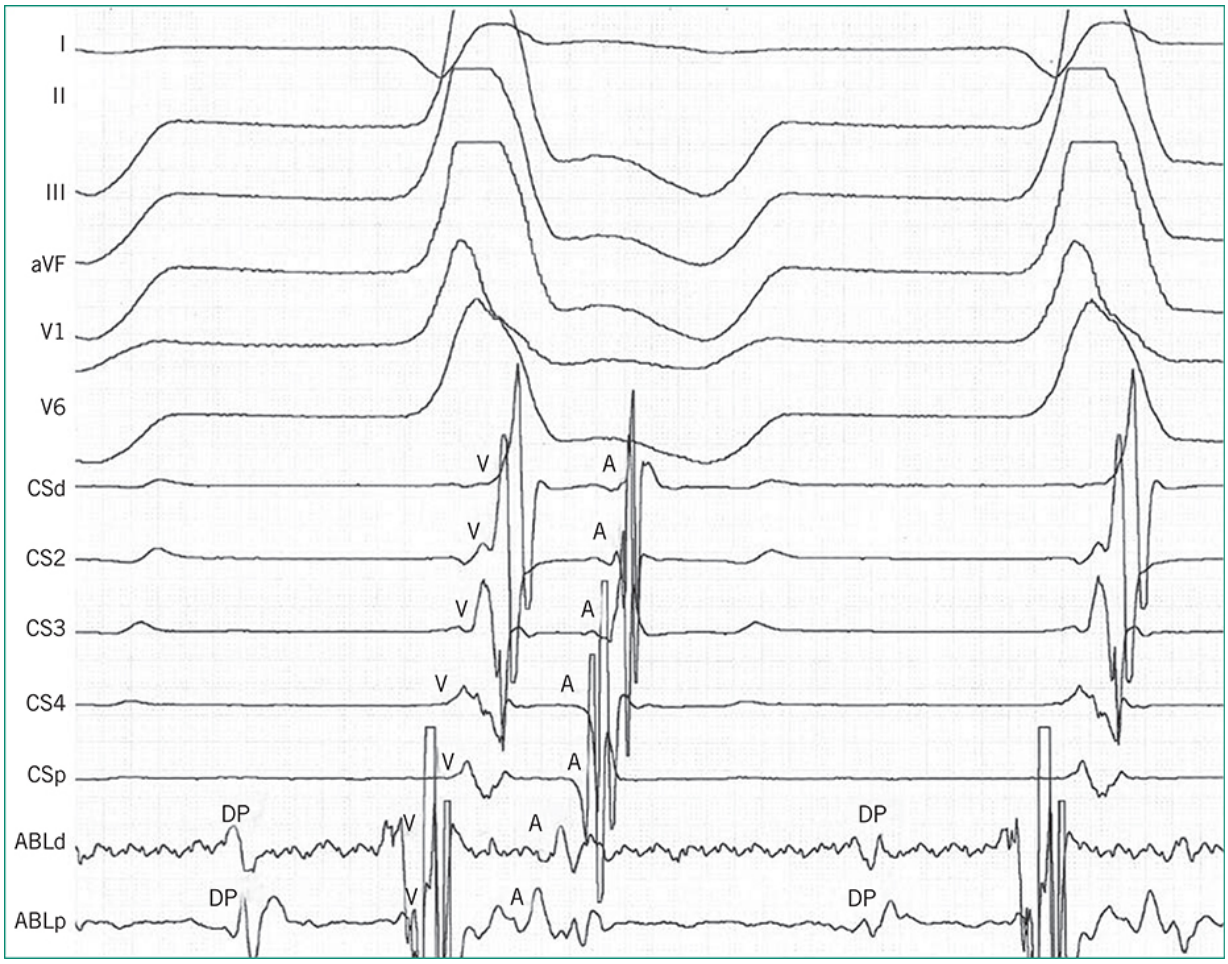


FIGURE 6.15. Endocardial mapping during ventricular tachycardia in an English Bulldog with segmental arrhythmogenic cardiomyopathy. The tracings include the six lead-surface electrocardiogram (I, II, III, aVF, V1, V6) and seven intracardiac electrograms from the proximal (CSp) to the distal (CSd) coronary sinus and the proximal and distal tips of the ablation catheter (ABLp, ABLd) placed at the epicardial side of the right ventricular outflow tract aneurysm. Note the presence of mid-diastolic potentials (DP) characteristic of isthmus sites with slow conduction. The ventricular (V) and atrial (A) potentials are dissociated. Speed, 300 mm/s; calibration, 22.8 mV/cm.

3D ELECTROANATOMICAL MAPPING

3D electroanatomical mapping enhances the visualization of the spatial distribution of localized electrical potentials of the heart by:

1. Facilitating nonfluoroscopic real-time visualization of intracardiac catheters on a 3D anatomical model.
2. Displaying electrophysiological data, such as activation sequences and voltages, in an intuitive color-coded manner.

The model is constructed by aggregating the information from the electrodes placed in the outermost locations to outline the endocardial surface of a chamber. Images from intracardiac echocardiography, computed tomography, and magnetic resonance imaging can also be integrated for more comprehensive anatomical displays (Fig. 6.16).[26] This section will discuss the major electroanatomical mapping systems, examine the main electroanatomical maps (activation maps, voltage maps, and pace maps), and review the current clinical experience. Although entrainment mapping is also performed to delineate reentrant tachyarrhythmias, the sites of interest are typically annotated onto activation maps.

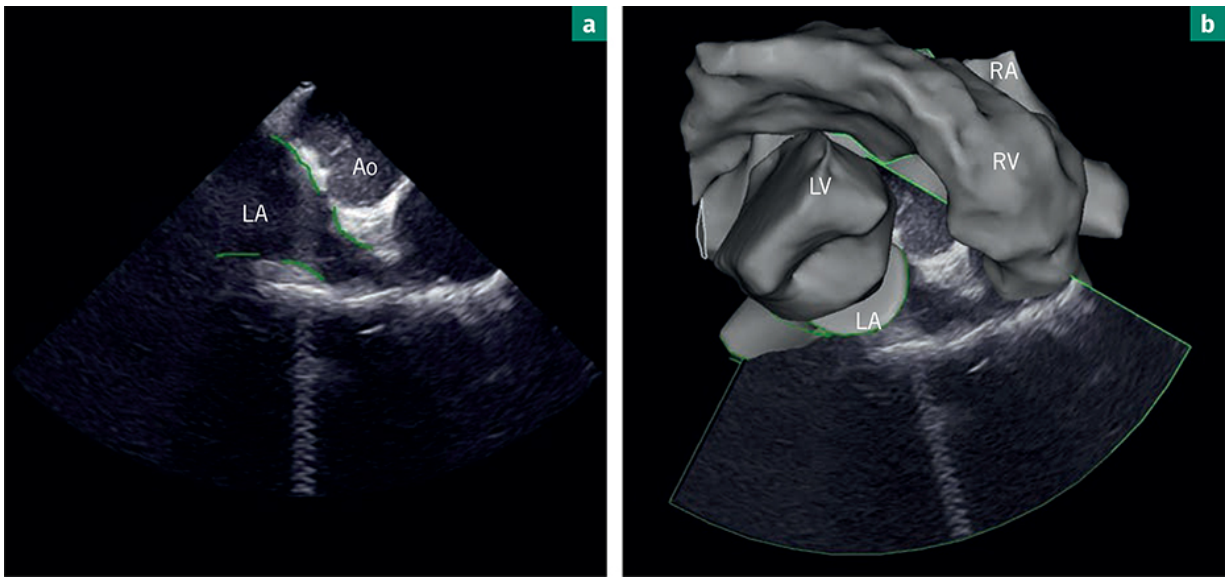


FIGURE 6.16. Integration of intracardiac echocardiography into electroanatomical mapping to construct anatomical shells. a) A SoundStar (Biosense Webster) intracardiac echocardiographic (ICE) catheter is placed in the right atrium and a view of the heart base is obtained. The SoundStar catheter is integrated with both the echocardiographic machine (Vivid IQ, GE Healthcare) and CARTO 3 system (Biosense Webster) via the CARTOSound module. The aorta and aortic valve cusps are visible, and the left atrium is traced using the CARTOSound module. b) The same ICE image is superimposed onto various anatomical shells of the heart. The heart is viewed from an inferior to superior perspective to show the same orientation as the ICE image. The CartoSound module is in the process of constructing the left atrium shell using multiple similar ICE images. One advantage of this is the ability to construct an anatomical shell without requiring a catheter to move throughout (or even be in) the cavity of interest. LA, left atrium; Ao, aorta; RA, right atrium; LV, left ventricle; RV, right ventricle.

All current commercially available electroanatomical mapping systems utilize a hybrid of magnetic- and impedance-based localization technologies with less than a 1 mm margin of error.[26] The CARTO 3 system (Biosense

Webster, Diamond Bar, California) consists of a location pad (containing three low-level magnetic-field-emitting coils arranged as a triangle) positioned under the patient table and six electrode patches placed around the thorax (Fig. 6.17a). The magnetic field strength of each coil is measured by a location sensor embedded in the tip of a specialized mapping catheter. By converting the measured strength to a distance from each coil, the catheter position can be triangulated and displayed in a three-dimensional space. Additionally, the system sends a distinct current across the electrodes on the mapping catheters, which is detected by each of the electrode patches. This impedance-based modality augments the accuracy of magnetic localization and enables respiratory motion compensation. EnSite X (Abbott, Chicago, Illinois) is the latest electroanatomical mapping platform that will soon replace its predecessor, EnSite Precision. The EnSite Precision platform primarily employs impedance-based localization, with the mapping catheter sensing electrical fields generated by three pairs of skin patches (placed on the sides of the patient for the x-axis, on the chest and back for the y-axis, and the back of the neck and inner left thigh for the z-axis), and a system reference patch. A magnetic field frame and two additional sensors can be added to incorporate magnetic-based tracking, with the EnSite X continuing to utilize both technologies. For Rhythmia HDx (Boston Scientific, Cambridge, Massachusetts), the magnetic tracking feature requires a magnetic field generator under the patient's table and a back patch with an embedded sensor coil; the impedance field is generated by the back patch, patches for the electrocardiographic limb leads, and the V1, V3, and V6 chest leads. All systems also offer unique high-density mapping catheters, with smaller electrodes and interelectrode distances that permit visualization of critical diminutive amplitude signals, and automated annotation methods for rapid creation of high-resolution maps (Fig. 6.17b).[26]

Activation mapping displays electrical activation sequences across the anatomical models. Local tissue depolarization correlates best with the steepest negative slope of the unipolar intracardiac electrogram and the first sharp peak of the bipolar intracardiac electrogram recorded by the mapping catheter tip.[26] The time difference between these features and a fixed reference (t = 0 ms) represents the local activation time; the reference can be chosen from a surface electrocardiographic feature or a consistent intracardiac electrogram obtained, for example, from a decapolar catheter

positioned in the coronary sinus. The electroanatomical mapping system can then graphically represent all the local activation times with a static color-coded map or a dynamic video portraying a moving wavefront.[27] A focal tachyarrhythmia spreads centrifugally from a circumscribed site of early activation, and ablation is targeted to the site of earliest activation (Fig. 6.18). In contrast, a macroreentrant tachyarrhythmia propagates around anatomical or conduction barriers that encompass the entire cycle length; ablation is then targeted to a vulnerable isthmus within the circuit (Fig. 6.19). However, one significant limitation of activation mapping is that it requires a sustained, hemodynamically tolerable tachyarrhythmia with a stable cycle length and morphology, which is especially challenging with rapid ventricular tachycardia.

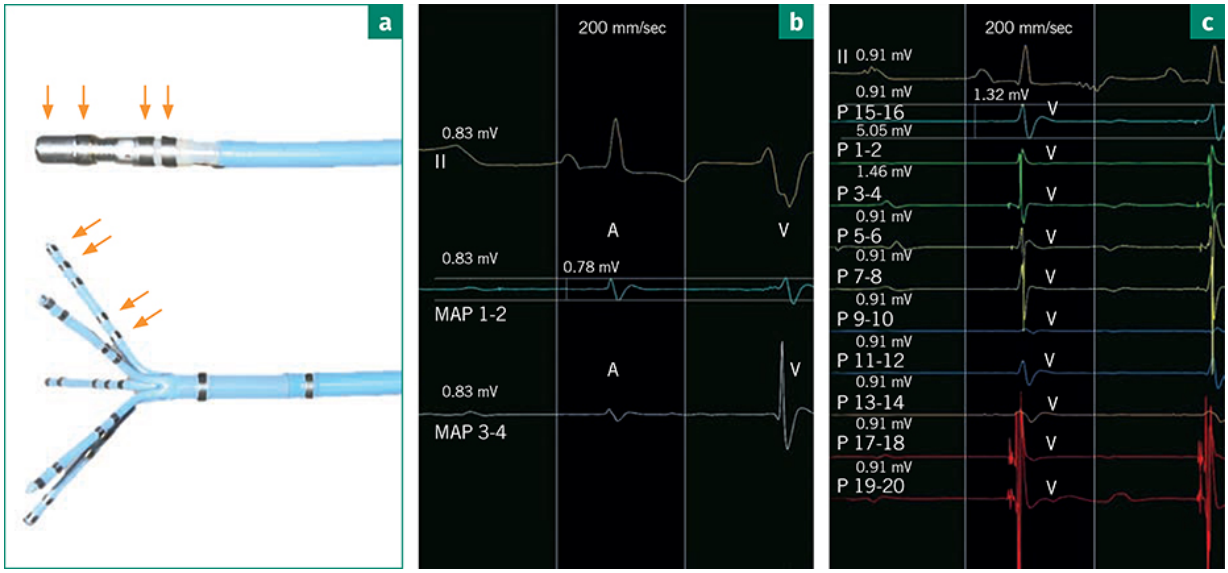


FIGURE 6.17. Point-by-point versus high density mapping. a) A point-by-point quadripolar mapping/ablation catheter (top; Thermocool Smarttouch Surroundflow) and a high-density multielectrode mapping catheter (bottom; Pentaray) associated with the CARTO 3 system are shown. The arrows point to various electrodes. The Pentaray has 20 electrodes spread over 5 splines (4 electrodes per spline). Note the smaller electrodes and interelectrode distances on the Pentaray. Although they are not shown here, grid and basket conformations are available for the EnSite and Rhythmia multielectrode catheters. b) Intracardiac electrograms obtained during sinus rhythm with intermittent ventricular premature complexes using the Thermocool catheter. The top tracing corresponds to lead II. The following tracings were obtained from the distal and proximal electrode pairs (MAP 1-2 and MAP 3-4, respectively) of the Thermocool catheter. Voltage scales are provided for each lead. Despite appropriate contact force (9 grams), the electrogram voltage in MAP 1-2 is reduced at 0.78 mV. c) Ten pairs of intracardiac electrograms obtained using the Pentaray catheter, with P 15-16 acquired at the same location as MAP 1-2 in image b). The Pentaray configuration enables visualization of a higher bipolar voltage amplitude (1.32 mV) and shorter electrogram duration than that of MAP 1-2 in b), facilitating more accurate annotation especially if there is

fractionation (not shown here). Additionally, many more electrograms can be acquired with one heartbeat for rapid mapping.

Because tachyarrhythmias associated with cardiomyopathies, especially ventricular tachycardia, are often caused by reentry in areas of patchy scar or at scar borders (where anisotropic conduction and unidirectional block frequently occur), substrate mapping aims to detect indicators of abnormal signal propagation and scar tissue during sinus rhythm. This may involve identification of late or split potentials, but it typically places emphasis on voltage mapping (Fig. 6.19).[24] Because scar tissue is electrically inert and does not have a voltage, admixtures of fibrosis and surviving tissue will be reflected as areas with very low voltages representing areas of dense scar. The standard voltage thresholds, derived from porcine models and humans with healthy hearts, are <0.5 mV for dense scar and 0.5–1.5 mV for the border zone.[26] In the atria, bipolar amplitudes of 0.2–0.45 mV correlated with scar in people who had undergone prior atrial fibrillation ablation. The advantage of this approach is that it can be performed during sinus rhythm (without potentially unstable sustained tachyarrhythmias). However, the main limitations of this technique include undetermined cutoffs in dogs and that not all scar tissue is necessarily involved in arrhythmogenesis (and vice versa). Moreover, various other factors can influence electrogram voltages, including conduction velocity, fiber orientation and curvature, direction of the propagating wavefront, tissue contact, and characteristics of the recording catheter.

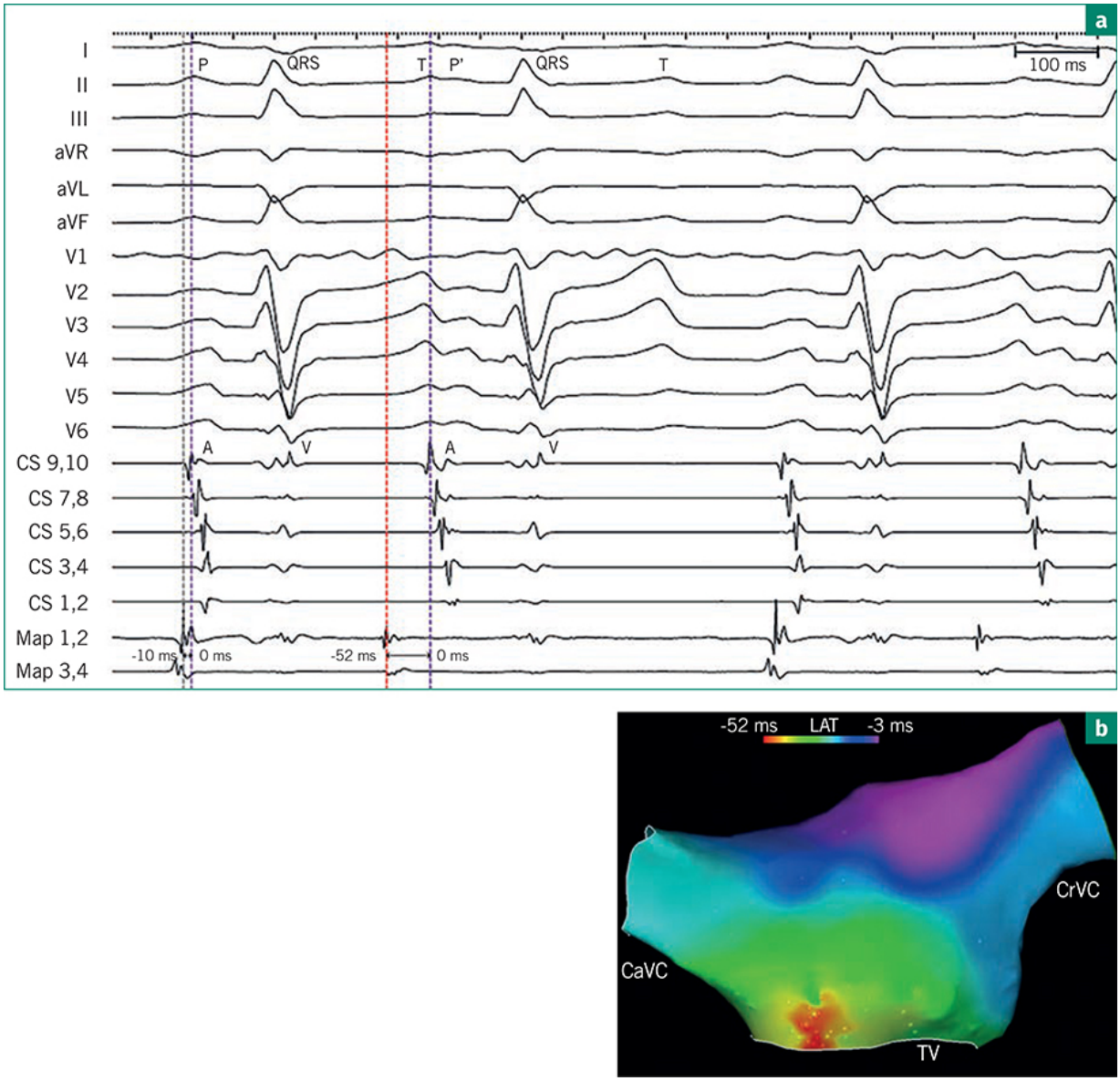


FIGURE 6.18. Creating a three-dimensional activation map of a focal atrial tachycardia. a) This panel shows a twelve-lead surface electrocardiogram and intracardiac bipolar electrograms from a decapolar catheter secured in the coronary sinus (CS 1,2; CS 3,4; etc.) and a quadripolar mapping catheter (Map 1,2 and Map 3,4) placed at the posterolateral aspect of the tricuspid annulus in the right atrium. The surface electrocardiogram demonstrates atrial bigeminy, with the P, QRS, and T waves of the first sinus complex and the P', QRS, and T waves of the subsequent atrial premature complex labeled in lead II. The A and V waves of the intracardiac electrograms are highlighted in CS 9,10. The reference time (t = 0 ms) is shown with the purple dotted line positioned over the maximum positive peak at CS 9,10. The local activation time (LAT) for the sinus complex corresponds to the distance between the gray and purple lines (LAT = –10 ms), while the LAT for the atrial premature complex corresponds to the distance between the red and purple lines (LAT = –52 ms). The location is associated with late activation during sinus rhythm but early activation during the ectopic rhythm. Sweep speed = 200 mm/s; the amplitudes of each lead have been individually modified to maximize their visualization. b) Right atrium seen from the right lateral aspect; the borders of the cranial vena cava (CrVC), caudal vena cava (CaVC), and tricuspid valve (TV) orifice

are shown. Each individual point signifies the local activation time (LAT) of an intracardiac electrogram, color-coded from red (≤ –52 ms) to purple (≥ –3 ms). There is evidence of centrifugal activation from the posterolateral aspect of the right atrium bordering the tricuspid valve annulus. After ruling out atrioventricular accessory pathways, this was interpreted as focal atrial tachycardia. From Hsue et al.,[27] with permission.

Pace mapping is an alternative modality that also does not require inducible tachyarrhythmias. It involves stimulating different endocardial sites in an attempt to reproduce the surface electrocardiographic features of the clinical tachyarrhythmia. Because the percent match between the paced and spontaneous morphologies is inversely correlated with the distance between the paced site and the site of origin of the focal arrhythmia, a perfect match suggests that the paced site is the ideal ablation target. This approach is primarily applied in ventricular tachycardia rather than in atrial tachycardia, as analyzing P' wave morphologies is more challenging. Computerized algorithms (e.g., the PASO module on CARTO) facilitate quantification of the concordance between paced and spontaneous ventricular ectopic morphologies and the generation of "pace maps" with precise spatial localization (Fig. 6.20).[25] However, it is crucial to recognize that matching of the QRS morphologies may be affected by the pacing settings and structural substrate. For example, high pacing outputs may capture both the "near" and "far" myocardium, altering the QRS morphology; the lowest possible output is thus advised. It is also recommended to pace at the ventricular tachycardia cycle length, as different rates may alter functional conduction and block. Additionally, origins in the deep muscle or the presence of scar with multiple exit sites may be difficult to visualize with endocardial pace mapping.

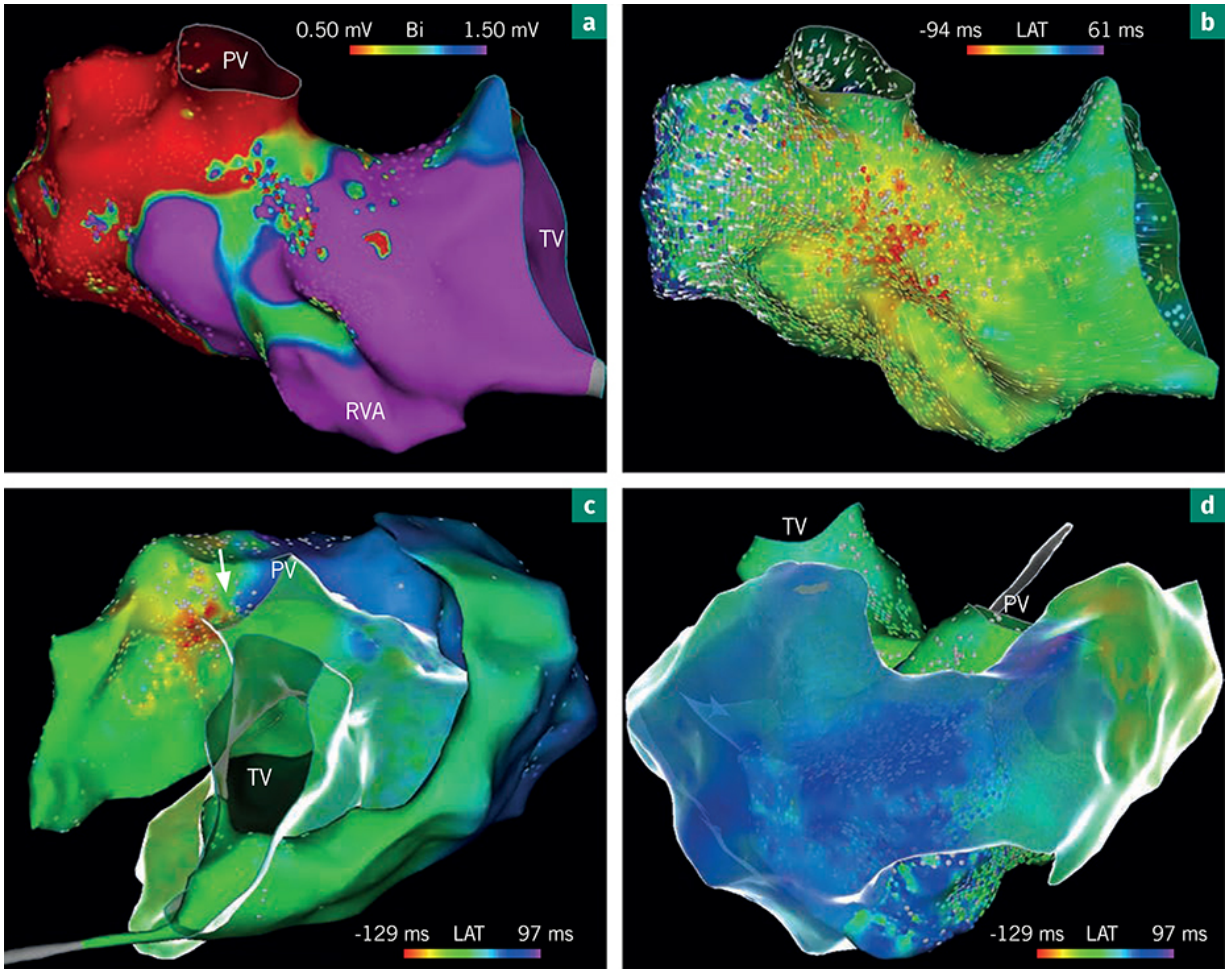


FIGURE 6.19. Three-dimensional electroanatomical maps of the right ventricular endocardium and epicardium in an English Bulldog with arrhythmogenic cardiomyopathy. a) Bipolar (Bi) voltage map of the right ventricle (RV) from the left lateral perspective, showing the delineated tricuspid valve (TV), right ventricular apex (RVA), and pulmonic valve (PV). Each individual point represents the Bi voltage amplitude of an intracardiac electrogram acquired during sinus rhythm, color-coded from red (≤0.5 mV) to purple (≥1.5 mV). This dog is noted to have an aneurysmal dilation at the right ventricular outflow tract associated with a dense scar (Bi voltage areas < 0.5 mV). b) Activation map of ventricular tachycardia. Each individual point represents the local activation time (LAT) of an intracardiac electrogram, color-coded from red (≤ –94 ms) to purple (≥ 61 ms); the reference time was selected as the peak positive deflection of a surface QRS complex (not shown). Conduction velocity vectors are also displayed that portray the direction and speed of conduction; the thin vectors reflect fast conduction, while the thick vectors reflect slow conduction. There is evidence of centrifugal activation from the septal aspect of the right ventricle, with notable slowing around the aneurysmal dilation. However, the ventricular tachycardia is suspected to be a reentrant rhythm with a cycle length of ~280 ms. The LATs cover only ~155 ms (94 ± 61). Therefore, parts of the reentrant circuit are not visible on this endocardial map. c) The same activation map of the right ventricle has been made semitransparent and is shown from the superior and posterior perspective. In addition, the mapping catheter has been placed in the pericardial space and an epicardial map has been obtained. The cycle length increased to ~226 ms, with evidence of early-meets-late (red connecting with purple) on the epicardial surface, reflecting the approximate location of a reentrant isthmus. Parts of the cycle length are still missing likely due to the difficulty in annotating very fractionated and low-

voltage signals that are common with scar tissue. d) Same activation map of ventricular tachycardia as in c), but positioned from the anterior perspective, with the epicardial map made semitransparent.

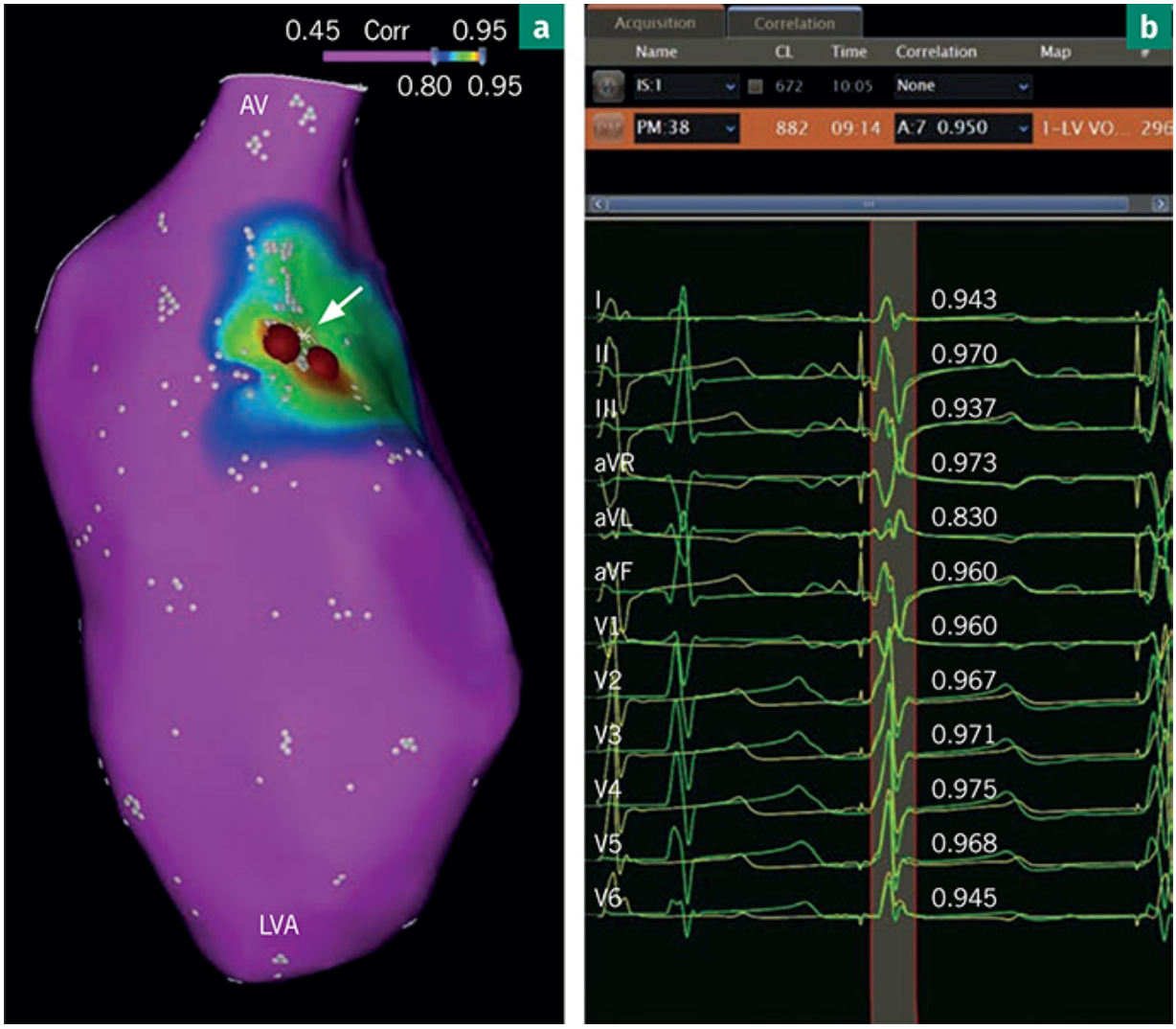


FIGURE 6.20. Three-dimensional pace map of the left ventricle. a) The left ventricle is viewed from the right anterior surface. The color scale represents the percentage of correlation (correlation index or Corr) between ventricular complex morphologies of paced-mapped signals (PM) and intrinsic signals (IS), ranging from purple (≤ 80%) to red (≥ 95%). The location with the highest correlation is denoted by the white arrow. Ablation targeting this area, symbolized by the large red points, successfully terminated the underlying ventricular arrhythmia. b) The PASO module, an automated template matching program in the CARTO 3 mapping system, has calculated a correlation index for the point marked in (a). Here, the morphologies of the 38th PM (PM:38, illustrated in green in the 12-lead electrocardiogram) and the 1st IS (IS:1, illustrated in yellow) are compared, with individual correlations calculated for each lead. The overall correlation is 0.950 or 95%. AV, aortic valve; LVA left ventricular apex. From Hsue et al.,[28] with permission.

Despite routine use of the technique in human medicine for decades, the feasibility, outcomes, and safety of electroanatomical mapping have only

been documented in select laboratory dogs[5] and in clinical patients consisting of dogs[24,27,28] and horses.[29] Electroanatomical mapping systems and specialized mapping catheters, which are often time-stamped for single use only, may be cost-prohibitive to both veterinary hospitals and pet owners. For small breed dogs and cats, patient size can be a major limiting, and even excluding, factor since the ablation and high-density mapping catheters of the three major electroanatomical systems are typically 7 to 8 French in size. Nevertheless, Hellemans et al.[18] successfully mapped up to all four chambers during sinus rhythm using the CARTO system in 8 healthy Beagles (11.2–15.7 kg), demonstrating that electroanatomical mapping can be feasible in medium-sized dogs. On the other hand, although resolution of the clinical arrhythmia has been achieved in isolated cases with no echocardiographic evidence of diseases,[27,28] most dogs presenting with significant tachyarrhythmias exhibit structural heart disease and their outcomes are less straightforward. In 5 Boxers with symptomatic ventricular tachycardia, only the number of ventricular tachycardia runs showed consistent improvement following electroanatomical mapping and catheter ablation, while results related to the ventricular ectopic burden were more variable.[24] Additionally, structural heart diseases are often progressive in nature and the long-term survival benefits of these interventions is currently unclear. Published complications mainly involve self-limiting perioperative arrhythmias, including tachyarrhythmias and even third-degree atrioventricular block.[18,24] Pericardial effusion relating to atrial transseptal puncture, induction of valvular regurgitation, and peri- and postoperative hemorrhage have also been reported.[18,24] Nevertheless, perioperative deaths appear to be uncommon, although only a small number of cases of dogs treated with electroanatomical mapping and catheter ablation have been published. Overall, electroanatomical mapping appears to have low morbidity and mortality, and outcomes and safety will likely improve as more experience is accumulated.

Electroanatomical mapping can increase spatial understanding of tachyarrhythmias, although it is still paramount to follow basic electrophysiological principles to navigate the limitations of each mapping technique and correctly interpret the colors on the map. Furthermore, integrating multiple mapping modalities may compensate for individual weaknesses. For example, the sites of origin of focal tachyarrhythmias may

be characterized by fractionated and low-voltage electrograms even in the absence of structural heart disease, and searching for these characteristics may further refine potential target sites identified on activation mapping. Electroanatomical mapping facilitates visualization and intuitive comprehension of intracardiac electrogram sequences and contact electrogram characteristics, and it will likely become instrumental in successful ablation of complex tachyarrhythmias including ventricular tachycardias.

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SECTION III

THERAPEUTIC MODALITIES

CHAPTER 7

Antiarrhythmic therapy

Manuela Perego, Lucia Ramera

GENERAL CONSIDERATIONS

The primary purpose of antiarrhythmic therapy is to resolve or mitigate the clinical signs induced by rhythm disturbances. Different clinical signs may be present during arrhythmias depending on the type of underlying arrhythmia, the duration of the disturbance, the status of the autonomic nervous system, the vasomotor reflex, and ventricular systolic function. Depending on their characteristics and the corresponding hemodynamic consequences, rhythm disturbances can be treated with antiarrhythmic drugs, electric therapy (cardiac stimulation, defibrillation, radiofrequency catheter ablation), or both.

Most of the available antiarrhythmic drugs can be classified according to whether they exert blocking actions predominantly on sodium, potassium, or calcium channels or whether they block receptors or pumps (Fig. 7.1).

The most commonly used classification is that proposed by Vaughan Williams[1] in 1984 and of which a modernized version was published in 2018.[2] In this book, we will refer to this latter classification, although it has some limitations because it is mainly based on the drug's electrophysiological effects on normal, and not diseased, cardiac tissue. The

reality is that the effects of antiarrhythmic drugs are more complex and depend on several factors such as the species, age, heart rate, type of tissue damage, stage of the myocardial damage (acute or chronic), and intra- and extracellular ion composition. Despite these limitations, the Vaughan Williams classification is widely accepted (Table 7.1).

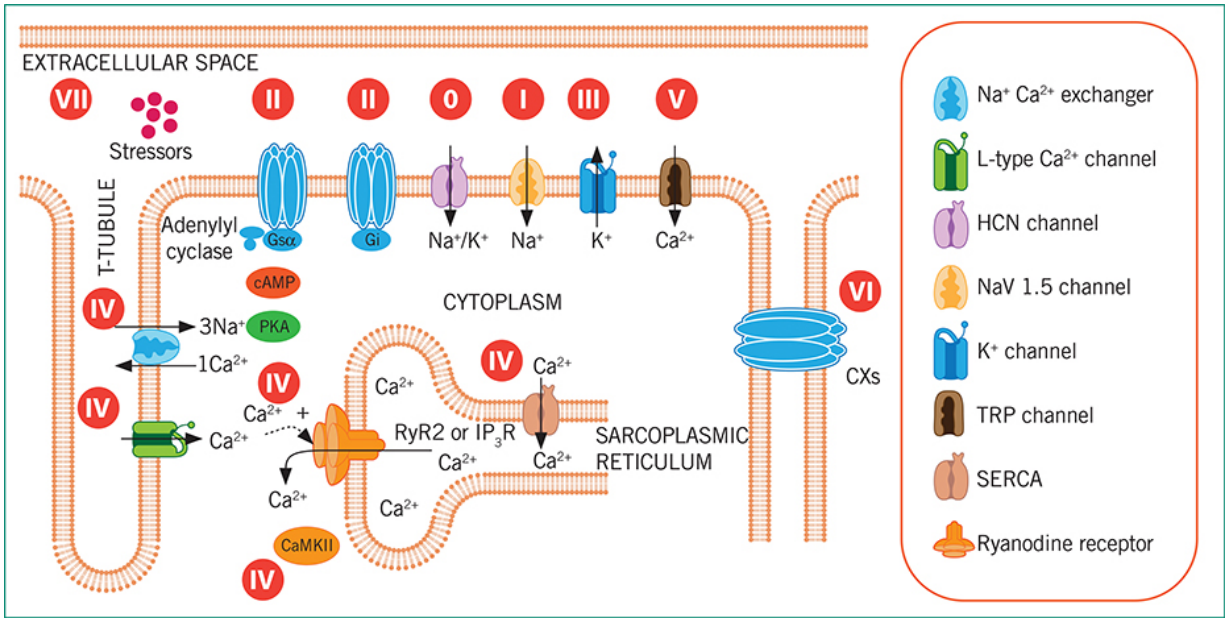


FIGURE 7.1. Surface and intracellular membrane ion channels, ion exchangers, transporters, and ionic pumps involved in cardiomyocyte electrophysiological excitation and activation. Their grouping by pharmacological targets is listed in Table 7.1. HCN channel, hyperpolarization-activated cyclic nucleotide-gated channel; NaV 1.5 channel, cardiac K^+ channel protein; TRP channel, transient receptor potential channel; SERCA, sarco-endoplasmic reticulum calcium ATPase; RyR2, cardiac ryanodine receptor type 2; IP_3R, inositol 1,4,5-trisphosphate receptor. Gsα, alpha subunit stimulatory G-protein; Gi, inhibitory G protein; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; CXs, connexins; CaMKII, calcium/calmodulin kinase II.

TABLE 7.1. Updated classification of current antiarrhythmic pharmacological drugs.

Class	Subclass	Pharmacological targets	Electrophysiological effects	Examples of drugs
HCN channel blockers				
0		HCN channel–mediated pacemaker current (I_f) block	Inhibition of I_f with consequent reduction in the SN phase 4 pacemaker depolarization rate and therefore heart rate; possible decreased AVN and Purkinje cells automaticity	Ivabradine
Voltage-gated Na^+ channel blockers				
I	Ia	NaV 1.5 in open state; intermediate dissociation kinetics; often concomitant K^+ channel block	Reduction in peak I_{Na}, AP generation, and slope of phase 0 with increased excitation threshold; slowing of AP conduction in the atria, ventricles, and specialized intraventricular system; concomitant I_k block, with consequent increase in AP duration and effective refractory period	Quinidine Disopyramide Procainamide
	Ib	NaV 1.5 in open state; rapid dissociation; I_{Na}; window current	Reduction in peak I_{Na}, AP generation, and slope of the phase with increased excitation threshold; reduced velocity of conduction in the atria, ventricles, and intraventricular conduction system; shortening of AP duration and effective refractory period in normal ventricular and Purkinje cells; prolongation of effective refractory period and postrepolarization refractoriness with reduced window current in ischemic, partially depolarized cells	Lidocaine Mexiletine
	Ic	NaV 1.5 in inactivated state; slow dissociation	Reduction in peak I_{Na}, AP generation, and slope of the phase with increased excitation threshold; reduction in the velocity of conduction in the atria, ventricles, and intraventricular conduction system; shortening of AP duration and effective refractory period in normal ventricular and Purkinje cells; reduced overall excitability; prolongation of AP duration at high heart rates	Propafenone Flecainide
	Id	NaV 1.5 late current	Reduction in late Na^+ current affecting AP recovery, refractoriness, and repolarization reserve	Ranolazine
Autonomic inhibitors and activators				
II	IIa	Nonselective ß- and selective $ß_1$-adrenergic receptor inhibitors	Prevent the normal ligand (norepinephrine or epinephrine) from binding to the β-adrenergic receptor by competing for the binding site. β-Adrenergic receptors are coupled to a Gs protein, which activates adenylyl cyclase to form cAMP from ATP, with effects including slowed SN discharge rate caused by reduced I_f and I_{CaL}. Increased AVN conduction time and refractoriness; decreased SN pacing and triggered activities resulting from reduced I_{CaL}; reduced RyR2-mediated sarcoplasmic reticulum Ca^{2+} release and triggered activities	Nonselective ß-inhibitors: ■ Carvedilol ■ Propanolol ■ Nadolol Selective $ß_1$-adrenergic receptor inhibitors: ■ Atenolol ■ Esmolol ■ Metoprolol

II	IIb	Nonselective ß-adrenergic receptor activators	Activation of adrenergically induced Gs protein effects of increasing adenylyl kinase activity and cAMP	Isoproterenol
	IIc	Muscarinic M2 receptor inhibitors	Inhibition of supraventricular (SN, atrial, AVN) muscarinic M2 cholinergic receptors	Atropine Glycopyrrolate
	IId	Muscarinic M2 receptor activators	Activation of supraventricular (SN, atrial, AVN) muscarinic M2 cholinergic receptors with consequent activation of K_{ACh} channels (which hyperpolarizes the SN and shortens AP duration in atrial and AVN tissue), and reduction in cAMP and therefore in I_{CaL} and SN I_f; inhibitory effect on adenylyl cyclase and cAMP activation, with resulting reduction in its stimulatory effects on I_{CaL}, I_{Ks}, I_{Cl}, I_b in adrenergically activated ventricular tissue	Digoxin
	IIe	Adenosine receptor inhibitors	Amynophilline is a combination of theophylline and ethylenediamine. Aminophylline enhances atrioventricular nodal and His–Purkinje fiber system conduction and decreases the duration of the effective refractory period of ventricular myocytes. In conscious dogs, the predominant effect of intravenous amynophilline is vasoconstriction of the systemic, coronary, mesenteric, and iliac beds. These findings involve an α-1 adrenergic mechanism. Only the renal bed shows modest and transient vasodilation.	Aminophylline
K^+ channel blockers and openers				
III				
Voltage-dependent K^+ channel blockers	IIIa	Nonselective K^+ channel blockers	Block of multiple K^+ channel targets resulting in prolonged atrial, Purkinje, and /or ventricular myocyte AP recovery, increased effective refractory period, and reduced repolarization reserve	Amiodarone, dronedarone
	IIIb	Kv 11.1 (HERG) channel -mediated rapid K^+ current (I_{Kr}) blockers	Prolonged atrial, Purkinje, and ventricular myocyte AP recovery, increased effective refractory period, and reduced repolarization reserve	Sotalol
	IIIc	Kv 1.5 channel-mediated, ultrarapid K^+ current (I_{Kur}) blockers	Prolonged atrial AP recovery, increased effective refractory period, and reduced repolarization reserve	Vernakalant
Ca^+ handling modulators				
IV				
Surface membrane Ca^{2+} channel blockers	IVa	Cav 1.2 and Cav 1.3 channel–mediated L-type Ca^{2+} current (I_{CaL}) blockers	Block of Ca^{2+} current (I_{Ca}), resulting in inhibition of SN pacing, inhibition of AVN conduction, prolonged effective refractory period, increased AP recovery time, increased refractory period, diminished repolarization reserve, and suppression of intracellular Ca^{2+} signaling	Verapamil Diltiazem
Intracellular Ca^{2+} channel blockers	IVb	Sarcoplasmic reticulum RyR2-Ca^{2+} channel blockers	Reduced sarcoplasmic reticulum calcium release: reduced cytosolic and sarcoplasmic reticulum calcium concentration	Flecainide Propafenone

Upstream target modulators				
V		Angiotensin-converting enzyme inhibitors	Electrophysiological and structural (fibrotic, hypertrophic or inflammatory) remodeling	Enalapril, benazepril, lisinopril
		Omega-3 fatty acids	Electrophysiological and structural (fibrotic, hypertrophic or inflammatory) remodeling	Omega-3 fatty acids: ■ Eicosapentaenoic acid ■ Docosahexaenoic acid ■ Docosapentaenoic acid

SN, sinus node; AVN, atrioventricular node; AP, action potential. Source: Modified from Lei M. et al.[2]

A different approach was provided with the "Sicilian Gambit", which attempts to classify antiarrhythmic drugs based on the arrhythmogenic mechanism of the specific arrhythmia, thus defining the target that should be modified by the antiarrhythmic drug.[3]

Other antiarrhythmic drugs not included in these two classifications are currently regularly used for supraventricular tachycardias or bradyarrhythmias. These include magnesium, potassium, terbutaline, and theobromine.

DRUG CLASSIFICATION

Based on the 1984 Vaughan Williams classification, antiarrhythmic drugs are divided in four categories. Class I antiarrhythmics predominantly block fast sodium channels and partially block potassium channels. Class I antiarrhythmics are divided into three subgroups (Ia, Ib, Ic).

Class Ia drugs act by reducing the rate of rise of the action potential during phase 0 and prolong the action potential duration. The onset and the offset of their effects are of intermediate rapidity (less than 5 seconds). Quinidine, procainamide, and disopyramide are included in this group.

Class Ib drugs do not reduce the maximum upstroke velocity of the cardiac action potential (V_{max}) and shorten the duration of the action potential. They significantly slow down conduction in depolarized tissues at elevated heart rates. Their action in blocking sodium channels is rapid (less than 500 milliseconds). Lidocaine and mexiletine are included in this group.

Class Ic drugs reduce V_{max} by slowing down conduction velocity and minimally prolong the duration of the action potential. These drugs have

slow onset and offset kinetics (10–20 seconds). Flecainide and propafenone are included in this group.

Class II drugs include substances with different $ß_1$- and $ß_2$-blocking activity, membrane-stabilizing activity, and, depending on the dose, an intrinsic sympathomimetic activity. $ß_1$ receptors are involved in inotropic activity through the increase in troponin I phosphorylation, which induces a faster interaction between myosin heads and actin filaments, and through the opening of calcium channels, which promotes sarcomere contraction. These receptors also control lusitropy by stimulating phospholamban phosphorylation, which allows calcium reuptake by the sarcoplasmic reticulum, inducing myocardial relaxation. Stimulation of $ß_1$ receptors induces a positive chronotropic effect on the conduction system tissue by increasing the sodium current through the I_f channels, and a dromotropic effect by increasing calcium currents through the calcium channels. For these reasons, ß-adrenergic receptor blockers decrease the sinus node discharge rate and have a negative inotropic, dromotropic, and lusitropic effect. The consequence of these actions is a reduced oxygen and energetic myocardial consumption. ß-Blockers depress the automaticity of damaged cells, which are in a partial depolarized state and more sensitive to the action of catecholamines, and reduce the ventricular rate through a negative dromotropic effect. Higher ß-blocker concentrations cause a membrane stabilizing effect similar to that of quinidine.

Class III antiarrhythmic drugs (e.g., amiodarone, sotalol, bretylium, and ibutilide) delay the repolarization phase by blocking the I_{Kr} channels. This leads to an increased action potential duration and effective refractory period. Class III antiarrhythmic drugs also have antiadrenergic properties like those of ß-blockers, and antifibrillating effects by blocking sodium channels.

Class IV antiarrhythmic drugs predominantly block calcium channels. They can be divided in dihydropyridines and nondihydropyridines. Dihydropyridines induce strong peripheric vasodilation with reflex sinus tachycardia, while nondihydropyridines act on the nodal structures. Dihydropyridines (e.g., amlodipine and nifedipine) block I_{CaT} channels and have a high selectivity for smooth vascular muscles, while nondihydropyridines (e.g., diltiazem and verapamil) inhibit I_{CaL} channels and include an additive depressant effect on the sinus and atrioventricular

nodes, with a consequent reduction in sinus rate and conduction velocity. Diltiazem and verapamil reduce the inward I_{CaL} and therefore have important electrical and mechanical effects that lead to reduced nodal tissue excitability. Therefore, they induce bradycardia, slow down atrioventricular node conduction, reduce myocardial contractility, and lead to slight systemic and coronary vasodilation. In 2018, a modernized version of the Vaughan Williams classification was proposed, with 7 classes, 5 of which can be used in veterinary medicine (see Table 7.1).

USE DEPENDENCE

Use dependence is defined as the ability of some drugs to exert a greater inhibitory effect on the upstroke of the action potential after a prolonged period of rapid heart rate. The term *use-dependent* behavior refers to an increase in drug binding at a faster stimulation rate. In the case of class Ib antiarrhythmic agents, the depression of V_{max} induced by these drugs during phase 0 is greater as more channels are blocked during a period of rapid rate. This property relies on the preferential interaction of the antiarrhythmic drug with the active channels rather than with the resting channels of unstimulated cells. At slower heart rates, with the increased amount of time in diastole, a greater percentage of receptors become drug free and the drug exerts less effect. This consideration is particularly true for those antiarrhythmic drugs that exhibit a fast onset and offset or use-dependent block of fast channels.

REVERSE USE DEPENDENCE

Some drugs have a greater antiarrhythmic effect at slower heart rates. This property is evident for drugs that lengthen the action potential and in particular the repolarization phase.

MECHANISMS OF SUPPRESSION OF ARRHYTHMIA

Cardiac arrhythmias can be caused by enhanced automaticity, triggered activities, or reentrant circuits. The ways in which antiarrhythmic drugs suppress arrhythmias can be postulated based on these different

mechanisms. In case of enhanced automaticity, antiarrhythmic drugs can suppress the arrhythmia by depressing the slope of diastolic depolarization (phase 4 of the action potential), by shifting the threshold potential toward 0, or by shifting the resting membrane potential toward more negative values. Antiarrhythmic drugs can also act by suppressing early or delayed afterdepolarizations, thereby inhibiting rhythm disturbances related to these mechanisms. The induction and maintenance of a reentrant circuit depends on several factors: the conduction velocity along the circuit, the presence of a unidirectional block of one of the two pathways of the circuit, and the presence of a slow conducting area in the circuit called isthmus. The role of antiarrhythmic drugs is to stop the ongoing reentry mechanism or to prevent it from starting by improving or depressing conduction along the circuit. Improving conduction along a circuit can eliminate a unidirectional block or make conduction faster so that reentrant wavefronts propagate too quickly and encounter refractory cells. An antiarrhythmic drug can also depress the conduction velocity along the circuit and cause a bidirectional block instead of a unidirectional block in the reentrant pathway. However, a drug that slows down conduction along the pathway without blocking the reentrant circuit can significantly promote reentrant arrhythmias. Some drugs can also prolong the refractory period of the accessory pathway so that it may not recover the excitability in time to be depolarized by the reentrant wavefront, thereby leading to termination of the reentrant arrhythmia. There are different types of reentry, and the type of reentry is crucial to define the effectiveness of the antiarrhythmic drug.

Since the electrophysiological, hemodynamic, and pharmacological effects of a drug can differ significantly between healthy patients and patients presenting arrhythmias with different underlying mechanisms, it is very important to carefully define the specific mechanism causing the arrhythmia.

PROARRHYTHMIC EFFECTS

Drug-induced cardiac arrhythmias represent a major clinical problem. Proarrhythmia is defined as an increase in the frequency of a preexisting arrhythmia or development of a rhythm disturbance that the patient did not display before. The most frequent electrophysiological mechanisms underlying proarrhythmia are related to the prolongation of the duration of the repolarization phase, the development of early afterdepolarizations,

which is associated with bradycardia-induced polymorphic ventricular arrhythmias, and alterations in the electrophysiological properties of the pathways of a reentrant circuit able to initiate or sustain a reciprocating tachycardia. The presence of congestive heart failure can promote the proarrhythmic effects of antiarrhythmic drugs.

CLASS 0

IVABRADINE

Electrophysiological properties

Ivabradine is a strong selective inhibitor of the hyperpolarization-activated, cyclic nucleotide–gated I_f involved in pacemaker generation and responsiveness of the sinus node. It decreases heart rate with no other apparent direct cardiovascular effects. Ivabradine blocks the intracellular aspect of the I_f channels by inhibiting cation movement with a high degree of selectivity; this leads to a reduction in the slope of diastolic depolarization of the P cell action potential, thereby slowing heart rate. Ivabradine blocks the I_f channels in an open state, creating a use-dependence of the drug (the drug becomes more potent at a faster heart rate) (Fig. 7.2). Ivabradine causes a dose-dependent decrease in heart rate and, based on its specific mechanism of action, it does not affect cardiac inotropy and systemic vascular resistance.[4] In aging dogs, ivabradine could reduce the induction of atrial fibrillation and firing from the pulmonary veins[5] as it has been reported to reduce the I_f and intracellular calcium transient in pulmonary vein cardiomyocytes,[6] which may contribute to its inhibitory effect on spontaneous activity in the pulmonary veins.[5]

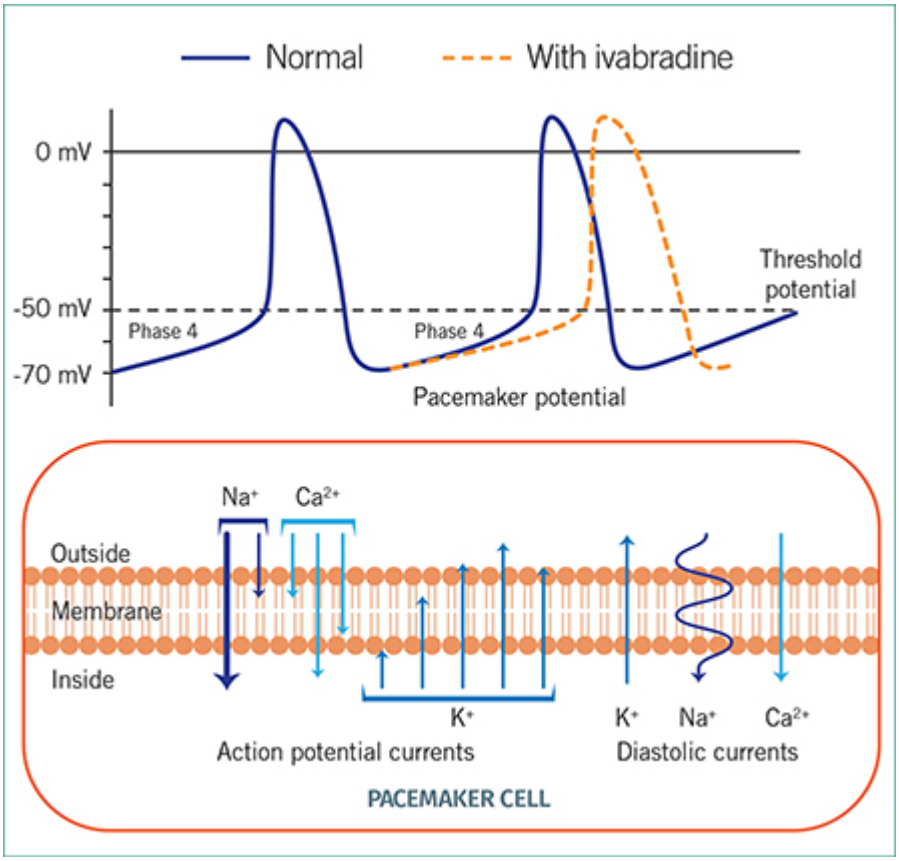


FIGURE 7.2. Schematic diagram of the effects of class 0 antiarrhythmics. Blocking of the intracellular aspect of funny (I_f) channels induces a reduction in the slope of diastolic depolarization of the action potential, thereby slowing the heart rate.

Hemodynamic effects

Ivabradine causes a dose-dependent reduction in sinus discharge with no negative inotropic, lusitropic, or dromotropic effects. Ivabradine induces positive effects on stroke volume and coronary flow, with reduced myocardial oxygen consumption. In healthy cats, studies have shown that an oral dose of 0.3 mg/kg every 8 hours acts on the sinus rate without affecting systolic function or hemodynamic parameters.[7,8] A recent study on ivabradine use in dogs with asymptomatic mitral valve degeneration has shown that a single oral dose of 1 mg/kg is a valid option to reduce heart rate and myocardial oxygen consumption.[9] By lowering the heart rate, ivabradine reduces cardiac work, thereby reducing myocardial oxygen demand. The beneficial effect of ivabradine associated with heart rate lowering has also been demonstrated in several experimental studies in animals, including dogs and pigs. Several studies in human medicine have

shown that ivabradine significantly reduces major risks associated with heart failure when added to guideline-based and evidence-based treatment.

Dose and administration

The recommended dose is 0.5–1 mg/kg per os (PO) every 12 hours in dogs and 0.3 mg/kg PO every 12 hours in cats (see Table 7.2).

TABLE 7.2. Doses of antiarrhythmic drugs reported in dogs and cats.

Drugs	Doses in dogs	Doses in cats
Amiodarone	10–25 mg/kg PO every 12 h for 7 days, followed by 5–7.5 mg/kg PO every 12 h for 14 days, followed by 7.5 mg/kg PO every 24 h	12.5 mg/kg PO every 24 h
Aminophylline	6–11 mg/kg PO or SC every 8 h	5 mg/kg PO every 8–12h
Atenolol	0.2–1 mg/kg PO every 12–24 h or 6.25–25 mg (total dose) PO every 12 h	6.25–12.5 mg PO per cat every 12–24 h. Starting dose should be low and titrated to effect
Atropine	0.022–0.044 mg/kg IM, SC, or IV; or 0.04 mg/kg PO every 6–8 h	0.022–0.044 mg/kg IM, SC, or IV; or 0.04 mg/kg PO every 6–8 h
Carvedilol	0.08–1.5 mg/kg PO every 12 h	
Digoxin	0.003–0.01 mg/kg PO every 12 h (up to a maximum of 0.375 mg, or rarely, 0.5 mg/day)	0.007 mg/kg PO every 48 h
Diltiazem	For acute treatment of focal atrial tachycardia: 0.05–0.15 mg/kg slowly IV, repeat every 5 min to effect	For acute management of supraventricular tachycardias: 0.125–0.35 mg/kg IV

Drugs	Doses in dogs	Doses in cats
	or until a total dose of 0.1–0.3 mg/kg; or give 0.5 mg/kg PO followed by 0.25 mg/kg PO every hour until conversion or a total oral dose of 1.5–2 mg/kg For chronic treatment: 0.5–2 mg/kg PO every 8 h	For chronic management: 7.5 mg (per cat) PO every 8 h or 0.5–1 (up to 1.5) mg/kg PO every 8 h
Disopyramide	10–20 mg/kg PO every 6 h	
Esmolol	Loading dose of 200–500 µg/kg IV over 1 min, followed by a CRI at 25–200 µg/kg/min	Loading dose of 200–500 µg/kg IV over 1 min, followed by a CRI at 25–200 µg/kg/min
Isoproterenol	0.04–0.08 µg/kg/min IV	
Ivabradine	0.5–1 mg/kg PO every 12 h	0.3 mg/kg PO every 12 h
Flecainide	5 mg/kg/day PO	
Glycopyrrolate	0.01 mg/kg IV, IM, or SC	0.005–0.01 mg/kg IV or IM, 0.01–0.02 mg/kg SC.
Lidocaine	2 mg/kg IV bolus, up to 8 mg/kg followed by a CRI at 25–80 µg/kg/min	0.25–0.5 mg/kg in a slow IV bolus, which can be repeated at 0.15–0.25 mg/kg in 5–20 min, followed by a CRI at 10-20 µg/kg/min
Metoprolol	5–50 mg (total dose) PO every 8–12 h; initial dose should be low followed by individual dosage titration	2–15 mg (total dose) PO every 8 h
Mexiletine	4–8 mg/kg PO every 8 h	
Nadolol	1 mg/kg PO every 24 h	

Drugs	Doses in dogs	Doses in cats
Nexterone	2 mg/kg IV bolus over 10 minutes followed by a CRI at 0.8 mg/kg/h for 6 hours (then decrease to 0.4 mg/kg/h for 18 hours)	
Procainamide	To treat supraventricular arrhythmias: 6–8 mg/kg IV over 3 minutes or 6–20 mg/kg IM or 10–20 mg/kg PO every 6–8 hours. To treat ventricular arrhythmias: 10–15 mg/kg in an IV bolus over 1–2 minutes, followed by a CRI at 25–50 µg/kg/min or 10–20 mg/kg PO every 6 hours	To treat supraventricular arrhythmias: 1–2 mg/kg slowly IV followed by 10–20 µg/kg/minute or 3–8 mg/kg PO every 6–8 hours
Propafenone	9–25 mg/kg/day PO	
Propranolol	To treat ventricular arrhythmias: 0.02–0.06 mg/kg IV over 2–3 min or 0.2 mg/kg PO every 8 h; maximum 1 mg/kg/day. In case of ventricular hypertrophy: 0.125–0.25 mg/kg PO every 12 h To treat arrhythmias correlated with pheochromocytomas: 0.15–0.5 mg/kg PO every 8 h or 0.03–0.10 mg/kg IV	To treat ventricular arrhythmias: 0.02 mg/kg slowly IV (up to a maximum of 1 mg/kg). The oral dose is: 2.5 mg (up to 10 mg) total dose per cat every 8–12 h. In case of hypertrophic cardiomyopathy: cats 4.5 kg or less: 2.5 mg PO every 8–12 h; cats 5 kg or more: 5 mg PO every 8–12h In case of systemic hypertension: 2.5–5.0 mg PO every 8-12 h

Drugs	Doses in dogs	Doses in cats
Quinidine	6–20 mg/kg IM every 6 h (loading dose 14–20 mg/kg); 6–16 mg/kg PO every 6 h; sustained action oral preparations: 8–20 mg/kg PO every 8 h	6–20 mg/kg PO every 6–8 h
Sotalol	0.5–2 mg/kg PO every 12–24 h	1–3 mg/kg PO every 12 h
Verapamil	Initial dose of 0.05 mg/kg slowly IV, which can be repeated every 5 min up to a total dose of 0.15–0.2 mg/kg; oral dose: 0.5–2 mg/kg every 8 h	Initial dose of 0.025 mg/kg slowly IV, which can be repeated every 5 min up to a total dose of 0.15–0.2 mg/kg; oral dose: 0.5–1 mg/kg every 8 h

Indications

Ivabradine is indicated to treat some forms of automatic focal atrial tachycardia (pulmonary vein tachycardia) and focal junctional tachycardia.

Contraindications and adverse effects

Ivabradine is contraindicated in the following situations: decompensated heart failure, decreased heart pressure, conduction abnormalities such as sinus node dysfunction and atrioventricular blocks, unless a pacemaker determines the heart rate.

CLASS Ia

QUINIDINE

Electrophysiological properties

Quinidine exerts little effect on the automaticity of the normal sinus node, but it suppresses arrhythmias arising from enhanced normal automaticity of

the Purkinje fibers. It reduces the upstroke velocity of phase 0 and conduction velocity (Fig. 7.3). Because of its anticholinergic effects and the resulting reflex sympathetic stimulation due to α-adrenergic blockade, which causes peripheral vasodilation, quinidine can increase the sinus node discharge rate and improve atrioventricular nodal conduction velocity. Furthermore, quinidine causes a selective block of the I_{to} and I_{Kr} potassium channels, with prolongation of the repolarization phase. This effect is more prominent at a slower rate (reverse use dependence).

Quinidine prolongs the effective refractory period of the atrial and ventricular cells, His–Purkinje system, and accessory pathways; this promotes the interruption of sodium-dependent reentrant circuits. Electrocardiographically, as well as an increase in sinus rate, a minimal increase in the QRS complex and QT interval duration can be observed, while the PQ interval does not change.[10]

Hemodynamic effects

Due to its α-adrenergic receptor blocking effects, quinidine decreases peripheral vascular resistance and thus significantly decreases systemic arterial pressure. The concomitant administration of vasodilator agents is contraindicated. Quinidine does not affect myocardial function if administered orally.[10]

Pharmacokinetics

After oral administration, quinidine sulfate has a 70–80% bioavailability and reaches peak levels in blood 1 to 3 hours after ingestion (maximum therapeutic effect). About 20–50% is excreted unchanged by the kidneys; the rest undergoes hepatic hydroxylation processes. Quinidine has a half-life of 5–7 hours and plasma therapeutic values of 2.5–5 μg/mL, with toxic effects occurring at a plasma concentration above 10 μg/mL. The peak plasma concentration is reached 1–2.8 hours following intravenous (IV) administration, and the drug is no longer present in plasma after 24 hours. Intravenous infusion of quinidine must be done slowly due to the potential vasodilation, hypotension, and cardiac depression (α-adrenergic block) the drug may cause.[11]

Dose and administration

In dogs, quinidine can be administered at an intramuscular (IM) dose of 6–20 mg/kg every 6 hours (loading dose 14–20 mg/kg), or 6–16 mg/kg PO every 6 hours. Sustained-action oral preparations should be administered at a dose of 8–20 mg/kg PO every 8 hours.[12]

Quinidine sulfate is administered in dogs at a dose of 5–10 mg/kg IV every 6 hours or 6–20 mg/kg PO every 6–8 hours.

Quinidine gluconate is administered in dogs at a dose of 6–20 mg/kg IM every 6 hours or 6–20 mg/kg PO every 6–8 hours.

The suggested quinidine dose in cats is 6–20 mg/kg PO every 6–8 hours.[12]

See Table 7.2 for a summary of the routes of administration and doses of antiarrhythmics in dogs and cats.

Indications

The main indications for quinidine are ventricular and supraventricular arrhythmias, particularly if these are induced by a reentry mechanism (as occurs with accessory pathway–mediated tachycardia), because quinidine prolongs the refractory period of atrioventricular connections. In dogs with non-long-standing persistent atrial fibrillation and normal systolic function, quinidine can restore sinus rhythm, even though it may initially induce a high ventricular response due to its vagolytic effect.

Contraindications and adverse effects

Contraindications for the administration of quinidine are myasthenia gravis, atrioventricular conduction disturbances, intraventricular conduction disturbances, arrhythmias induced by digoxin intoxication and hypokalemia, hypoxia, and acid–base imbalances. In patients with hepatic or renal insufficiency, quinidine must be used with caution because of the potential increase in the drug's plasma concentration due to reduced metabolism and excretion.

Since quinidine prolongs the ventricular repolarization phase, it promotes arrhythmias associated with QT interval prolongation, especially in association with bradycardia, hypokalemia, or systolic dysfunction. In dogs,

quinidine may induce gastrointestinal signs such as anorexia, vomiting, and diarrhea. Quinidine is rarely used in dogs and cats.

PROCAINAMIDE

Electrophysiological properties

Procainamide, a class Ia antiarrhythmic agent, has a similar action on the heart as quinidine. Procainamide prolongs the effective and relative refractory period in both the atrial and ventricular myocardium, decreasing myocardial excitability. It also depresses automaticity and conduction velocity in the atrial and ventricular myocytes and has anticholinergic properties that may contribute to its effects. In general, procainamide does not alter the sinus rate, but it may exhibit a negative inotropic effect on the ventricular myocardium although the cardiac output is generally not affected. On the electrocardiogram, QRS widening and prolonged PQ and QT intervals can be observed.

Hemodynamic effects

Procainamide can produce negative inotropic effects and has been shown to decrease cardiac performance in dogs (as assessed by changes in left ventricular dP/dt) and humans (as assessed by changes in systolic time intervals and invasively measured hemodynamic variables). In patients with normal ventricular function, the drug's cardiodepressant effect is partially offset by its direct vasodilator effects; however, procainamide may depress cardiac performance when ventricular function is impaired.[13]

Pharmacokinetics

The pharmacokinetics of procainamide hydrochloride have been studied in dogs.[14] When administered intravenously at a dose of 8 mg/kg, its elimination half-life was 2.43 hours, its apparent volume of distribution 1.44 L/kg, and its systemic clearance 0.412 L/kg/h. For an orally administered dose (25.5 mg/kg), its bioavailability was 85%, and its absorption half-life was 0.5 hours.[14]

In an experimental model, procainamide has been shown to suppress induced ventricular arrhythmias after attaining a mean plasma concentration of 33.8 µg/mL (range, 25.0–48.5 µg/mL).[15]

The elimination half-life in dogs has been reported to be variable, with most studies giving values between 2–3 hours. In humans, procainamide is metabolized to N-acetyl-procainamide, an active metabolite. It appears, however, that dogs do not form appreciable amounts of N-acetyl-procainamide from procainamide. In this species, approximately 90% (50–70% unchanged) of an intravenous dose is excreted in urine as procainamide and metabolites within 24 hours after dosing. In a 2019 study, oral administration of sustained-release procainamide twice daily achieved targeted plasma concentrations in most dogs.[16]

Dose and administration

In dogs, procainamide is used for the acute management of supraventricular tachycardias at 6–8 mg/kg IV over 3 minutes or 6–20 mg/kg IM. For chronic management, the suggested dose is 10–20 mg/kg PO every 6–8 hours. Procainamide is also used in dogs for the acute treatment of ventricular tachycardias at a dose of 10–15 mg/kg administered as an IV bolus over 1–2 minutes, followed by a CRI at 25–50 µg/kg/min. The suggested dose of procainamide for the chronic treatment of ventricular tachycardias is 10–20 mg/kg PO every 6 hours.[17]

In cats, procainamide has been reported to be used for the chronic management of supraventricular tachycardias at a dose of 3–8 mg/kg PO every 6–8 hours or 1–2 mg/kg slowly IV, followed by a 10–20 µg/kg/min IV CRI.

Indications

Procainamide is indicated for the treatment of monomorphic ventricular tachycardias and supraventricular tachycardias mediated by an accessory pathway and atrial flutter. In general, higher doses may be needed to treat supraventricular tachycardias, although procainamide is not considered a first-line agent for this type of tachycardias.[17]

Contraindications and adverse effects

Procainamide may be contraindicated in patients with myasthenia gravis and in those hypersensitive to it, procaine, or any other chemically related drugs. Procainamide is contraindicated in patients with polymorphic

ventricular tachycardia or with second- or third-degree atrioventricular block (unless artificially paced).

It should be used with caution in patients with significant hepatic or renal disease or with congestive heart failure, and the suggested dosages should be reduced in these patients.

The adverse effects of procainamide are generally dose-related in the dog and mainly include gastrointestinal signs such as anorexia, vomiting, or diarrhea.

Procainamide has been reported to cause cardiovascular system adverse effects such as weakness, hypotension, decreased systolic function, and prolongation of the QRS complex and PQ and QT intervals, and it can be associated with the development of atrioventricular blocks and polymorphic ventricular tachycardia.

DISOPYRAMIDE

Electrophysiological properties

Disopyramide produces effects similar to those of quinidine and procainamide and causes use-dependent blockade of I_{Na} channels and non-use-dependent blockade of I_{Kr} channels (Fig. 7.3). Disopyramide also exhibits muscarinic receptor–blocking properties, with a consequent increase in the sinus node discharge rate and a faster atrioventricular nodal conduction velocity.[18]

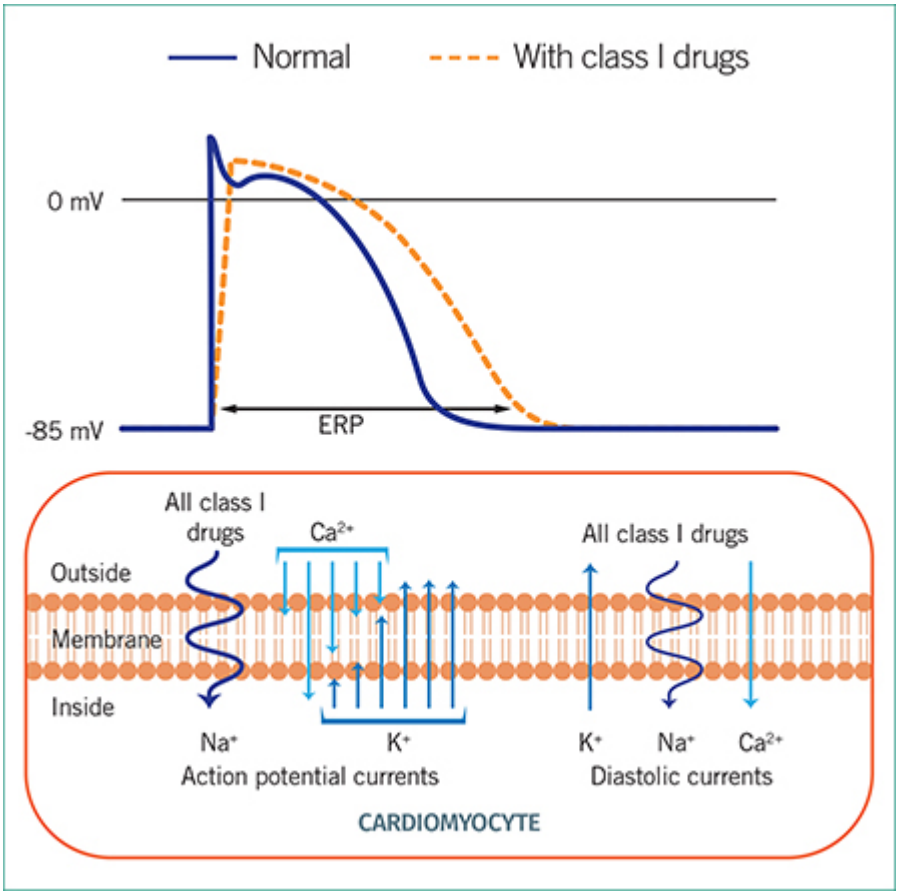


FIGURE 7.3. Schematic diagram of the effects of class I antiarrhythmics. All class I drugs reduce the sodium current both during phase 0 and phase 4 (wavy lines), but there are also some differences between class Ia, Ib and Ic drugs. Class Ia drugs prolong the action potential duration by reducing the potassium current (I_K) during phase 3, a characteristic associated with prolongation of the effective refractory period (ERP). In contrast, class Ib and Ic drugs have different (or no) effects on the phase 3 current; as a result, they shorten or have no effect on the action potential duration. Note, however, that the ERP is prolonged by all class I drugs as these slow the recovery of sodium channels from inactivation.

Hemodynamic effects

Disopyramide depresses ventricular systolic function and should be avoided in patients with systolic dysfunction. It also acts as a mild arterial vasodilator.[18]

Pharmacokinetics

Disopyramide quickly distributes to the extravascular tissues. Depending on its concentration, it binds to α-1-acid glycoprotein, with a consequent variation in volume distribution. Disopyramide undergoes hepatic

metabolization, and about 40–65% of it is excreted via the kidneys. In dogs, its half-life is 2–3 hours.

Dose and administration

The suggested dosage for dogs is 10–20 mg/kg PO every 6 hours (see Table 7.2).

Indications

Disopyramide is indicated for ventricular tachycardias, but due to its short half-life and negative inotropic effects, it is generally not considered as a first choice and can be combined with other drugs, such as mexiletine, to treat dogs unresponsive or partially responsive to monotherapy. Disopyramide can be used to prevent recurrence of atrial fibrillation after successful cardioversion.

Contraindications and adverse effects

Because of its anticholinergic effects, disopyramide must be avoided in patients with myasthenia gravis, glaucoma, or urinary retention and is contraindicated in patients with sinus node dysfunction, atrioventricular and intraventricular conduction disturbances, accessory pathway–mediated tachycardias, cardiogenic shock, or in case of hypersensitivity.[19] When used with other class Ia agents or with propranolol, disopyramide can cause a synergistic negative inotropism. Some side effects of disopyramide are related to its anticholinergic properties (e.g., mucous membrane dehydration, constipation, urinary retention) and cardiovascular effects (e.g., hypotension, dyspnea, syncope, conduction disturbances with high-degree atrioventricular blocks). Finally, great caution must be exercised when using dysopiramide with macrolide antibiotics, more particularly erythromycin, since this drug combination may have deleterious effects on ventricular repolarization.[20]

CLASS Ib

LIDOCAINE

Electrophysiological properties

Lidocaine blocks I_{Na} channels, predominantly those in the open state. Lidocaine has a rapid onset and offset of action and does not influence the sinus node discharge rate owing to a use-dependence inhibition of I_{Na}. However, it depresses other normal and abnormal forms of enhanced automaticity (Fig. 7.3). Lidocaine is a mild depressant of V_{max}, but changes correlated with myocardial ischemia, such as a fast heart rate, reduced blood pH values, increased extracellular potassium concentrations, and a reduced membrane potential, increase the drug's ability to block I_{Na} channels (Fig. 7.4). In case of ischemia, lidocaine can convert a unidirectional block into a bidirectional block and prevent ventricular tachycardia and/or ventricular fibrillation. Lidocaine has a mild effect on the atrial myocardial cell action potential and minimal effect on accessory pathways. Therapeutic concentrations of lidocaine do not affect the duration of the PQ and QT intervals or that of the QRS complex; however, high plasma concentrations of the drug prolong the PQ interval and QRS complex duration, while shortening the QT interval.

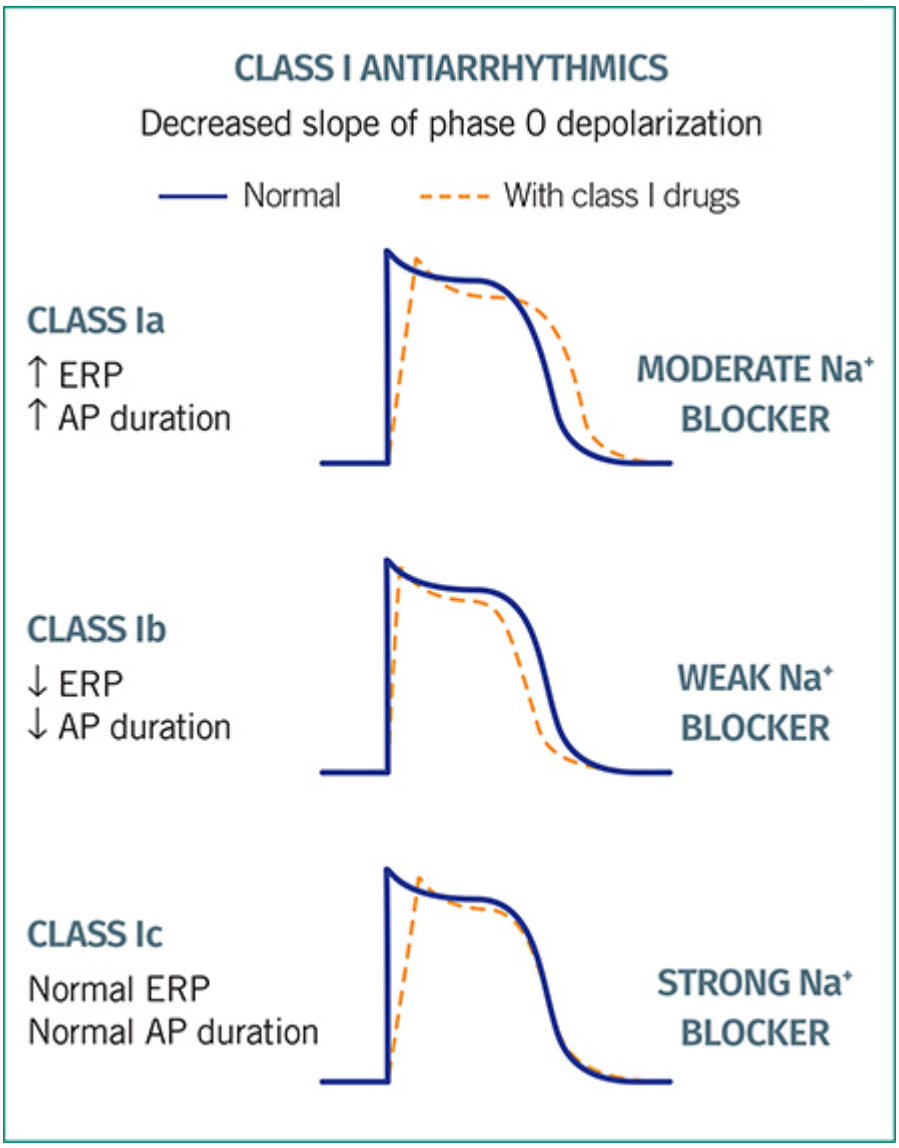


FIGURE 7.4. Different actions of class I agents.

Hemodynamic effects

Unless severe ventricular systolic dysfunction is present, no clinically significant hemodynamic effects are usually noted with lidocaine administration.

Pharmacokinetics

Therapeutic levels of lidocaine are reached in 2 minutes when the drug is administered IV as a bolus (with an efficacy lasting about 10–20 minutes) and after 1 hour when administered as a constant rate infusion (CRI).

Lidocaine shows a strong affinity for adipose tissues and plasma proteins such as α-1-acid glycoprotein. In dogs, the distribution volume is 4.5 L/kg. The drug is converted by the liver into active metabolites and its half-life in dogs is 1 hour, although it is prolonged in patients with hepatic or cardiac insufficiency. Less than 10% of the active principle is excreted unchanged with urine, and its clearance rate is 1.71 L/kg/h.

Dose and administration

Although lidocaine can be administered IM, the IV route is the most commonly used. In dogs, an initial bolus of 2 mg/kg is administered IV (up to 8 mg/kg), followed by a CRI at 25–80 µg/kg/min. In cats, lidocaine is administered IV as a slow bolus of 0.25–0.5 mg/kg, which can be repeated at a dose of 0.15–0.25 mg/kg after 5–20 min, followed by a CRI at 10–20 µg/kg/min. Patients requiring more than one bolus to reach the therapeutic effect usually suffer from arrhythmias that only respond to higher lidocaine plasma concentrations, so higher maintenance doses are required to sustain higher concentrations. CRIs achieve adequate steady state concentrations in normal patients and in patients with uncomplicated systolic dysfunction, but these rates must be reduced in case of congestive heart failure, concomitant shock or reduced hepatic blood flow. For intratracheal administration in dogs, the lidocaine dose is increased 2–2.5 times and the drug should be diluted in sterile water.[21]

See Table 7.2 for a summary of the routes of administration and doses in dogs and cats.

Indications

Lidocaine is indicated for treating ventricular arrhythmias, particularly monomorphic sustained ventricular tachycardia. In the last decade, lidocaine has been used successfully to treat supraventricular tachycardias. In particular, it has been reported to be effective in restoring sinus rhythm in 84% of patients presenting with orthodromic atrioventricular reciprocating tachycardia.[22,23] Lidocaine has been reported in one dog with atrial dissociation (a condition in which polarization of an isolated area of atrial myocardium occurs from an ectopic atrial focus exhibiting both an entrance and exit block). In this dog, the administration of lidocaine abolished P' waves superimposed on the sinus rhythm.[24] Lidocaine has been reported to

be well absorbed via the intratracheal route during cardiopulmonary resuscitation.[21] In clinical trials, in comparison with amiodarone, lidocaine resulted in decreased restoring of spontaneous circulation and increased incidence of asystole after defibrillation.[25] Because of this, lidocaine should only be considered an alternative treatment to amiodarone. Lidocaine is not recommended for treatment of ventricular fibrillation if defibrillation is planned, because it may reduce effectiveness of electrical defibrillation by increasing the defibrillation threshold and decreasing myocardial automaticity.[26,27] Lidocaine may be beneficial for ventricular arrhythmias after resuscitation, and should be considered if amiodarone is not available.[28,29] Lidocaine has been reported to be effective in the treatment of dexmedetomidine-induced bradycardia in healthy research dogs.[30] It is also reported to be a stabilizer of plasma and mitochondrial membranes and a protector of myofibrils. It is supposed that preservation of these structures contributes to the ability of the heart to function upon reperfusion; lidocaine infusion may therefore provide a safe and effective means to assist in myocardial preservation during long-term bypass procedures.[31] Lidocaine can also be used to treat atrial fibrillation induced by increased vagal tone, since it prolongs the refractory period of atrial myocytes enough to be effective in converting atrial fibrillation into sinus rhythm.[32]

Contraindications and adverse effects

Lidocaine should be avoided in patients with demonstrated hypersensitivity to the drug and in presence of atrioventricular or intraventricular conduction disturbances. Lidocaine must be carefully used in patients with hepatic insufficiency, congestive heart failure, shock, hypovolemia, respiratory depression, severe hypoxia, and bradycardia.

Transient and reversible signs of ataxia, sensory depression, tremors, nausea, and vomiting can occur in case of overdose, and disappear when the infusion is stopped. To prevent these side effects, the maximum recommended dose is 8 mg/kg in 1 hour. Rapid IV infusion, which could induce severe hypotension, should be avoided.

High plasma levels can reduce the upstroke velocity of the action potential and slow down the conduction velocity, thereby worsening preexisting arrhythmias due to conduction abnormalities or reentry;

irreversible asystole may occur. In dogs, signs of toxicity develop with a concentration higher than 8 μg/mL and include ataxia, nystagmus, sensory depression, bradycardia and hypotension; extremely high serum levels can also lead to cardiocirculatory collapse. Fortunately, the rapid metabolism of lidocaine makes it possible to reverse the clinical signs by stopping or reducing the infusion rate. The development of tonic-clonic seizures has been reported following suspected intra-arterial administration of lidocaine.[33] IV administration of lidocaine together with diltiazem or verapamil has been reported to be associated with an inability to maintain a mean arterial pressure above 50 mmHg.[34] Complications described after lidocaine use to treat supraventricular tachycardias include ventricular tachycardias, paroxysmal atrial flutter, and prolonged bradycardia.[35]

MEXILETINE

Electrophysiological properties

Mexiletine is a local anesthetic congener of lidocaine used for the oral treatment of patients with ventricular tachycardias. Mexiletine is similar to lidocaine in many of its electrophysiological properties, exhibiting use-dependence inhibition of I_{Na} (Fig. 7.3). In vitro, mexiletine shortens the action potential duration and the effective refractory period of the Purkinje fibers and, to a lesser extent, of myocardial ventricular cells. Mexiletine depresses the V_{max} of phase 0 by blocking I_{Na}, especially at faster rates, and depresses the automaticity of the Purkinje fibers, but not that of the normal sinus node. Mexiletine can result in severe bradycardia and abnormal sinus node recovery time in patients with sinus node dysfunction, while it does not alter electrophysiological parameters in patients with normal sinus node function. Mexiletine does not affect atrioventricular nodal conduction and can moderately depress the His–Purkinje conduction, unless preexistent intraventricular conduction abnormalities are present. Mexiletine does not seem to affect atrial muscle properties.

Hemodynamic effects

The hemodynamic effects of mexiletine are attributable to two different mechanisms: the direct negative inotropism, with a reduced stroke volume, and the neurohormonal reflex secondary to the peripheral vasodilation,

which acts to maintain the stroke volume and heart rate unchanged. Sinus node arrest, bradycardia, intraventricular and atrioventricular conduction delays are seldom reported.

Pharmacokinetics

Mexiletine is completely absorbed after oral administration. It mostly undergoes hepatic metabolism, which is influenced by the hepatic flow, and is inactivated by the mixed-function oxidase system, while only 10–15% is excreted in urine. In the blood, 70% of the drug is bound to plasma proteins. The volume distribution of mexiletine is broad due to its pronounced lipophilicity, and the therapeutic serum concentration is reached after three doses. A reduced efficacy can occasionally be noted after 3 to 6 months of continuous treatment with mexiletine. The drug's half-life in the dog is 4.5–7 hours.

Dose and administration

The recommended dose is 4–8 mg/kg PO every 8 hours in the dog (see Table 7.2).

Indications

Mexiletine is indicated for the treatment of ventricular tachycardias. A combination of mexiletine at 8 mg/kg PO every 8 hours and sotalol 2.5 mg/kg PO every 12 hours, but neither of the two drugs given alone, reduced ventricular ectopic beats and in general ventricular arrhythmias in a population of German Shepherds affected by inherited ventricular tachycardias[36] and in Doberman Pinschers with dilated cardiomyopathy.[37]

Contraindications and adverse effects

High doses first induce a progressive lengthening of the PQ interval and then also prolong the QT interval and QRS complex.

Mexiletine, similarly to lidocaine and tocainide, may cause gastrointestinal (e.g., nausea, vomiting) and central nervous system (e.g., sensory depression, tremors) side effects. Administration during feeding or in association with antacid drugs can mitigate these signs. Mexiletine can

also induce shortening of the QT interval, and high doses can induce depression of contractility.

CLASS Ic

PROPAFENONE

Electrophysiological properties

Propafenone blocks the fast sodium current in a use-dependent manner in the Purkinje fibers and to a lesser degree in the ventricular myocytes. Dissociation of propafenone from its receptors is slow, similar to that of flecainide. Propafenone decreases excitability and suppresses abnormal enhanced automaticity and triggered activities. It displays a weak I_{Kr} channel–blocking activity and a weak ß-adrenergic receptor–blocking activity. Propafenone reduces the sinus node discharge rate and increases interatrial, atrioventricular, and intraventricular conduction times, thereby prolonging the refractory period of atrial myocytes, ventricular myocytes, the atrioventricular node and accessory pathways.

Hemodynamic effects

Propafenone produces negative inotropic effects at high concentrations and may worsen the hemodynamic status in patients with preexisting systolic dysfunction.

Pharmacokinetics

In human beings, propafenone has shown great interindividual variability in its pharmacokinetic and pharmacodynamic properties. Propafenone undergoes extensive presystemic clearance that appears to be saturable, with bioavailability increasing as the dose increases. The drug is highly protein bound. Its elimination half-life is 5–8 hours in most human patients, although a range of 2–32 hours has been reported. Propafenone slows intracardiac conduction in a concentration-dependent manner. It is a weak ß-adrenergic blocker, but this property is of uncertain clinical significance. The major metabolic pathway for propafenone begins with aromatic ring hydroxylation, a pathway that may be determined by genetic factors.

Dose and administration

The suggested dose in dogs is 9–25 mg/kg/day PO (see Table 7.2).

Indications

Propafenone appears to be highly effective against postinfarction ventricular arrhythmias in experimental dogs. Propafenone depresses myocardial excitability of the left ventricle; ischemic left ventricular fibers are even more sensitive to the electrophysiological effects of propafenone than normal left ventricular fibers. This drug may be a suitable alternative in cases of lidocaine-resistant ventricular tachycardia during acute myocardial infarction.[38] Propafenone has also been described to be effective in the treatment of accessory pathway–mediated tachycardia.[39]

Contraindications and adverse effects

Propafenone depresses myocardial contractility and is contraindicated in patients presenting systolic dysfunction.

FLECAINIDE

Electrophysiological properties

Flecainide exhibits a marked use-dependent depressant effect on rapid sodium channels, decreasing the V_{max} with slow onset and offset kinetics. Dissociation of the drug from sodium channels is slow, with a time constant of 10–30 seconds (compared with 4–8 seconds for quinidine and less than 1 second for lidocaine). Thus, marked drug effects can occur at physiological heart rates. Flecainide shortens the action potential duration of the Purkinje fibers and at the same time prolongs that of the ventricular myocardium. It causes loss of the action potential dome in the epicardium but not in the endocardium, thus inducing a marked dispersion of repolarization and refractoriness within these layers. The heterogeneity induced by this condition provides the substrate for the development of arrhythmias, which explains the proarrhythmic effect of this drug.

Flecainide prolongs the conduction times of the atrial myocardium, atrioventricular node, and ventricular myocardium. The antegrade and retrograde refractory periods of accessory pathways can also increase

significantly in a use-dependent manner. At high concentrations, flecainide also exhibits calcium channel–blocking activity.[40]

Hemodynamic effects

Flecainide produces negative inotropic effects, particularly in patients affected by systolic dysfunction; it should therefore be used with caution or avoided in these patients.

Pharmacokinetics

In human beings, flecainide has been proven to be hepatically metabolized via the CYP450 system; specifically, it is a CYP2D6 substrate. It is excreted in urine and, to a lesser extent, in feces. Its half-life is approximately 20 hours.

Dose and administration

The suggested dose in dogs is 5 mg/kg/day PO (see Table 7.2).

Indications

The use of flecainide in dogs affected by idiopathic atrial fibrillation has been reported as it can reverse enhanced rate-dependent shortening of atrial refractoriness and decreases regional heterogeneity in the effective refractory period and wavelength of the functional microreentrant circuit, thus restoring sinus rhythm.[41] Flecainide has also been described to be effective in the treatment of accessory pathway–mediated tachycardia.[39]

Contraindications and adverse effects

Flecainide produces proarrhythmic effects and can induce ventricular tachycardia. The occurrence of proarrhythmia in dogs seems to be related to the drug's plasma concentration, with reentry appearing to be the underlying mechanism.[42]

CLASS Id

RANOLAZINE

At the moment, no clinical studies in the literature have proved the antiarrhythmic efficacy of ranolazine in dogs and cats.

CLASS IIa

ATENOLOL

Electrophysiological properties

Atenolol is a relatively specific $ß_1$ receptor blocker. At higher doses, this specificity may be lost and $ß_2$ blockade can occur. Atenolol does not possess any intrinsic sympathomimetic or membrane stabilizing activity (Fig. 7.5).

The cardiovascular effects of atenolol are secondary to the drug's negative inotropic and chronotropic activity and include a decreased sinus rate, slowed atrioventricular conduction, reduced cardiac output at rest and during exercise, decreased myocardial oxygen demand, and lower blood pressure.

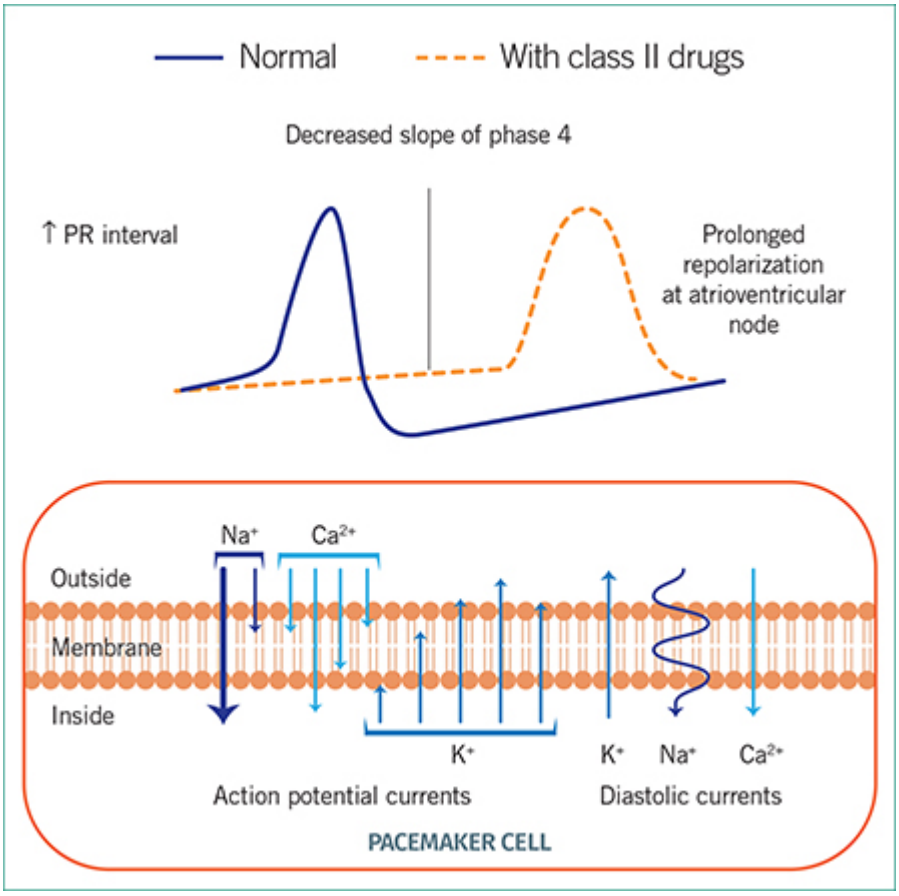


FIGURE 7.5. Schematic diagram of the effects of class II antiarrhythmics. Their mechanisms in arrhythmias are primarily cardiac ß-adrenoceptor blockade and a reduction in cAMP, which results in the reduction of both sodium and calcium currents and the suppression of abnormal pacemakers.

Hemodynamic effects

Atenolol, like propranolol, has negative inotropic effects and can precipitate or worsen congestive heart failure.

Pharmacokinetics

In cats, atenolol has been reported to have a bioavailability of approximately 90%. The drug has very low protein-binding properties (5–15%) and is distributed well into most tissues.

Atenolol has low lipid solubility and unlike propranolol, only small amounts of the drug are distributed into the central nervous system.

Atenolol is minimally biotransformed in the liver; 40–50% is excreted unchanged in urine and the bulk of the remainder is excreted unchanged in

feces (unabsorbed drug). Reported half-lives are 3.2 hours in dogs and 3.7 hours in cats.

The drug's ß-blockade effect in cats lasts for about 12 hours.[43,44]

Dose and administration

The suggested dose of atenolol in dogs is 0.2–1 mg/kg PO every 12–24 hours, or 6.25–25 mg (total dose) PO every 12 hours.

The suggested dose in cats is 6.25–12.5 mg PO per cat every 12–24 hours. The starting dose should be low and titrated to effect.

See Table 7.2 for a summary of the routes of administration and doses of antiarrhythmics in dogs and cats.

Indications

Atenolol is used in the treatment of supraventricular tachyarrhythmias, ventricular rhythm disturbances, and systemic hypertension, and in cats with hypertrophic cardiomyopathy.[43] Unlike propranolol, atenolol is relatively safe to use in animals with bronchospastic disease.

Contraindications and adverse effects

Atenolol is contraindicated in patients presenting overt heart failure, hypersensitivity to this class of agents, atrioventricular conduction disturbances, or sinus node dysfunction.

It should be used with caution in patients with significant renal insufficiency. Adverse effects have been reported to occur most commonly in geriatric animals and in those with acute congestive heart failure. Adverse effects include bradycardia, lethargy and depression, impaired atrioventricular conduction, congestive heart failure or worsening of congestive heart failure, hypotension, hypoglycemia, and bronchoconstriction.

Atenolol should be gradually withdrawn in patients who have been receiving the drug chronically. Concurrent use of atenolol and myocardial depressant anesthetic agents may lead to additive myocardial depression. Phenothiazines, furosemide, hydralazine, and other hypotension-producing drugs may increase the hypotensive effects of atenolol. Atenolol may prolong the hypoglycemic effects of insulin therapy. Coadministration of ß-

blockers with calcium channel blockers (or other negative inotropes) should be done with caution, particularly in patients with a preexisting cardiomyopathy or congestive heart failure. In dogs, exacerbation of keratoconjunctivitis sicca has also been described.[45]

CARVEDILOL

Electrophysiological properties

Carvedilol is an adrenergic-receptor antagonist, more specifically, a nonselective ß-blocker with α-1 antagonist properties and peripheral vasodilating effects (see Fig. 7.5). Carvedilol induces a moderate prolongation of the action potential duration and effective refractory period, slows atrioventricular conduction velocity, and reduces the dispersion of repolarization both of the atrial and ventricular myocardium.

Hemodynamic effects

Carvedilol can decrease blood pressure mainly by reducing arterial vascular resistance through its α-1 antagonist properties, causing a reduction in afterload. It also shows antioxidant effects and leads to a reduction in neutrophil infiltration, apoptosis inhibition, a reduction in vascular smooth muscle migration, and improvement of myocardial remodeling after acute myocardial infarction. Because carvedilol can prevent the formation of oxidized low-density lipoproteins and inhibit vascular smooth muscle cell proliferation and migration, it shows great promise in treating atherosclerotic disease formation and progression.

Pharmacokinetics

Carvedilol is rapidly absorbed and undergoes extensive first-pass metabolism in the liver, with some of its metabolites having biological activity. It reaches a peak concentration 1 to 2 hours postdosing and has an elimination half-life of about 4–7 hours. Its absorption is delayed by food. The drug is highly lipophilic and is highly protein bound. Its pharmacokinetic profile is not altered in the elderly or in patients with renal disease.

Dose and administration

The ideal dose of carvedilol in dogs with heart disease is unknown. In healthy dogs, doses ranging from 0.08–1.5 mg/kg PO every 12 hours have been reported. In dogs with experimental heart disease, doses ranging from 0.2–0.4 mg/kg PO every 24 hours have been shown to significantly reduce heart rate (see Table 7.2).

Indications

In humans, carvedilol is indicated for the chronic therapy of heart failure with reduced ejection fraction, hypertension, and left ventricular dysfunction following myocardial infarction in clinically stable patients.

In dogs, carvedilol administration did not improve echocardiographic or neurohormonal indicators of heart function. The lack of effect may be related to the severity of the disease, carvedilol dose, or brevity of follow-up time.[46]

Contraindications and adverse effects

Absolute contraindications to the use of carvedilol include severe hypotension, second- or third-degree atrioventricular block, sick sinus syndrome, severe bradycardia in the absence of a functional pacemaker, severe decompensated heart failure requiring inotropic support, and a history of serious hypersensitivity reaction. Clinicians should use caution in patients with a history of asthma or reactive airway disease; the recommendation is to avoid using carvedilol in patients with active wheezing due to its ß-blocking properties. Additionally, carvedilol is contraindicated in case of severe hepatic impairment.

ESMOLOL

Electrophysiological properties

Esmolol is a weakly fat-soluble ß-blocker for IV use (see Fig. 7.5). It is relatively cardioselective and does not possess an intrinsic sympathomimetic effect or membrane stabilizing action. Its electrophysiological effects, which include a decrease in the sinus discharge rate, a prolongation of the sinus node recovery time, and a delay in the atrioventricular conduction velocity, can be observed within 5 minutes of its IV administration.

Esmolol's antiarrhythmic activity is thought to result from its blockade of adrenergic stimulation of cardiac pacemaker potentials.

Hemodynamic effects

Esmolol has a negative inotropic and chronotropic activity, which can lead to reduced myocardial oxygen demand. Its administration results in a reduction of systolic and diastolic blood pressures at rest and during exercise.

Pharmacokinetics

Esmolol is an ultra-short-acting ß-adrenergic blocking agent. Its short duration of action is attributable to rapid enzymatic hydrolysis by red blood cell esterase. Steady state is achieved approximately 5 minutes after intravenous administration of a loading dose; it is achieved after 30 minutes if a no-loading dose is administered.

Esmolol is rapidly metabolized in the blood by esterase. Renal or hepatic dysfunction do not appreciably alter the drug's elimination characteristics. Its terminal half-life is about 10 minutes and its duration of action after discontinuation of IV infusion is 10–20 minutes.

Twenty-four hours after administration, 88% of the drug is excreted in urine as inactive acid metabolites.

Dose and administration

In dogs and cats, ultra short-acting ß-blockade is achieved with a loading dose of 200–500 µg/kg IV over 1 minute, followed by a CRI at 25–200 µg/kg/min (see Table 7.2).

Indications

Esmolol may be used as test drug to indicate whether ß-blocker therapy is warranted to treat the arrhythmia, or administered as an infusion in the short-term treatment of supraventricular tachycardias.

The use of esmolol resulted in decreasing morbidity and mortality in septic shock patients and in patients with tachycardia due to intoxication.[47]

ß-Blockers have been shown to have beneficial effects in systemic inflammatory response syndrome (SIRS) and sepsis thanks to their ability

to control heart rate and to improve lipid and glucose metabolism, glucose homeostasis, cytokine expression, and myocardial function. A case series reported the successful use of esmolol in 2 dogs with septic shock and persistent tachycardia.[48]

Contraindications and adverse effects

Esmolol is contraindicated in patients with overt congestive heart failure, atrioventricular conduction disturbances, sinus node dysfunction, or cardiogenic shock. In addition, esmolol should be used with caution in patients with bronchoconstrictive lung disease or diabetes mellitus.

As the other ß-blockers, esmolol has a great negative inotropic effect. The most frequent side effect is a dose-dependent hypotension, and in presence of cardiac failure it can worsen the congestion.

As esmolol may increase serum digoxin levels by up to 20%, it should be used with caution in patients under digoxin therapy, with increased monitoring when necessary. Esmolol should be titrated cautiously in patients receiving morphine, since morphine may increase steady-state esmolol serum concentrations by up to 50%.

METOPROLOL

Electrophysiological properties

Metoprolol is a relatively specific $ß_1$ blocker (see Fig. 7.5). At higher doses, this specificity may be lost and $ß_2$-blockade may occur. Metoprolol does not possess any intrinsic sympathomimetic activity like pindolol, or any membrane stabilizing activity like pindolol or propranolol. Metoprolol has negative inotropic and chronotropic effects, which include decreased sinus rate, slowed atrioventricular conduction, reduced cardiac output at rest and during exercise, decreased myocardial oxygen demand, reduced blood pressure, and inhibition of isoproterenol-induced tachycardia.[49]

Hemodynamic effects

Due to metoprolol's effects on the heart rate and vessels, its administration may be associated with reduced blood pressure.

Pharmacokinetics

Metoprolol is rapidly and nearly completely absorbed in the gastrointestinal tract, but it has a relatively high first-pass effect (50%), so systemic bioavailability is reduced.

The drug has very low protein-binding characteristics (5–15%) and is distributed well into most tissues. Metoprolol is primarily biotransformed in the liver; the unchanged drug and metabolites are then mainly excreted in urine. The reported half-lives in dogs and cats are 1.6 hours and 1.3 hours, respectively.

Dose and administration

In dogs, the suggested dose of metoprolol is 5–50 mg (total dose) PO every 8–12 hours; the initial dose should be low, followed by individual dose titration. In cats, the recommended dose is 2–15 mg (total dose) PO every 8 hours.

See Table 7.2 for a summary of the routes of administration and doses of antiarrhythmics in dogs and cats.

Indications

Metoprolol may be effective to treat automatic focal atrial tachycardia and premature ventricular ectopic beats.

Contraindications and adverse effects

Metoprolol is contraindicated in patients with overt congestive heart failure, hypersensitivity to this class of agents, atrioventricular conduction disturbances, and sinus node dysfunction. It is also relatively contraindicated in patients with bronchospastic lung disease.

Metoprolol should be used cautiously in patients with significant hepatic insufficiency.

Safe use during pregnancy has not been established, but adverse effects to fetuses have apparently not been documented. Adverse effects have been reported to occur most commonly in geriatric animals or in those with acute decompensating heart disease. Adverse effects considered to be clinically relevant include bradycardia, lethargy and depression, impaired atrioventricular conduction, congestive heart failure or worsening of heart

failure, hypotension, hypoglycemia, and bronchoconstriction. Syncope and diarrhea have also been reported in canine patients taking ß-blockers.

Metroprolol should be withdrawn gradually in patients under chronic treatment with this drug.

Furosemide, hydralazine, and other hypotension-producing drugs may increase the hypotensive effects of metoprolol.

Coadministration of ß-blockers with calcium channel blockers (or other negative inotropes) should be done with caution, particularly in patients with a preexisting cardiomyopathy or congestive heart failure.

NADOLOL

Electrophysiological properties

Nadolol is a nonselective ß-adrenergic antagonist. It competitively blocks $ß_1$ receptors at the level of the heart and vascular smooth muscle, thus inhibiting the effect of catecholamines on these receptors. In the vascular smooth muscle, nadolol causes a reduction in peripheral resistance, which results in decreased systolic and diastolic blood pressures. Furthermore, nadolol slows conduction velocity at the atrioventricular node and suppresses automaticity, which decreases the heart rate both at rest and during exercise.

Hemodynamic effects

Administration of nadolol leads to a decrease in both blood pressure and heart rate. The decrease in blood pressure is partial and short-lasting. Nadolol effectively inhibits isoproterenol-induced tachycardia and decreases cardiac output by 18%. The hemodynamic effects of nadolol may be enhanced by the addition of a diuretic. A single daily dose of nadolol alone can reduce blood pressure significantly with minimal cardiodepressant effects and no important side effects.

Pharmacokinetics

Nadolol is most commonly administered orally in humans. It is given once daily as it has a long half-life. After oral and IV administration, nadolol is excreted unchanged in the urine and feces and its half-life at night is prolonged due to a decrease in nocturnal urine flow.

Dose and administration

The dose used in experimental studies in dogs was 1 mg/kg PO once daily.

Indications

In human medicine, nadolol is a medication used to treat angina and hypertension. It is also used off-label for the management of different arrhythmias. Nadolol is used in patients with atrial fibrillation to reduce ventricular response and in case of paroxysmal atrial fibrillation.[50] It is also prescribed for the treatment of ventricular ectopic beats or ventricular tachycardia in individuals with long QT syndrome to avoid syncopal episodes and prevent sudden cardiac death.[50] Nadolol is effective in the treatment of severe ventricular arrhythmias in patients affected by catecholaminergic polymorphic ventricular tachycardia as it reduces the effect of catecholamines on ß-adrenergic receptors.[51] As a nonselective ß-blocker, nadolol prevents arrhythmias and cardiac arrest much more effectively than other selective $ß_1$-blocking drugs. It is effective in the termination of acute onset supraventricular tachycardia and can be used to control the ventricular rate in patients with sustained and incessant supraventricular tachycardia.[52]

Contraindications and adverse effects

Nadolol has been described as a well-tolerated drug with minimal side effects.[53,54] Its adverse effects are mainly correlated with $ß_2$ receptor blockade. No major organ injuries have been reported after the administration of nadolol. In human medicine, a mild to moderate increase in liver enzymes has been described after its administration, with no evidence of clinically relevant hepatic disease.[55]

PROPRANOLOL

Electrophysiological properties

Propranolol blocks both $ß_1$- and $ß_2$-adrenergic receptors in the myocardium, bronchi, and vascular smooth muscle (see Fig. 7.5). Propranolol does not have any intrinsic sympathomimetic activity. Additionally, propranolol

exhibits a membrane-stabilizing activity (quinidine-like), which affects the cardiac action potential, as well as a direct myocardial depressant activity. Cardiovascular effects induced by propranolol include decreased sinus rate, depressed atrioventricular conduction, reduced cardiac output at rest and during exercise, decreased myocardial oxygen demand, decreased hepatic and renal blood flow, reduced blood pressure, and inhibition of isoproterenol-induced tachycardia. The drug's electrophysiological effects on the heart include decreased automaticity and increased or no effect on the effective refractory period; it does not alter conduction velocity.

Hemodynamic effects

Propranolol has a negative inotropic effect and can precipitate or worsen congestive heart failure.

Pharmacokinetics

After oral administration, propranolol is rapidly absorbed and metabolized in the liver with a variable bioavailability of 2% to 27% depending on the vascular flow (influenced by feeding) and on the possible presence of hepatic or cardiac venous congestion.[56]

Dose and administration

In dogs, propranolol can be used to treat ventricular arrhythmias. It should be administered at a dose of 0.02–0.06 mg/kg IV over 2–3 minutes or 0.2 mg/kg PO every 8 hours, with a maximum dose of 1 mg/kg/day.

Propranolol can also be used in case of ventricular hypertrophy at a dose of 0.125–0.25 mg/kg PO every 12 hours, and to treat arrhythmias correlated with pheochromocytomas at a dose of 0.15–0.5 mg/kg PO every 8 hours, or 0.03–0.10 mg/kg IV.

In cats, propranolol can be used to treat ventricular arrhythmias at a dose of 0.02 mg/kg in a slow IV infusion (up to a maximum of 1 mg/kg). The oral dose is 2.5 mg (up to 10 mg) per cat every 8–12 hours.

Propranolol can also be used in cats with hypertrophic cardiomyopathy at the following doses: 2.5 mg PO every 8–12 hours in cats weighing 4.5 kg or less, and 5 mg PO every 8–12 hours in cats weighing 5 kg or more.

For systemic hypertension, the recommended dose is 2.5–5.0 mg PO every 8–12 hours.

See Table 7.2 for a summary of antiarrhythmic drug routes of administration and doses in dogs and cats.

Indications

Propranolol is indicated to treat rhythm disturbances such as supraventricular rhythm disturbances, focal atrial tachycardia secondary to digitalis toxicity, and atrial fibrillation (generally in combination with digoxin). Furthermore, propranolol reportedly improves cardiac performance in animals with hypertrophic cardiomyopathy. It has been used to treat systemic hypertension and clinical signs associated with thyrotoxicosis and pheochromocytoma.

Contraindications and adverse effects

Propranolol is contraindicated in patients with congestive heart failure, hypersensitivity to this class of agents, atrioventricular conduction abnormalities, and sinus node dysfunction.

Propranolol should be used cautiously in patients with significant renal or hepatic insufficiency, in those that are being treated with digoxin, or in digitalis-intoxicated patients, because it may lead to severe bradycardia.

Propranolol can mask the clinical signs associated with hypoglycemia. It can also cause hypoglycemia or hyperglycemia and should therefore be used with caution in labile diabetic patients.

Propranolol can interact with different drugs: cimetidine may decrease its metabolism and thus increase its concentration in blood, furosemide and hydralazine may increase its effects, and rifampin or phenytoin may increase its metabolism. Propranolol increases hepatic enzyme induction correlated with phenobarbital administration. It may also prolong the hypoglycemic effects of insulin therapy, impair lidocaine clearance, and block the effects of theophylline (bronchodilation). Coadministration of ß-blockers with calcium channel blockers (or other negative inotropic agents) should be done with caution, particularly in patients with a preexisting cardiomyopathy or congestive heart failure.

CLASS IIb

ISOPROTERENOL

Electrophysiological properties

Isoproterenol is a synthetic $ß_1$- and $ß_2$-adrenergic agonist with no appreciable α-activity at therapeutic doses.

Isoproterenol induces an increase in the sinus node discharge rate by increasing the slope of phase 4 of the action potential. It also enhances atrioventricular conduction by decreasing the effective refractory period of the atrioventricular node. Isoproterenol has no effect on the His–Purkinje conduction time.

Hemodynamic effects

The hemodynamic effects of isoproterenol include decreased total peripheral resistance, increased cardiac output, increased venous return to the heart, and increased rate of discharge by cardiac pacemaker cells.

Pharmacokinetics

Isoproterenol is immediately active upon infusion. Its half-life is 2.5 to 5 minutes. Conjugation in hepatic and pulmonary tissues is the drug's major method of metabolism, and it is excreted in urine in the form of sulfate conjugates.

Dose and administration

The suggested dose of isoproterenol in dogs is 0.04–0.08 µg/kg/min IV (see Table 7.2).

Indications

Isoproterenol is a drug used to treat bradycardia and has a structural resemblance to epinephrine.

Contraindications and adverse effects

Isoproterenol is contraindicated in patients with tachycardia or atrioventricular block caused by cardiac glycoside intoxication. It is also contraindicated in ventricular arrhythmias that do not require increased inotropic activity.

Isoproterenol should be used with caution in patients with coronary insufficiency, hyperthyroidism, renal disease, hypertension, or diabetes.

CLASS IIc

ATROPINE

Electrophysiological properties

Atropine is an antimuscarinic agent with a direct vagolytic action. Atropine increases the sinus node discharge rate and shortens its recovery time. It also shortens the sinus node conduction time and the refractoriness of the atrial myocardium. Atropine improves atrioventricular conduction by shortening the effective refractory period of the atrioventricular node but appears to have no direct effects on His–Purkinje conduction or refractoriness.

Hemodynamic effects

When given at a parasympathetic blocking dose, atropine induces an increase in heart rate and arterial pressure, while at the same time decreasing the stroke volume and ejection fraction due to the decreased diastolic filling time.

Pharmacokinetics

After IV administration of 1.35 and 2.15 mg of atropine in human beings, the urinary excretion of unchanged drug was 57% of the dose. The steady-state volume of distribution was 210 L, which implies extensive tissue binding and/or partitioning. Renal plasma clearance was 660 mL/min, suggesting significant tubular secretion. The renal clearance of atropine depended on urine flow. Urinary excretion of tropine, one of its metabolites, amounted to 29% of the dose. The kinetics of the metabolite were first order.[57] In dogs, the pharmacokinetics of atropine were studied after

endotracheal and endobronchial administration. The maximal atropine concentration was significantly higher with endobronchial administration, with a half-life of 39.3 +/– 5.2 min. Endobronchial administration resulted in a 16% increase in heart rate, beginning immediately after drug delivery and peaking after 5 min.[58]

Dose and administration

The suggested dose in dogs and cats is 0.02–0.04 mg/kg by IM, subcutaneous (SC) or IV route; or 0.04 mg/kg PO every 6–8 hours (see Table 7.2).

Indications

Atropine or atropine sulfate is indicated to achieve antisialagogue/antivagal effects, in cases of organophosphate/muscarinic poisoning, and to treat bradycardia. Atropine is the first-line therapy for symptomatic bradycardia in the absence of reversible causes. If there is no improvement in the patient's clinical status after repeated doses of atropine, additional treatment with atropine is unlikely to be effective. However, transient improvements with repeat dosing are an indication to continue treatment with atropine and maximum recommended cumulative doses may be exceeded.

Contraindications and adverse effects

The most common adverse effects of atropine are related to the drug's antimuscarinic properties, including xerostomia, blurred vision, photophobia, tachycardia, flushing, and hot skin. Constipation, difficulty with urination, and anhidrosis may occur. Atropine decreases the rate of mexiletine absorption; this can be prevented by combined IV delivery of metoclopramide with atropine.

GLYCOPYRROLATE

Electrophysiologycal properties

Glycopyrrolate, also known as glycopyrronium, is an anticholinergic drug. Glycopyrrolate has been widely used as a preoperative medication to inhibit salivary gland and respiratory secretions, to create a sedative and amnesic

effect, and to prevent reflex bradycardia. Its primary mechanism of action is the blockage of the effects of acetylcholine at the parasympathetic sites in various tissues. This blockage primarily occurs in the central nervous system, smooth muscle, and secretory glands.

Pharmacokinetics

Glycopyrrolate is an antimuscarinic agent with similar actions to those of atropine. Glycopyrrolate is a quaternary ammonium compound, but, unlike atropine, it does not cross appreciably into the central nervous system. In dogs, following IV administration, the onset of action generally occurs within 1 minute. The peak effects are described to occur approximately 30–45 minutes after IM or SC administration. The effects persist for 2–3 hours. Glycopyrrolate is eliminated rapidly after IV administration. Only a small amount is metabolized, and most of it is eliminated unchanged in the feces and urine.

Dose and administration

Glycopyrrolate can be used in dogs at a dose of 0.01 mg/kg IV, IM, or SC and in cats at a dose of 0.005–0.01 mg/kg IV or IM or 0.01–0.02 mg/kg SC.

Indications

Glycopyrrolate has been widely used as a preanesthetic anticholinergic agent to inhibit salivary gland and respiratory secretions. It has been used for its antisialagogue effect, for reflex bradycardia prevention, and to treat sinus bradycardia, sinoatrial arrest, and low grade atrioventricular block in which anticholinergic therapy may be beneficial.

Contraindications and adverse effects

Glycopyrrolate should be used with caution in dogs and cats hypersensitive to it, and it should not be used in pregnant animals. It is advised to refer to the recommendations listed in the atropine section regarding contraindications and adverse effects.

CLASS IId

DIGOXIN

Electrophysiological properties

The antiarrhythmic effect of the cardioactive glycoside digoxin is related to the central and peripheral vagal effect induced by stimulation of the M2 muscarinic receptors. The vagotonic effect of digoxin on the atrioventricular node induces a decrease in its conduction velocity and a prolongation of its refractory period. Digoxin does not affect (or only slightly reduces) sinus node automaticity but reduces the atrial myocyte refractory period. In addition, it inhibits the sodium/potassium pump, thereby increasing the intracellular calcium concentration acting on the I_{CaL} channels, which induces a positive inotropic effect. Digoxin shows dose-dependent effects: low doses induce the vagotonic M2-mediated action, while higher doses inhibit the sodium-potassium pump. Electrocardiographic effects at therapeutic ranges are minimal. Sinus rate and QRS complex duration are unchanged, except in those patients with sinus dysfunction or atrioventricular conduction disturbances, or in patients with atrial fibrillation, in which digoxin increases the RR interval.

Pharmacokinetics

After oral intake, absorption occurs almost totally in the small intestine. At therapeutic ranges, 20–30% of the active principle is bound to plasma proteins. Renal excretion predominates, with both glomerular filtration and tubular secretion. In dogs, the half-life of digoxin varies greatly, between 14.4 and 56 hours.

Dose and administration

The suggested initial dose in dogs is 0.003–0.01 mg/kg PO every 12 hours (up to a maximum of 0.375 mg/dog/day or, rarely, 0.5 mg/dog/day). The suggested initial dose for cats is 0.007 mg/kg PO every 48 hours. Lean body weight should be used to determine dosage. Serum digoxin levels should be measured 5–10 days after the first administration and 8–10 hours after dosing. The therapeutic level of digoxin is 0.5–1.2 ng/mL. If toxicity is suspected, therapy should be stopped for at least 1–2 days and then resumed at half the initial dose (see Table 7.2).

Indications

Digoxin is mainly used to treat ventricular response during atrial fibrillation in patients with congestive heart failure, but the antiarrhythmic action due to its vagotonic effect may be limited or counteracted by exercise, stress, or any condition that may increase the sympathetic drive. Therefore, digoxin is often associated with sustained-release diltiazem.[59]

Contraindications and adverse effects

Digoxin should be used with caution in patients with severe pulmonary disease, hypoxia, acute myocarditis, myxedema, acute myocardial infarction, frequent ventricular premature contractions, ventricular tachycardias, chronic constrictive pericarditis, or incomplete atrioventricular block.

The side effects of digoxin are correlated with high plasma levels and are both cardiac and noncardiac. The former are mainly rhythm disturbances, such as high-degree atrioventricular blocks or bidirectional ventricular tachycardias. Noncardiac effects include anorexia, vomiting, diarrhea, weight loss, and cone dysfunction.[60] Digoxin must be carefully used in patients with renal failure or hypokalemia.

CLASS IIe

AMINOPHYLLINE

Electrophysiological properties

Even if the mechanism of action is not completely understood, amynophylline primary acts as an adenosine receptor inhibitor. Aminophylline enhances atrioventricular nodal and His–Purkinje fiber system conduction and decreases the duration of the effective refractory period of ventricular myocytes.[61]

Pharmacokinetics

In human medicine, aminophylline has been proven to be rapidly and completely absorbed by the body and converted to theophylline, which is up to 40% bound by albumin. The remaining unbound theophylline

distributes freely throughout the body except for body fat. The volume of distribution ranges from 0.3 to 0.7 L/kg. Theophylline passes across the placenta and is present in breast milk. Theophylline metabolism occurs in the liver via the cytochrome CYP450 system. At lower concentrations, it is a substrate of CYP1A2, and at higher concentrations, CYP2E1 may also participate in its metabolism. The pharmacokinetics of theophylline are not predictable by sex, age, or other characteristics.

Dose and administration

The suggested dosage is 6–11 mg/kg PO or SC every 8 hours in dogs and 5 mg/kg PO every 8–12 hours in cats (see Table 7.2).

Indications

Aminophylline has a weak positive inotropic and chronotropic effect; it can therefore be used in patients with sinus node dysfunction and in cats with third-degree atrioventricular block.

Contraindications and adverse effects

Aminophylline has a narrow therapeutic index and is associated with a wide range of adverse effects. The adverse effects depend on the peak serum concentrations of theophylline in the body. The most common of these effects include nausea, vomiting, increase in urine volume, increased gastric acid secretion, cardiac arrhythmias including focal atrial tachycardia, and central nervous system depression. Aminophylline contraindications include patients with hypersensitivity to theophylline, ethylenediamine, or any component of the drug formulation. It should be used with caution in patients with concurrent illnesses such as cardiac disease complicated by congestive heart failure, renal impairment, hepatic dysfunction due to any cause, hypo/hyperthyroidism, epilepsy.

CLASS IIIA

AMIODARONE

Electrophysiological properties

Amiodarone is a benzofuran derivate. It shows class III effects (blocks I_{Kr}), but also class I (blocks I_{Na}), class II (antiadrenergic) and class IV (blocks I_{CaL}) actions. Its most significant electrophysiological effect is that it prolongs the repolarization and refractoriness of the atrial myocardium, His–Purkinje system, and ventricular myocardium (Fig. 7.6). However, amiodarone has not been shown to have a significant effect on the sinus node and atrioventricular nodal action potential. The drug has use-dependence properties and depresses conduction at fast heart rates more than at slower rates. It depresses phase 0 in the Purkinje fibers; this use-dependent effect appears to result from a selective block of inactivated sodium channels. Amiodarone noncompetitively antagonizes α- and ß-receptors and blocks the conversion of thyroxine (T_4) to triiodothyronine (T_3), which may account for some of its electrophysiological effects. Amiodarone shows slow channel–blocking effects, and chronic oral therapy has been found to slow the spontaneous sinus node discharge rate in anesthetized dogs.[62]

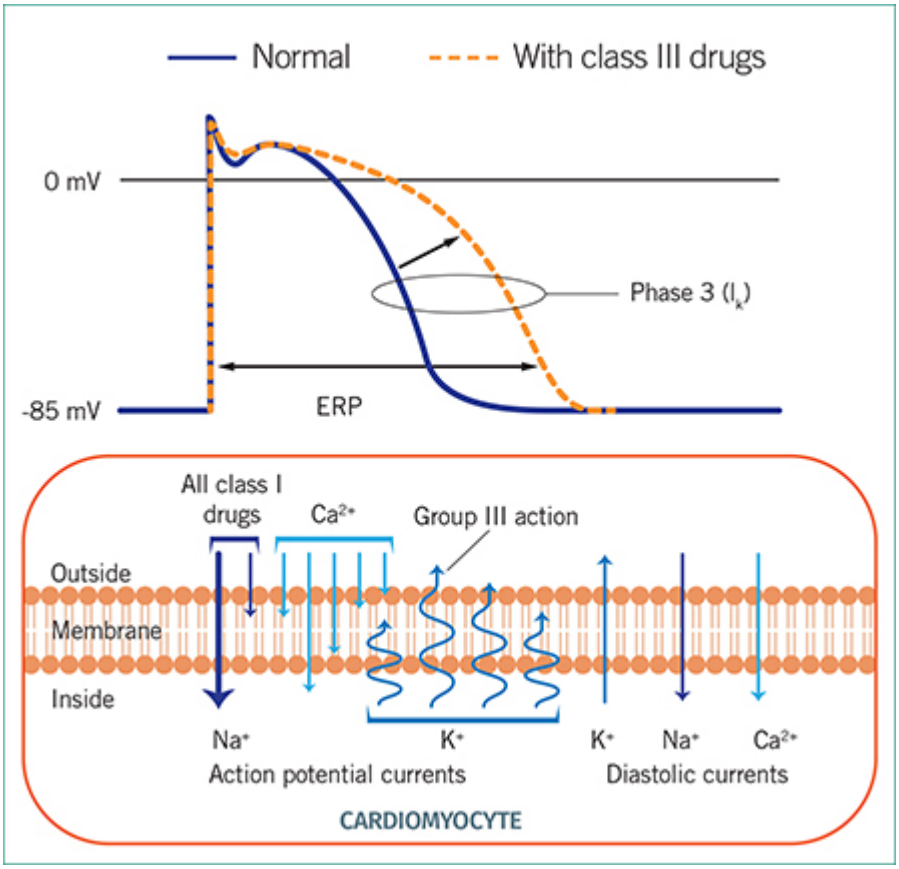


FIGURE 7.6. Schematic diagram of the effects of class III agents. Class III drugs block the I_{Kr} channels responsible for repolarization during phase 3 of the action potential. Amiodarone therefore increases the duration of the action potential and the effective refractory period (ERP) of atrial and ventricular myocytes.

Hemodynamic effects

Amiodarone shows a vasodilatory effect on peripheral and coronary vasculature. When administered IV, amiodarone decreases the heart rate, systemic vascular resistance, and left ventricular systolic function. Oral doses of amiodarone effective to treat arrhythmias do not depress left ventricular systolic function, even in patients with a reduced ejection fraction, and the ejection fraction and cardiac output can slightly improve. However, due to its antiadrenergic effect, amiodarone should be used with caution in patients with congestive heart failure, particularly if it is administered IV.[62]

Pharmacokinetics

Amiodarone is a lipophilic molecule with a high volume of distribution and long half-life (3 days). During prolonged and chronic oral treatment, its active metabolite (N-desmethyl-amiodarone) accumulates in the myocardium, liver, and lungs. In dogs, several studies have demonstrated that a loading oral dose of 25 mg/kg every 12 hours followed by a maintenance dose of 30 mg/kg/day for 3–5 weeks had effects on arterial pressure, left ventricular performance indices, electrocardiogram, exercise tolerance, and biochemical parameters. Another study in dogs demonstrated that amiodarone administered in IV boluses at cumulative doses of up to 12.5 mg/kg did not produce acute cardiovascular effects.[63] In healthy Beagles, therapeutic serum concentrations of amiodarone between 1 and 2.5 µg/mL were achieved within 4 days when given 25–30 mg/kg every 12 hours. When serum concentrations were 4 times the recommended dose, the dogs became anorexic and lost weight, but their left ventricular function and exercise capacity was unchanged. No changes were observed when dogs were maintained on 25–30 mg/kg every 24 hours.

Dose and administration

For recurrent ventricular tachycardia not controlled with other less toxic drugs, the administration of amiodarone can be considered at a dose of 10–25 mg/kg PO every 12 hours for 7 days, followed by 5–7.5 mg/kg PO every 12 hours for 14 days, and finally by 7.5 mg/kg/day PO.

In cats, the use of IV amiodarone was described in an animal with ventricular tachycardia caused by ventricular fibrillation after direct-current defibrillation. An initial slow bolus (2 mg/kg in 10 minutes) was administered, followed by a CRI (0.8 mg/kg/h for 6 hours and 0.4 mg/kg/h for a further 18 hours); after 4 hours of CRI, sinus rhythm was restored. Sinus rhythm was then maintained with a daily amiodarone dose of 12.5 mg/kg PO (see Table 7.2).

Indications

Amiodarone has been used to suppress supraventricular and ventricular tachycardias. Success rates vary widely depending on the population of patients, type of arrhythmia, underlying heart diseases, and length of follow-up.

Contraindications and adverse effects

A prolonged use of amiodarone can induce important side effects including anorexia, hepatopathy, pulmonic infiltrations, thyroid dysfunction, keratopathy,[64] photosensitivity, hyperpigmentation, thrombocytopenia and anemia,[65] and peripheral neuropathies. Its IV administration can cause severe hypotension (due to the vasoactive solvent polysorbate 80) and cutaneous rash with subcutaneous edema. These reactions can be avoided using an injectable formulation devoid of this solvent (amiodarone HCl or nexterone). A 2 mg/kg IV bolus administered over 10 minutes, followed by a CRI at 0.8 mg/kg/h for 6 hours (then decreased to 0.4 mg/kg/h for 18 hours) of a formulation that does not include the polysorbate or benzyl alcohol carriers showed no adverse acute side effects in 17 dogs.[66] Amiodarone can induce hepatopathy with increased hepatic enzyme and cholesterol levels. The thyroid dysfunction induced by amiodarone is due to the iodine content of amiodarone (organic iodine represents about 37% of the drug's weight, 10% of which is deiodinated to be released as free iodine), and to inhibition of peripheral and pituitary 5'-deiodinase, which

stops the conversion of T_3 into T_4, with a paradoxical increase in TSH. For this reason, careful monitoring of thyroid hormones during amiodarone treatment is suggested.

There are several potentially significant interactions that may occur with amiodarone use. The following is a partial list of interactions that are most likely seen in veterinary patients: amiodarone may significantly increase the serum levels and/or pharmacological effects of anticoagulants, ß-blockers, calcium-channel blockers (e.g., diltiazem, verapamil), cyclosporin, digoxin, lidocaine, methotrexate, procainamide, quinidine, and theophylline. Cimetidine may increase serum levels of amiodarone.

DRONEDARONE

Dronedarone is the deiodinated analogue of amiodarone, with similar electrophysiological effects when used to treat arrhythmias in an acute setting. Experimental studies in dogs have shown that after 4 weeks of administration with an oral dose of 25 mg/kg, dronedarone does not induce prolongation of the QT interval and of the action potential of the papillary muscles. Dronedarone at 2.5 mg/kg significantly lengthened the PQ interval, reduced cardiac output, and increased systemic vascular resistance. Dronedarone produced acute negative dromotropy, inotropy, and lusitropy effects in anesthetized dogs.[67] It reduces the early and late afterdepolarizations induced by dofetilide and strophantin in the Purkinje fibers. In ventricular myocytes, dronedarone reduces the I_{CaL} and I_{Kr} currents. In a canine experimental model of third-degree atrioventricular block with torsades de pointes, it showed therapeutic efficacy with a dose of 2.5 mg/kg administered twice a day. The antiarrhythmic effect was correlated with an increase in the action potential duration, and with the suppression of early afterdepolarizations, ventricular ectopic beats, and torsades de pointes.[66] Oral chronic dronedarone administration at 20 mg/kg every 12 hours for 3 weeks prolongs the PP interval, the idioventricular rhythm cycle length, and the QT interval. Oral dronedarone attenuates the duration of sustained atrial fibrillation in dogs by prolonging the atrial effective refractory period more than the atrial action potential duration, thus inducing postrepolarization refractoriness.[68]

Poyendarone, a deuterated analogue of dronedarone, was tested on a canine model of paroxysmal atrial fibrillation to evaluate the reduction of

cardiovascular adverse events such as congestive heart failure and excessive QT interval prolongation with respect to dronedarone. Poyendarone attenuated the inhibition of sinus automaticity and prolonged the atrial effective refractory period, maintaining blood pressure and ventricular rate stable. Therefore, poyendarone showed a more potent anti–atrial fibrillation action and cardiovascular safety margin than dronedarone.[69,70]

CLASS IIIb

SOTALOL

Electrophysiological properties

Sotalol is a racemic mixture of two different isomers: L-sotalol and D-sotalol. It is a selective ß-blocker with class III properties due to the isomers (see Fig. 7.6), while the ß-blocking action is due to the L-isomer. The ß-blocking potency of sotalol is about 1/3 of that of propranolol, and it does not have any sympathomimetic or anesthetic properties. The drug's ß-blocking effects predominate with low doses, while class III effects are evident with high doses. The prolongation of the repolarization phase depends on the blood concentration of sotalol and results from I_{Kr} repolarization current blockade. The class III electrophysiological effects prolong the effective refractory period of the atrial cells, ventricular cells, and accessory pathways. The prolongation of the action potential is greater at slower rates (reverse use dependence). The resting membrane potential, action potential amplitude, and V_{max} are not significantly altered.

Hemodynamic effects

Sotalol has negative inotropic effects only through its ß-blocking action, and in human patients with reduced cardiac function, it can decrease the cardiac index, increase the filling pressure, and cause overt heart failure. Therefore, sotalol must be used with caution in patients with marginal cardiac compensation but appears to be well tolerated in patients with normal cardiac function. In dogs, sotalol causes a mild decrease in left ventricular systolic function, both in individuals with ventricular

arrhythmia[71] and in healthy dogs, in which a negative chronotropic effect at higher heart rates has also been described.[72]

Pharmacokinetics

Sotalol is almost entirely absorbed after oral administration and is excreted renally. Since it is not hepatically metabolized, its bioavailability is nearly 100%, with a peak plasmatic concentration reached in 1.5–2 hours after oral administration. Sotalol does not bind to plasma proteins.

Dose and administration

The recommended doses of sotalol are 0.5–2 mg/kg PO every 12–24 hours in dogs and 1–3 mg/kg PO every 12 hours in cats (see Table 7.2).

Indications

Sotalol is useful for the treatment of supraventricular and ventricular tachycardia in dogs.

Contraindications and adverse effects

Sotalol is contraindicated in patients with asthma, sinus node dysfunction, atrioventricular conduction disturbances, repolarization disturbances, cardiogenic shock, or congestive heart failure. Because of its potential negative inotropic effects, sotalol must be used with caution in patients presenting with congestive heart failure, particularly with right ventricular systolic dysfunction. Sotalol must also be used with caution in patients with diabetes mellitus, hyperthyroidism, and renal dysfunction.

Furosemide, hydralazine or other hypotensive drugs may increase the hypotensive effects of sotalol. Coadministration of ß-blockers with calcium channel blockers (or other negative inotropes) should be done with caution.

CLASS IIIc

VERNAKALANT

At the moment, no clinical studies in the literature have proved the antiarrhythmic efficacy of vernakalant in dogs and cats.

CLASS IVa

VERAPAMIL AND DILTIAZEM

Electrophysiological properties

By blocking I_{CaL} in all cardiac fibers, verapamil reduces the height of the action potential plateau, slightly shortens the action potential duration of muscular fibers, and slightly prolongs the action potential of the Purkinje fibers (Fig. 7.7). Verapamil does not influence the amplitude of the action potential, the V_{max} of phase 0, and the resting membrane voltage in cells that have a fast response due to I_{Na}, such as atrial and ventricular muscular cells and Purkinje fibers.

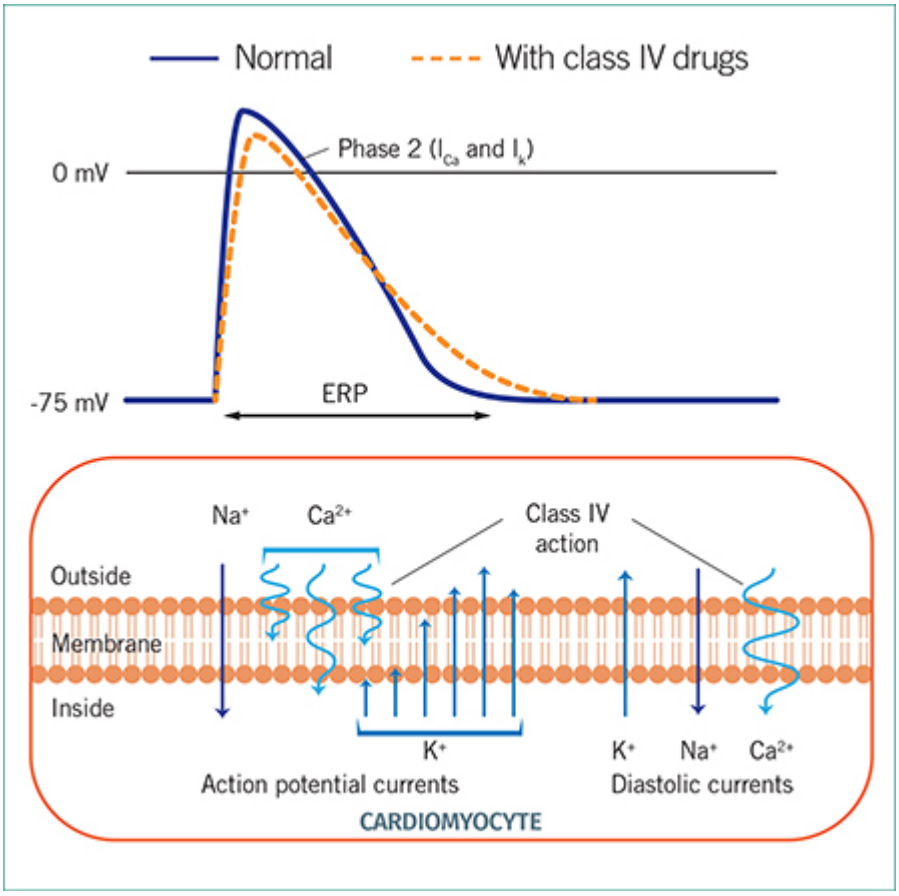


FIGURE 7.7. Schematic diagram of the effects of class IV drugs in a calcium-dependent cardiac cell in the atrioventricular node. Verapamil and diltiazem bind only to open depolarized voltage-sensitive channels, thus decreasing the inward calcium current. As a result, they decrease the sinus node automaticity and prolong the atrioventricular node conduction time.

Verapamil and diltiazem depress the electrical activity of the sinus and atrioventricular nodes by depressing the V_{max} of phase 0 in sinus node cells, and by prolonging the conduction time and refractory period in the atrioventricular node, without affecting the depolarization time of the atria and ventricles. The atrioventricular node–blocking effects of verapamil and diltiazem are more evident at a faster rate (use dependence) and in depolarized fibers (voltage dependence). The spontaneous sinus rate may slightly decrease even if, in most cases, it does not change significantly because of the presence of peripheral vasodilation, transient hypotension, and consequent reflex sympathetic stimulation that mitigates any direct slowing effect of verapamil on the sinus node.

Hemodynamic effects

Verapamil influences the excitation–contraction coupling and inhibits vascular smooth muscle contraction, thus causing severe vasodilation in the coronary and peripheral vessels. Verapamil decreases the myocardial oxygen demand, and these changes may have antiarrhythmic effects.

Pharmacokinetics

In humans, diltiazem is a lipophilic molecule with a 90% absorption rate after oral intake, but because a high amount is metabolized by the liver, its bioavailability is low (24%). Approximately 75% of diltiazem is bound to serum proteins. Its serum half-life in cats is about 2 hours. Renal impairment may only slightly increase half-lives. Slow-release formulations have therefore been developed and have an increased bioavailability of 90%. The plasma concentration of diltiazem with these formulations is greater and its metabolites last longer. In addition, it displays a double-peak behavior, which can be explained by the fact that these formulations contain 15% rapid-release diltiazem with rapid reabsorption, and 85% slow-release diltiazem with delayed reabsorption; reabsorption primarily takes place in the colon.[73]

In cats, diltiazem has a 94% bioavailability, a 2-hour half-life, and a volume of distribution of 1.88 L/kg. The concentration peak is reached 30 minutes after oral administration, with a therapeutic concentration maintained for about 8 hours. The sustained-release formulation has a lower bioavailability in cats than in dogs (38%) and a 6.5-hour half-life; the

plasmatic peak is reached 6 hours after oral administration, with a therapeutic range lasting for 24 hours.[73]

Dose and administration

Verapamil can be administered at the following doses:

In dogs:

- 0.05 mg/kg slowly IV, which can be repeated every 5 minutes up to a total dose of 0.15 –0.2 mg/kg.
- 0.5–2 mg/kg PO every 8 hours.

In cats:

- 0.025 mg/kg slowly IV, which can be repeated every 5 minutes up to a total dose of 0.15–0.2 mg/kg.
- 0.5–1 mg/kg PO every 8 hours.

In dogs, diltiazem can be administered at the following doses:

- For treatment of acute focal atrial tachycardia:
  - 0.05–0.15 mg/kg slowly IV, which can be repeated every 5 minutes to effect or until a total dose of 0.1–0.3 mg/kg.
  - 0.5 mg/kg PO, followed by 0.25 mg/kg PO every hour until conversion to normal sinus rhythm or up to a total oral dose of 1.5–2 mg/kg.
- Chronically, at a dose of 0.5–2 mg/kg PO every 8 hours.

In cats, diltiazem can be administered for acute management of supraventricular tachycardia at a dose of 0.125–0.35 mg/kg IV, and for chronic management at a dose of 7.5 mg (per cat) PO every 8 hours or 0.5–1 (up to 1.5) mg/kg PO every 8 hours.

See Table 7.2 for a summary of the routes of administration and doses of antiarrhythmics in dogs and cats.

Indications

Verapamil is used to treat supraventricular tachycardias, accelerated idioventricular rhythms during ischemic diseases, digoxin-induced ventricular tachycardias, and fascicular ventricular tachycardias. It can also

be used to slow down the ventricular rate during atrial fibrillation, because it prolongs the atrioventricular node conduction time and refractory period.

Diltiazem is useful in treating atrioventricular node–independent supraventricular tachycardias, and when associated with digoxin it reduces the ventricular response in atrial fibrillation[69] and prolongs the median survival time in non-small-breed dogs with myxomatous mitral valvular disease.[74]

Contraindications and adverse effects

Verapamil and diltiazem must be avoided in case of cardiogenic shock, congestive heart failure and systolic dysfunction, hypotension, sick sinus syndrome, high-degree atrioventricular block, and hypersensitivity. They should be used with caution in patients with hepatic or renal failure. The most common side effects are hypotension, bradycardia, congestive heart failure, atrioventricular blocks, nausea, and constipation.

PO, per os; IM, intramuscularly; SC, subcutaneously; IV, intravenously; CRI, constant rate infusion.

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CHAPTER 8

Anesthesia in patients with arrhythmias

Stefania Scarabelli

INTRODUCTION

Cardiac arrhythmias are considered one of the most common complications associated with general anesthesia in small animal patients; they are frequently encountered after certain types of surgical procedures, such as splenectomy[1] and gastric dilatation–volvulus surgery,[2] or in patients with trauma. Physiological alterations during anesthesia and the effects of the drugs used in the perioperative period are the major causes of autonomic derangements resulting in perioperative arrhythmias. However, arrhythmias seen in patients with no preexisting cardiac disease and in the context of noncardiac surgery are relatively benign and short-lived.[3] Patients with an underlying structural heart disease or undergoing cardiac surgery are at greatest risk for developing arrhythmias and, due to their primary disease, the hemodynamic sequelae may be more detrimental. Knowledge of the pathophysiology of the underlying cardiac disease and the effects of the drugs used in the perianesthetic period on the cardiovascular system is of paramount importance for the anesthetist.

RISK ASSESSMENT

Health status is associated with anesthetic morbidity and mortality both in human and veterinary medicine; an increased American Society of

Anesthesiologists (ASA) grade[4] (Table 8.1) has been associated with an increased risk of death in small animals.[5,6] In human medicine, several indices are used to quantify the anesthetic risk in patients with cardiac disease and the risk of adverse perioperative cardiac events;[7,8] no similar tools are available in veterinary medicine. However, it is possible to use the classification for anesthetic risk reported by the New York Heart Association as a guide (Table 8.1).

Perioperative risk assessment is fundamental for ensuring patient safety, optimizing the perioperative outcome, and providing the owner with adequate information before signing the informed consent.

TABLE 8.1. American Society of Anesthesiologists (ASA) and New York Heart Association (NYHA) classifications for anesthetic risk and heart failure.

ASA class	Physical status	NYHA Class	Clinical signs
II	Mild systemic disease	Class I	Asymptomatic heart disease (i.e., cardiovascular disease is present, but no clinical signs are observed)
III	Severe systemic disease	Class II	Heart disease with clinical signs observed during strenuous exercise
IV	Severe systemic disease that is a constant threat to life	Class III	Heart disease with clinical signs shown during routine daily activity or mild exercise
V	Moribund patients expected to die in 24 hours with or without operation	Class IV	Heart disease with clinical signs present at rest

GENERAL CONSIDERATIONS

When dealing with patients with cardiovascular disease and/or arrhythmias, some aspects of perioperative management must be considered.

- The expected complications related to the patient's underlying disease and the type of procedure must be known. An adequately trained staff, the required equipment, and emergency drugs must be available. It is suggested to precalculate doses.
- Stress and pain should be minimized to avoid an increase in sympathetic tone and catecholamine release and to ensure animal welfare.
- Preoxygenation is warranted to minimize hypoxia and hypoxemia after induction of general anesthesia.
- Placement of arterial catheter is recommended to invasively monitor blood pressure and perform arterial blood gas analysis.

- Postoperative intensive care may be required.

ANESTHETIC DRUGS

The choice of anesthetic protocol is mainly based on the underlying pathology, the degree of cardiovascular compromise, and systolic function. The expected level of pain related to the procedure must also be considered.

SEDATIVES

Acepromazine

Peripheral α-1 receptor blockade with consequent vasodilation and suppression of sympathetic activity will lead to hypotension; a reflex increase in heart rate may be seen. Cardiac output and stroke volume have been shown to decrease by 20–30% in conscious dogs administered high doses of acepromazine.[9] A dose-dependent decrease in hematocrit can be seen in dogs after administration of acepromazine due to splenic engorgement.[10]

α-2 Adrenergic receptor agonists

The cardiovascular effects of α-2 agonists (medetomidine, dexmedetomidine) are generally described as biphasic. Hypertension due to peripheral postsynaptic α-2 receptor activation and peripheral vasoconstriction is initially seen with a consequent vagally mediated reflex bradycardia. Vascular resistance then returns to normal, but a centrally mediated bradycardia due to decreased central sympathetic outflow will persist. Cardiac output will also be reduced.[11]

Benzodiazepines

The effects of diazepam and midazolam on the cardiovascular system are minimal. Benzodiazepines are not generally used alone in fit and healthy animals due to possible paradoxical effects, with excitement and agitation. In patients with cardiac disease, diazepam and midazolam are more commonly used for coinduction of general anesthesia in order to decrease the dose of the hypnotic agent and its cardiovascular side effects.[12]

Opioids

Butorphanol, buprenorphine, and methadone (or hydromorphone) are the opioids most commonly used in dogs and cats in the perioperative period to provide sedation and/or analgesia. In general, clinically relevant doses of opioids have minor direct effects on the cardiovascular system. Mild bradycardia can be seen due to centrally mediated enhanced parasympathetic activity, but cardiac output is usually maintained by an increased stroke volume with no detrimental effects on arterial blood pressure.[13]

INDUCTION AGENTS

The hemodynamic effects of the most commonly used induction agents are reported in Table 8.2.

TABLE 8.2. Common induction agents and their hemodynamic effects.

Induction agent	Heart rate	Systemic vascular resistance	Contractility	Cardiac output	Blood pressure	Others
Propofol	↔	↓	↓	↓	↓	Dose-dependent effect Marked venodilation
Alfaxalone	↑	↔↓	↔	↔↑	↔↓	Dose-dependent effects
Ketamine	↑	↔↑	↑	↑	↑	Increase in hemodynamic parameters due to sympathetic stimulation Direct negative cardiac inotropic effect: caution in shocky animals
Etomidate	↔	↔	↔	↔	↔	Good cardiovascular stability Not licensed for veterinary use

↔ unaffected; ↓ decreased; ↑ increased.

Source: Modified from Scarabelli S. and Bradbrook C.[14]

MAINTENANCE OF GENERAL ANESTHESIA

Maintenance of general anesthesia can be achieved with either inhalant anesthetics (isoflurane, sevoflurane) or total intravenous anesthesia (TIVA) (propofol, alfaxalone). Both techniques have advantages and disadvantages, the description of which is beyond the scope of this chapter.

All volatile anesthetics can decrease cardiac output in a dose-dependent manner; at clinically useful concentrations, myocardial contractility is

generally depressed, systemic vascular resistance is reduced, heart rate remains constant, and blood pressure is decreased.

If not otherwise contraindicated, variable rate infusions of short-acting opioids, ketamine, lidocaine, or benzodiazepines can be added to decrease the dose of hypnotic or inhalant agents and their cardiovascular side effects.

Positive pressure ventilation can be required in certain situations (e.g., open chest surgeries, use of neuromuscular blockade, hypoxemia, hypoventilation); due to a lack of strong evidence, the decision to perform positive pressure ventilation routinely is the anesthetist's preference. It should be remembered that positive pressure ventilation has relevant hemodynamic consequences and affects heart–lung interactions. Positive pressure ventilation is radically different from physiological spontaneous breathing due to the positive pressure generated into the chest during inspiration. It is important to note that the most important factor affecting hemodynamic changes throughout the respiratory cycle is the mean airway pressure, which will be increased every time positive end-expiratory pressure is applied, regardless of the ventilation strategy (pressure or volume controlled).

When positive pressure ventilation is performed, there will be a decrease in venous return, which will be more evident in hypovolemic patients, with a consequent decrease in right atrial filling, right ventricular preload, and right ventricular stroke volume. This will in turn decrease left ventricular preload and stroke volume, thus decreasing cardiac output. Moreover, the right ventricular afterload will be increased due to an increase in pulmonary vascular resistance, thus worsening the cardiac output. However, a left ventricular transmural pressure gradient is created in systole and reduces left ventricular work. Finally, due to the decreased venous return, venous and lymphatic drainage of extrathoracic organs will be impaired.[15]

ANESTHETIC DRUGS AND THE CONDUCTION SYSTEM

All the drugs used in the perioperative period may directly or indirectly affect the cardiac conduction system. There is controversy in the human literature regarding the effects of different drugs on the cardiac conduction system and different types of arrhythmias, and the information available on

this topic in the small animal literature is scarce. The main effects on cardiac electrophysiology of the most commonly used anesthetic drugs are reported in Table 8.3.

TABLE 8.3. Effects of commonly used anesthetic drugs on cardiac electrophysiology.

Drug	Effect on cardiac electrophysiology	Level of evidence	Source of evidence
Volatile anesthetics			
Isofluorane	Prolongs QT interval	B	Clinical prospective, randomized, double blind study
	Depresses automaticity in SN cells, slows the rate of SN discharge	C	Guinea pigs, dogs
	Produces depression of ventricular conduction and decreased AP duration and refractory period	C	Guinea pigs (in vitro), dogs
	Prolongs AV conduction time end refractoriness	C	Dogs, guinea pigs (isolated hearts)
Sevoflurane	Prolongs QT interval	B	Clinical prospective randomized study
	Prolongs AV conduction time and refractoriness (moderately)	C	Guinea pigs (isolated hearts)
	Depresses SN and AV function in a porcine model	C	
Intravenous anesthetics			
Propofol	May shorten or produce no effect on QT interval	B	Clinical, prospective, randomized study
	Is associated with episodes of sinus bradycardia, AV block, asystole	C	Pigs, Guinea pigs (isolated hearts), case reports
	Controversial results about benefits of propofol in EP studies		Humans
	Decreases vagal tone, mild prolongation of QT interval[20,21]	C	Dogs
	No effects on the conduction system under autonomic blockade[22]	C	Dogs
Etomidate	Decreases sinus rhythm, slows AV conduction (in high–not clinical—concentrations)	C	Guinea pigs (isolated hearts)
Ketamine	May prolong QT interval through sympathetic stimulation	C	Case series (children), mouse
	Less potent in prolonging AV conduction compared to the rest of IV anesthetics	C	Guinea pigs (isolated hearts)
	No prolongation of SN intrinsic rate	C	Guinea pigs (isolated hearts)
	Shortening of atrial wavelength and shortening of atrial conduction time	C	Guinea pigs (isolated hearts)
Alfaxalone	Mild prolongation of QTc interval in premedicated patients[17]	C	Dogs
Benzodiazepines			
Midazolam	No significant effects on cardiac driving system	B	Clinical, prospective, observational, before-after study
	No effects on QT or may shorten prolonged QT (via anxiolysis)	B	Clinical, prospective randomized study
	No effects on normal AV or accessory pathways	B	
	No effects on SN activity	B	
	Does not alter inducibility of reentrant tachycardia	B	

Drug	Effect on cardiac electrophysiology	Level of evidence	Source of evidence
Diazepam	Increases sinus rate and AV conduction without changing ventricular conduction and refractoriness	B	Clinical, prospective, observational, before-after study
	May facilitate AV node reentry arrhythmias		
Opioids	May shorten QT interval by reducing sympathetic response	C	Expert opinions, case reports
Morphine	May exhibit direct negative chronotropic (SN) and dromotropic (AV node) actions	C	Dogs
Methadone	Prolongs QT interval, above all in patients under sevoflurane anesthesia[19]	C	Dogs
Hydromorphone	Prolongs QT interval, above all in patients under sevoflurane anesthesia[19]	C	Dogs
Fentanyl	Not clinically significant reduction of sinus rate; prolongation of AV driving	C	Dogs, guinea pigs (isolated hearts)
	No significant adverse effects on arrhythmias inducibility	C	Dogs
	Raises ventricular fibrillation threshold[17]	C	Dogs
	At high doses and in association with thiopental, has been reported to induce spontaneous atrial fibrillation and facilitate induction of atrial fibrillation by pacing protocols[23]	C	German Shepherd dogs with inherited ventricular arrhythmias and atrial premature complexes
Remifentanil	Depresses SN function and automaticity/ prolongs SN conduction time /depresses AV conduction	C	Pigs
	Antiarrhythmic effects on mechanically induced atrial flutter e SVT[18]	C	Dogs
Neuromuscular blockers	Do not affect QT interval	C	Expert opinion, case reports
Rocuronium	No significant direct electrophysiological effects (mild vagolytic action)	B	Clinical, prospective, randomized studies
Atracurium	No significant direct electrophysiological effects	B	Cats, dogs, monkeys; clinical prospective randomized Study
Cisatracurium	No significant direct electrophysiological effects	B	Clinical prospective randomized Study
Dexmedetomidine	Increases sinus cycle length, AV nodal conduction, atrial refractory period and decreases atrial excitability	C	Children
	No effects on EPS parameters[16]	C	Pigs
Medetomidine	No effects on EPS parameters[16]	C	Pigs

Source: Modified from the *British Journal of Anesthesia*. Available online at: www.bjanaesthesia.org/cms/10.1093/bja/aes105/attachment/7e238f81-efb0-418f-a93d-d3e601930adb/mmc1.pdf

Level of evidence:

- Level A: High quality/large randomized controlled trials /meta-analysis (quantitative systematic review)
- Level B: Well-designed, nonrandomized clinical trials/nonquantitative systematic review; lower quality randomized controlled trials, clinical cohort studies and case-controlled studies.
- Level C: Consensus viewpoint or expert opinion, animal research, bench research.

SN, sinus node; AP, action potential; AV, atrioventricular; EPS, electrophysiological study; SVT, supraventricular tachycardia.

ANESTHESIA FOR ELECTROPHYSIOLOGICAL PROCEDURES

In humans, electrophysiological procedures can be performed under either sedation or general anesthesia, depending on type of arrhythmia, the patient's health factors, and the clinician's and patient's preference. Light sedation is the best condition to perform electrophysiological procedures for mapping and inducing the arrhythmia to be treated with no drug interference; however, in these conditions, catheter contact during mapping and ablation can be more easily affected by respiratory, cardiac, and patient motion, thereby leading to inaccuracies and increased procedure times. Moreover, patients can suffer from pain and stress.

In veterinary medicine, electrophysiological procedures are performed under general anesthesia. Some general considerations related to the procedure may be similar to those in human medicine:

- The anesthesia duration is prolonged; in the author's experience, procedures can last up to 5–6 hours, with a mean time at the author's institution of 3.5 hours.
- Pain levels intra- and postoperatively will generally be mild. A nonsteroidal anti-inflammatory drug may be administered postoperatively if not otherwise contraindicated; in dogs, paracetamol can be used instead (10 mg/kg intravenously or orally three times a day).
- In the electrophysiological laboratory, lighting and visibility are reduced. Due to the overhanging equipment, monitors and C-arm, access to the patient's head for monitoring is difficult. A stable connection between the endotracheal tube and breathing system must be ensured, together with an easily and promptly accessible intravenous line.
- Radiation exposure from fluoroscopy-guided procedures is hazardous for all healthcare providers. Regular use of heavy lead aprons and other protective gear predispose health care providers to fatigue and injury. A radiation safety protocol must be in place.
- A defibrillator with pacing capability must be available.

ANESTHESIA FOR ELECTROPHYSIOLOGICAL STUDIES AND ABLATION PROCEDURES

The main aim of the anesthetist during ablation procedures is to ensure patient safety and minimize interference with the underlying arrhythmia and its inducibility.

In dogs, electrophysiological studies are most commonly performed for supraventricular tachycardias. In human medicine, there is no standardized protocol for sedation/anesthesia in patients with supraventricular tachycardias, but the drugs most commonly used are midazolam, fentanyl, and propofol; low doses of ketamine and dexmedetomidine, according to some authors, have shown promising results for sedation in these patients, but further studies will be required to clarify their role in this patient population.[24]

In small animal anesthesia, there is a lack of clinical studies investigating anesthetic protocols for dogs with supraventricular tachycardias. The use of midazolam, butorphanol, propofol, fentanyl, and etomidate has been reported in previous studies in dogs.[25,26] In the author's laboratory, with cooperative patients in which an intravenous catheter can be placed without sedation, coinduction with midazolam (0.3 mg/kg IV) and propofol (2–4 mg/kg IV to effect) is usually performed. If a further hypnotic dose reduction is needed (e.g., in patients with congestive heart failure or poor systolic function), fentanyl (2–3 μg/kg/IV) can be added; due to its short duration of action after a single bolus, it should not interfere with arrhythmia inducibility during the procedure. General anesthesia can be maintained with a variable rate infusion (VRI) of propofol (0.2–0.4 mg/kg/min) or with inhalant anesthesia (isoflurane/sevoflurane); in both cases, a VRI of midazolam (0.2–0.4 mg/kg/h) can be added to decrease the dose of anesthetic agent and its cardiovascular side effects. Midazolam should be used over diazepam for VRI because it does not produce active metabolites. After prolonged administration, midazolam is generally stopped before ending the procedure to avoid dysphoria in recovery. For multimodal anesthesia, if the patient poorly tolerates the cardiovascular side effects of hypnotic and inhalant anesthetics, fentanyl VRI (5–10 μg/kg/h) or ketamine (5–10 μg/kg/min) are the author's preferred choice.

For procedures on the left side of the heart, adequate anticoagulation is necessary to prevent thromboembolic events. Heparin sodium is

administered starting at 150 IU/kg aiming at an activated clotting time that is 1.5–2.5 times the baseline patients' value. The activated clotting time is measured 5 minutes after heparin administration and measurements are repeated every 20 minutes until removal of the electrodes from the left side of the heart.

Possible complications during the procedure may include:

- Difficulties in inducing arrhythmias: isoprenaline 0.03–0.05 µg/kg/min. Hypotension may be seen due to ß-2 adrenergic receptor agonism and a decrease in systemic vascular resistance.
- Hypotension: treatment will vary depending on the cause and the underlying cardiac function. Dobutamine (1–10 µg/kg/min), noradrenaline (0.1–0.4 µg/kg/min), dopamine (1–20 µg/kg/min), and phenylephrine (1–5 µg/kg/min) can be used.
- Vascular injuries with hemorrhage, and cardiac perforation with cardiac tamponade. Fluids (lactated Ringer's, gelatins, hypertonic saline) should be available.

ANESTHESIA FOR ELECTRICAL CARDIOVERSION

Electrical cardioversion is a short-lasting but painful procedure; it is generally performed in hemodynamically compromised patients with the aim of restoring sinus rhythm.

The anesthetic protocol is based on the patient's condition. Intramuscular sedation is usually not required; hydromorphone and oxymorphone have been used in a previous study when premedication was deemed necessary based on patient activity and level of anxiety.[27] Coinduction with midazolam (0.2–0.3 mg/kg IV), fentanyl (2–3 µg/kg IV), and/or lidocaine (1–2 mg/kg IV) and propofol or alfaxalone to effect is usually performed in the author's laboratory. The trachea must always be intubated to provide oxygen and apply positive pressure ventilation if respiratory depression and hypercapnia develop. If the duration of the procedure exceeds 10–15 minutes, inhalant anesthetics or TIVA with propofol or alfaxalone can be initiated.

ANESTHESIA FOR PACEMAKER IMPLANTATION

Anesthetic management for patients undergoing pacemaker implantation depends on the patient's clinical condition, possible comorbidities, and the type of bradyarrhythmia on presentation. High-grade second- and third-degree atrioventricular block, sick sinus syndrome, and persistent atrial standstill are the most common indications for pacemaker implantation. A temporary pacing system (either transvenous or transthoracic) should be available if the bradyarrhythmia becomes unstable and treatment is needed while a permanent pacemaker is implanted. Temporary transvenous pacemaker placement can be performed with the aid of local anesthesia (lidocaine infiltration, 2–4 mg/kg), but additional sedation may be required. There is no standardized protocol for sedation; anesthetic drugs that do not adversely affect the animal's underlying cardiac disease and do not worsen the bradyarrhythmia should be used.

In case of high-grade second-degree atrioventricular block, drugs that enhance vagal tone and promote atrioventricular blockade should be avoided. In the author's practice, if intramuscular sedation is required, either for temporary pacing or to place an intravenous catheter, a combination of midazolam (0.3 mg/kg), alfaxalone (0.5–1 mg/kg), and butorphanol (0.2 mg/kg) is generally used. Induction of general anesthesia can be achieved with ketamine (5 mg/kg IV) plus diazepam or midazolam (0.25 mg/kg IV to effect; 1/3 to 2/3 of the total dose is generally required). Ketamine typically causes an increase in heart rate due to sympathetic stimulation, but it must be remembered that, in animals with a maximally stimulated sympathetic nervous system and catecholamine depletion, a direct myocardial depressant effect can be seen.[28] Propofol or alfaxalone to effect, as a sole agent if the animal was premedicated, or in coinduction with midazolam/diazepam can be used as another option.

In cases of tachycardia–bradycardia syndrome, an excessive increase in heart rate should be prevented. Despite recent studies showing no differences,[21] an increase in heart rate after alfaxalone administration is more commonly reported in the literature than with propofol; propofol may be therefore a better option for induction of general anesthesia in these patients. Ketamine should be avoided.

In cases of third-degree atrioventricular block, methadone (0.2 mg/kg IM) can be used as well for premedication. The main reported effect of methadone on the cardiac conduction system both in humans and dogs is QT prolongation and increased QT dispersion with increased predisposition

to torsades de pointes;[19] methadone administration through centrally mediated enhanced parasympathetic activity can reduce the sinus node discharge rate, the velocity of conduction along the atrioventricular node and, rarely, the automaticity of Purkinje fibers.[29]

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CHAPTER 9

Electrical cardioversion and defibrillation

Romain Pariaut

Electrical cardioversion and defibrillation are therapies that consist in delivering a direct current shock of variable intensity transthoracically, directly on the surface of the heart or within a cardiac chamber, in order to terminate tachyarrhythmias and restore sinus rhythm. Cardioversion is used for termination of reentrant supraventricular and ventricular tachyarrhythmias, except for pulseless ventricular tachycardia, ventricular flutter, and fibrillation, which are treated via defibrillation. The term cardioversion is used whenever the delivery of the electrical shock is synchronized with ventricular depolarization, which corresponds to the QRS complex of the surface electrocardiogram. Defibrillation is an unsynchronized shock, as no waveforms can be identified during ventricular flutter and fibrillation.

MECHANISMS OF CARDIOVERSION AND DEFIBRILLATION

Electrical cardioversion and defibrillation consist in the delivery of a direct current to the heart. Cardioversion is timed to the QRS complex of a tachyarrhythmia, as an electrical shock delivered during ventricular repolarization, around the peak of the T wave, can induce ventricular

fibrillation (Fig. 9.1).[1] The electrical shock of defibrillation is not synchronized to the underlying rhythm.

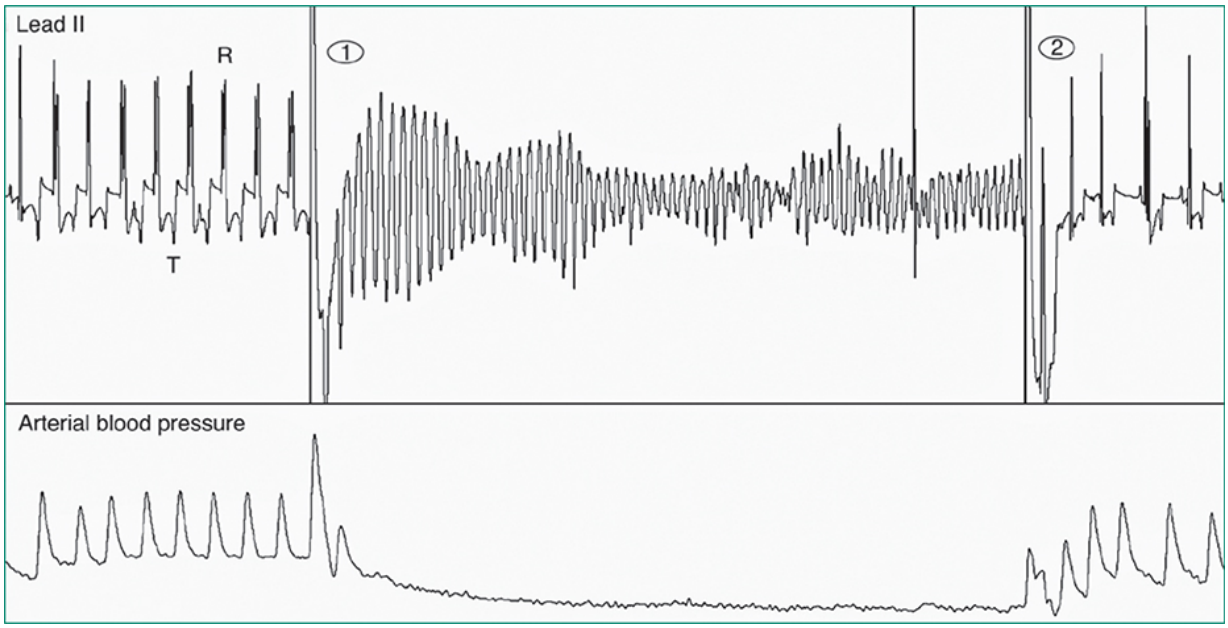


FIGURE 9.1. Single lead surface electrocardiogram and direct arterial pressure recording in a dog during an experimental study evaluating implantable defibrillators. On the electrocardiogram, the first beat is sinus followed by 8 ventricular paced beats; a 400-volt (approximately 9 Joules) stimulus (1) is precisely timed to the peak of the T wave, which corresponds to the vulnerable period of ventricular repolarization and induces ventricular fibrillation. Within a few seconds, the arrhythmia is detected by the defibrillator—spike before (2)—and followed by a 600-volt biphasic defibrillation shock (2), which restores sinus rhythm. At the time of the shock on the T wave, an increase in systolic blood pressure is noted, which corresponds to the strong mechanical contraction of the ventricles stimulated by the electrical shock. During ventricular fibrillation, no pulse pressure is generated.

The exact mechanism by which a strong electrical shock applied to the heart can stop an arrhythmia has yet to be fully explained.[2] A shock must:[3]

1. Terminate all the electrical wavefronts that sustain the tachyarrhythmia.
2. Not reinduce the arrhythmia.
3. Not suppress the recovery of the sinus node function after termination of the arrhythmia.

The requirement for a successful shock is usually stated to be a strong enough electrical shock that places approximately 70% of the myocardial mass into a refractory state, either by prolonging the refractory period of depolarized cells or by depolarizing the excitable cells and thereby

preventing further propagation of the electrical wavefronts.[3,4] The most recent theory of defibrillation, known as the ”virtual electrode hypothesis” indicates that the electrical shock also shortens the refractory period, and even restores full excitability of myocytes. This phenomenon explains the failure of a shock to terminate the arrhythmia when myocytes that have recovered excitability from the shock are reexcited by the same shock; these cells can be the source of a new reentrant wavefront and episode of ventricular fibrillation if there has been sufficient time for the surrounding tissue to recover excitability.[3] Therefore, rather than failing to stop an episode of ventricular fibrillation, a failed defibrillation shock is considered to first terminate the initial episode and then trigger a new episode by allowing some myocytes to reinitiate a reentrant wave.[3] Two values can be described to characterize the ability of a shock to terminate ventricular fibrillation: the defibrillation threshold (DFT) and the upper limit of vulnerability (ULV). If the intensity of the shock is below the DFT, it will fail to terminate ventricular fibrillation because the portion of fibrillating myocardium that remains unaffected by the shock is too large. If the shock intensity is between the DFT and the ULV, it can terminate ventricular fibrillation, but it can sometimes reinduce ventricular fibrillation, giving the impression of a failed shock. Finally, if the shock intensity is above the ULV, it will terminate ventricular fibrillation successfully without the risk of reinducing ventricular fibrillation. It is because the recovery of excitability in small regions of myocytes happens so quickly when the energy of a shock is above the ULV that the surrounding myocardium is still refractory and therefore a reentrant wavefront cannot occur.[3] Strong electrical shocks also damage the membranes of the myocytes by a mechanism known as electroporation. Electroporation causes the formation of low-resistance pores on the membrane that need time to be resealed before the cell can restore normal transmembrane potentials. Electroporation explains the delay frequently noticed after a successful defibrillation shock before the return of spontaneous sinus node activity.[3]

EQUIPMENT

A defibrillator delivers a predetermined amount of electrical current to the heart with the intention of rapidly restoring normal cardiac rhythm. There are different methods of defibrillation, including external and internal approaches. External defibrillation involves delivering electrical shocks from the surface of the body, while internal defibrillation is performed by applying sterile paddles directly to the surface of the heart following a thoracotomy. Defibrillation can also be carried out percutaneously using catheters connected to the defibrillator and positioned within the cardiac chambers.

To ensure reliable termination of ventricular fibrillation, a transformer converts alternating current into a direct current power source. The defibrillator's primary internal component is the capacitor, which stores electrical energy supplied by the battery during the charging phase and rapidly releases it when the discharge function is activated. The operator can select the desired energy level to be delivered, and internal electronic components within the defibrillator adjust the energy, shock duration, and waveform when defibrillation is triggered.

Many defibrillators include a display that allows monitoring of different parameters and provides an electrocardiogram tracing obtained from leads directly attached to the patient's limbs or from the "quick-look" defibrillation paddles. The operator can choose between monitoring, pacing, or defibrillation functions (Fig. 9.2), and switch between synchronous and asynchronous modes using controls located on the front panel. Charging of the capacitor and shock delivery can be initiated either from the unit or directly from the paddles. During the charging process, defibrillators typically emit a continuous sound that changes in tone when the capacitor is fully charged. Most defibrillators are equipped with both adult-size and pediatric-size paddles. Self-adhesive patch electrodes can also be used and should be securely attached to both sides of the chest.



FIGURE 9.2. Front panel of an external biphasic defibrillator. This multifunction device includes defibrillation, synchronized cardioversion, and pacing capabilities. The shock energy can be selected and is displayed on the digital screen. A button is pressed to select the synchronized mode (Sync On/Off on the bottom right of the screen).

FACTORS ASSOCIATED WITH DEFIBRILLATION SUCCESS

SHOCK CONFIGURATION (MONOPHASIC VS. BIPHASIC)

Biphasic shocks are known to be less likely than monophasic shocks to fail to defibrillate. This is because the second phase of the biphasic shock eliminates the possible sources for a new reentrant wavefront that were created by the initial phase of the shock. Therefore, a monophasic shock needs to be above the ULV to terminate ventricular fibrillation without the risk of reinducing a new episode, whereas a lower intensity biphasic shock can be used successfully.[3]

ELECTRODE POSITION

Considering that as little as 4% of the energy delivered by the defibrillator reaches the myocardium, the orientation of the shock vector relative to the heart is critical.[4]

TRANSTHORACIC IMPEDANCE

Transthoracic impedance is the resistance associated with thoracic structures. A high impedance decreases the probability of a successful shock as it limits the amount of electrical current reaching the heart. The size and conformation of the patient's chest, its water and fat content, the pulmonary volume, the size and position of the paddles, and the force applied to the paddles are factors that influence thoracic impedance.[5] The largest paddles or self-adhesive patches that fit on the chest should be used because a large contact surface with the skin decreases the impedance at the body surface. Moreover, good contact between the paddles and the body is paramount. It is improved by applying electrode gel on the paddles and on both sides of the chest. Application of gel outside the areas covered by the paddles should be avoided because it can be the cause of short circuits. Ultrasound coupling gel is not a satisfactory alternative since it has poor electrical conductivity. Finally, the paddles should not be placed over electrocardiographic pads. Firm manual pressure is then applied to the paddles to literally squeeze the heart between the paddles and decrease thoracic impedance. Modern defibrillators can quickly measure thoracic impedance when the paddles are placed on the chest and can automatically adjust the shock waveform characteristics to match the preselected energy to the energy effectively delivered across the chest.[6]

TIMING

Studies in humans experiencing ventricular fibrillation indicate that the rate of hospital discharge decreases by approximately 10% for every minute of ventricular fibrillation.[7]

ROLE OF CARDIOVERSION AND DEFIBRILLATION IN SPECIFIC ARRHYTHMIAS

VENTRICULAR FIBRILLATION AND POLYMORPHIC AND PULSELESS VENTRICULAR TACHYCARDIA

Defibrillation is indicated for the termination of ventricular fibrillation, a life-threatening emergency characterized by the absence of organized ventricular activity on the surface electrocardiogram. Instead of well-defined QRST complexes on the surface electrocardiogram, there are rapid and chaotic undulations of varying amplitude. Defibrillation can also be used for the treatment of rapid polymorphic ventricular tachycardia, whether it is associated with a pulse or not. Ventricular fibrillation, pulseless ventricular tachycardia, asystole, and electromechanical dissociation are three rhythm disturbances that result in cardiac arrest. Therefore, defibrillation is always integrated into the advanced life support segment of cardiopulmonary resuscitation protocols.

There are safety measures to consider when using a defibrillator:

1. Ascertain no physical contact between the staff and the patient.
2. Avoid contact between the metallic parts of the paddles to prevent current arcing.
3. Disconnect oxygen and anesthetic circuits from the animal to prevent explosions.

It is the operator's responsibility to warn all personnel and confirm they are safe before shock delivery.

Ventricular fibrillation is treated with an unsynchronized shock that is delivered independently of the cardiac cycle. Shocks can be delivered in a monophasic or biphasic configuration depending on the system used (Fig. 9.3). The standard energy for biphasic shocks is 2 to 4 J/kg.[8] In an experimental setting, the author identified in a few healthy dogs that a biphasic shock with an energy of 4 J/kg was more likely to terminate ventricular fibrillation than a lower-energy shock. Each defibrillator manufacturer utilizes a unique configuration for the shock waveform and offers a recommended range of energy doses. The optimal defibrillation protocol remains a topic of debate. While it is often recommended to use the lowest energy possible, some studies suggest that higher energies should be initially selected to improve the chances of a successful first shock. Whenever several consecutive shocks are necessary to terminate the arrhythmia, it remains uncertain if a fixed-energy protocol should be used

or if the energy should be increased with each subsequent shock.[6] A recommendation with monophasic defibrillators is to deliver up to three successive shocks if the first one is unsuccessful in order to decrease transthoracic impedance and therefore increase the amount of energy delivered to the myocardium with the second and third shocks.[8] Current recommendations are to interpose one 2-minute cycle of chest compressions between each shock.[6] Although rarely performed, internal defibrillation uses small sterile paddles that are placed directly to the surface of the ventricles. The energy delivered via internal defibrillation is 10 to 30 J for medium to large dogs, with a maximum of 50 J.[9]



FIGURE 9.3. Single lead electrocardiogram strip recorded during external defibrillation. A rapid and chaotic rhythm corresponding to ventricular fibrillation is terminated by a biphasic shock. Immediately following the shock, P waves are present, but they are dissociated from the first four wide QRS complexes, which correspond to a ventricular rhythm. A sinus rhythm is then restored. Note the defibrillation shock is characterized by a first negative deflection followed by a positive deflection, indicating that it is a biphasic shock. Lead II; speed, 50 mm/s; calibration, 10 mm/1 mV.

MONOMORPHIC VENTRICULAR TACHYCARDIA

Indications for the treatment of monomorphic ventricular tachycardia via electrical cardioversion include:

1. Failure to terminate with antiarrhythmics.
2. Urgent termination of the tachycardia needed due to hemodynamic instability of the patient.
3. Tachycardia occurring during a cardiac procedure under anesthesia with the cardioversion patches already positioned on the patient.

Before attempting cardioversion, it is crucial to establish intravenous access and have airway management equipment readily available. Ideally,

electrolyte imbalances should be corrected, and proper oxygenation should be ensured. The success rate of electrical cardioversion does not seem to improve with the administration of antiarrhythmics before the procedure; however, drugs should be available to treat arrhythmias occurring postcardioversion.[10]

Anesthesia is required before cardioversion. The use of short-acting intravenous agents such as etomidate or propofol is recommended. Sometimes, tachyarrhythmias can spontaneously terminate after induction of anesthesia, partly due to the decrease in sympathetic activity associated with the administration of anesthetics. It is critical to perform cardioversion as soon as the animal loses consciousness. A delay could result in a decline in the animal's hemodynamic status and in ventricular fibrillation due to a loss of the vasomotor reflex secondary to the administration of anesthetic agents that cannot be compensated by an increase in cardiac output if the tachycardia persists.

After placing the animal in dorsal recumbency, electrocardiographic leads are connected to the patient and the left and right lateral sides of the thorax are clipped between the third and sixth intercostal spaces. The cardioversion paddles or adhesive patches should be placed over the ventricles. The defibrillator is set to the synchronous mode to avoid a shock during the peak of the T wave, which could potentially initiate ventricular fibrillation. In the synchronous mode, accurate detection of the R waves is essential. The R waves are indicated by a small arrowhead on the defibrillator display. However, if the T waves have increased amplitude, the defibrillator may have difficulty differentiating them from the R waves. This issue can be resolved by repositioning the electrocardiographic leads or selecting a different lead. It is standard for defibrillators to revert back to the asynchronous mode after delivery of a synchronous shock (Fig. 9.4). Therefore the "Sync" button needs to be reactivated after each cardioversion shock.

The energy for the first cardioversion shock is set at 1 to 2 J/kg. The energy of the subsequent shocks is increased until cardioversion occurs, which on occasion requires up to 10 shocks. It does not appear that the presence of an underlying heart disease has an influence on the energy required to terminate a tachycardia.[10]



FIGURE 9.4. Single lead electrocardiogram strips recorded during electrical cardioversion of atrial flutter. It is crucial to confirm, prior to the delivery of the electrical shock, that the shock will occur during ventricular depolarization (arrows on QRS complexes). Lead II; speed, 25 mm/s; calibration, 10 mm/1mV. Arrows are shown on top of the QRS complexes and T waves in the first strip (a), which indicates oversensing of the T wave and a risk of induction of ventricular fibrillation if the shock is delivered during the T wave. In this situation, another electrocardiographic lead should be displayed, or the electrocardiographic patches should be repositioned (b).

ATRIAL FIBRILLATION

Electrical cardioversion is a rhythm control strategy that aims at terminating atrial fibrillation and restoring sinus rhythm. This therapy is typically selected in patients that are more likely to remain in sinus rhythm post-treatment, i.e., dogs with no evidence of structural heart disease, no identifiable cause for the arrhythmia, and a recent onset of atrial fibrillation. Rarely, electrical cardioversion is attempted in dogs with structural heart disease because of the high recurrence rate of arrhythmia. Sinus rhythm restoration via electrical cardioversion has been retrospectively studied in a small number of dogs with atrial fibrillation and heart disease; the results suggest that atrial fibrillation reoccurs in 50% of dogs within approximately 2 months, and in most dogs within 5 months after cardioversion.[10,11] The need for general anesthesia, even of short duration, is another limitation of this treatment approach in dogs with severe cardiac dysfunction. Conversely, in dogs with lone atrial fibrillation of less than 75 days, 70% of animals remain in sinus rhythm for 100 days or longer. In the study by Bright et al., all dogs were maintained on chronic oral amiodarone therapy.[11] There are currently no veterinary studies that have confirmed the role of amiodarone in preventing the recurrence of lone atrial fibrillation after cardioversion. On occasion, dogs have remained in sinus rhythm for up to 2 years after cardioversion. It is important to note that the longer an

animal remains in atrial fibrillation, the less likely atrial fibrillation can be terminated and sinus rhythm maintained long term. In a group of dogs with a diagnosis of atrial fibrillation of 2.5 months or less, the recurrence rate of atrial fibrillation was 10% at 28 days and 30% at 100 days following electrical cardioversion in those animals with no structural heart disease, while it was 30% at 28 days if structural heart disease was present.[10]

The technique to perform electrical cardioversion for atrial fibrillation is comparable to the technique used to terminate monomorphic ventricular tachycardia. In the case of atrial fibrillation, however, the procedure is usually planned and there is not the same urgency in delivering the shock after induction. Moreover, it is critical that the shock vector travels through the atria and the patches should be placed high on the chest over the atria. It is especially important to confirm the correct position of the patches in giant breed dogs with a deep thorax. See p. 226.

SUPRAVENTRICULAR TACHYCARDIA

Other reentrant supraventricular tachyarrhythmias such as atrial flutter and accessory pathway–mediated tachyarrhythmias may be amenable to electrical cardioversion.

COMPLICATIONS

As indicated previously, recovery of the sinus node function can be delayed after delivery of a strong electrical shock, thus requiring artificial pacing. In addition, postshock myocardial dysfunction characterized by decreased systolic function and a reduction in cardiac output can occur. It is likely due to lesions of the myocyte cell membranes leading to electrolyte imbalances and electroporation. Lower-energy shocks and biphasic shocks may be associated with less myocardial injury. Postshock myocardial dysfunction can be reflected by alterations of the ST segment on the electrocardiogram.[12] The risk of myocardial damage secondary to the delivery of a small number of shocks seems limited, except for a transient decrease in cardiac output. In an experimental study in dogs, only a modest increase in cardiac troponin I levels was noted after multiple episodes of ventricular fibrillation induction followed by defibrillation.[13]

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CHAPTER 10

Cardiac pacemakers and implantable cardioverter-defibrillators

Shana Mintz, Romain Pariaut

Cardiac pacemakers and implantable cardioverter defibrillators are sophisticated medical devices engineered for targeted cardiac therapy. In veterinary medicine, pacemakers are indicated for the management of bradyarrhythmias and aim to restore and maintain optimal heart rhythm through the delivery of controlled electrical impulses.

Conversely, implantable cardioverter defibrillators are designed for patients identified as being at risk for sudden cardiac death arising from ventricular fibrillation. These devices employ continuous cardiac monitoring capabilities and promptly detect and respond to life-threatening ventricular arrhythmias. Upon identification of a critical arrhythmic event, implantable cardioverter defibrillators deliver precise and timely electrical shocks, mitigating the potential consequences of ventricular fibrillation and reinstating normal cardiac rhythm.[1]

CARDIAC PACEMAKERS

INDICATIONS FOR PACEMAKER THERAPY

For dogs and cats exhibiting clinical signs or experiencing progressive cardiac remodeling due to chronic bradycardia, pacemaker therapy is advised. The most common bradyarrhythmia requiring attention is third-degree atrioventricular block and symptomatic sinus node dysfunction; second-degree atrioventricular block and atrial standstill are less common

indications for pacemaker therapy.[2,3] While many animals typically rely on cardiac pacing for an extended period, some may regain a normal sinus rhythm after pacemaker implantation.[4] Pacemaker implantation is linked to prolonged survival times in dogs with atrioventricular block.[5] However, improved survival has not been conclusively established in dogs with sick sinus syndrome, although pacing does prevent the frequent syncopal events associated with this condition.[6] Atrial standstill was historically deemed a poor prognosis despite pacemaker implantation, but recent studies suggest that animals with this condition also benefit from pacing.[7,8] Pacemaker implantation can be considered in animals experiencing frequent syncopal episodes from vasovagal syncope with documented long periods of asystole, but complete resolution of the clinical signs is expected in only a small number of them.[2,9] Ultimately, biventricular pacing involves implanting a lead in the coronary sinus and is employed in individuals with heart failure to enhance synchronization between the left and right ventricles when a bundle branch block is present. Small-scale studies in dogs have demonstrated the feasibility and beneficial effects of biventricular pacing on cardiac output and systolic function.[10,11]

PRINCIPLES OF PACING

The objective of artificial pacing is to consistently activate the heart muscle, thus ensuring a steady cardiac output when the natural pacemakers fail to sustain a sufficient heart rate. The effectiveness of the impulse in stimulating the heart depends on its voltage and duration. To avoid excessive battery depletion, a specific range of values is identified during device programming (Fig. 10.1).[12] Moreover, the pacemaker must possess the capability to detect intrinsic cardiac activity (sensing function).

The goal of pacing is twofold: to perform a life-saving intervention or alleviate pronounced clinical signs and to replicate the natural conduction system and sequence of cardiac contractions as closely as feasible. Pacing can be achieved through either epicardial or endocardial methods. Presently, the preference leans towards the endocardial approach due to its lower invasiveness. Nevertheless, there are situations in which epicardial pacing is favored, for example, a small patient size, an ongoing infection, a hypercoagulable state, immunosuppressive therapy, suspected

arrhythmogenic cardiomyopathy, and concurrent thoracic or abdominal surgery.[13] The choice of pacing site can range from a single site to the less common deployment of two or even three sites. In veterinary medicine, the predominant practice often involves opting for a single right ventricular site, a strategy that proves to be both technically less challenging and effective in alleviating the clinical signs in most cases.[5,6] While the single right ventricular site serves as a reliable and straightforward method for pacemaker implantation, physiological pacing can be enhanced by incorporating additional pacing sites. Introducing a second pacing site at the atrial level, for instance, contributes to a more physiologically natural cardiac rhythm. This approach seeks to mimic the heart's intrinsic electrical conduction pathway more closely, thereby potentially improving the overall functionality of the pacemaker. In rare instances, a third pacing site within the ventricles may be considered, adding another layer of complexity to the pacing strategy. This three-site pacing approach aims to achieve an even more nuanced and finely tuned coordination of the heart's chambers.[10,11] In veterinary medicine, no long-term benefit of these advanced techniques has been found over single chamber right ventricular pacing. However, employing more sensitive measures of quality of life in studies might unveil potential benefits within specific patient groups.[14–16]

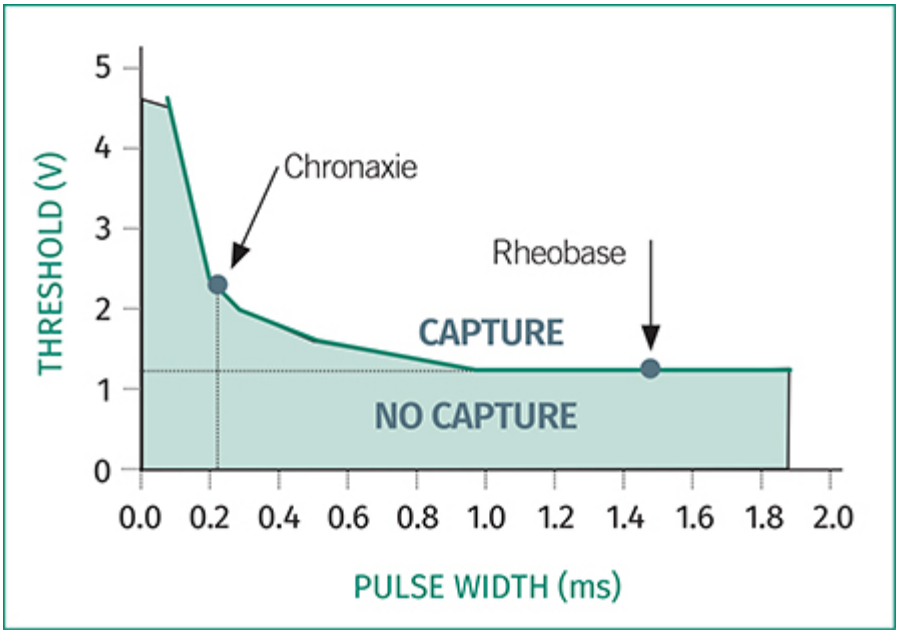


FIGURE 10.1. Strength–duration curve. The green curve delineates all the pacing voltage/pulse width combinations that capture the heart in a specific patient (failure to capture below the curve and

above the curve). There are two remarkable points that can be identified on this curve: rheobase and chronaxie. The rheobase is the lowest voltage at the longest pulse width, practically, the voltage that captures the heart for a pulse width of 1.5 or 2 ms. The chronaxie is the pulse width at twice the rheobase. This point is close to the optimal voltage/pulse width combination that captures the heart with the least energy expenditure. To construct a strength-duration curve, clinicians perform multiple consecutive threshold tests. This process is automated in modern pacemaker programmers, which conduct the tests and provide recommendations for voltage and pulse width settings, incorporating a safety margin to enhance patient safety.

EQUIPMENT

Pulse generator

The standard pulse generator comprises a titanium casing that houses various electronic components and a long-lasting lithium iodine battery, typically with a lifespan of 10 years or beyond. Approximately 50% of the battery capacity is used for pacing, and the other half is used for all the monitoring and data collection functions of the pacemaker.[12] Atop the casing, there is a clear epoxy connector block or "header" featuring one, two, or three ports for inserting the pacing leads. Unused ports should be sealed with "connector caps" to prevent contaminants from entering the ports (Fig. 10.2a). Generators equipped with one port provide single-chamber pacing, whereas those featuring two ports can perform dual-chamber pacing. Pulse generators are designed to deliver an output pulse at a programmable rate, which can be inhibited if an intrinsic beat from the patient is detected. They also come equipped with diverse technologies to adjust the pacing rate to the patient's activity. The operational mode of a pulse generator is programmable (Fig. 10.3). Modern pacemaker generators continually accumulate substantial data concerning both the device and the patient's rhythm, facilitating periodic retrieval and evaluation of this information.

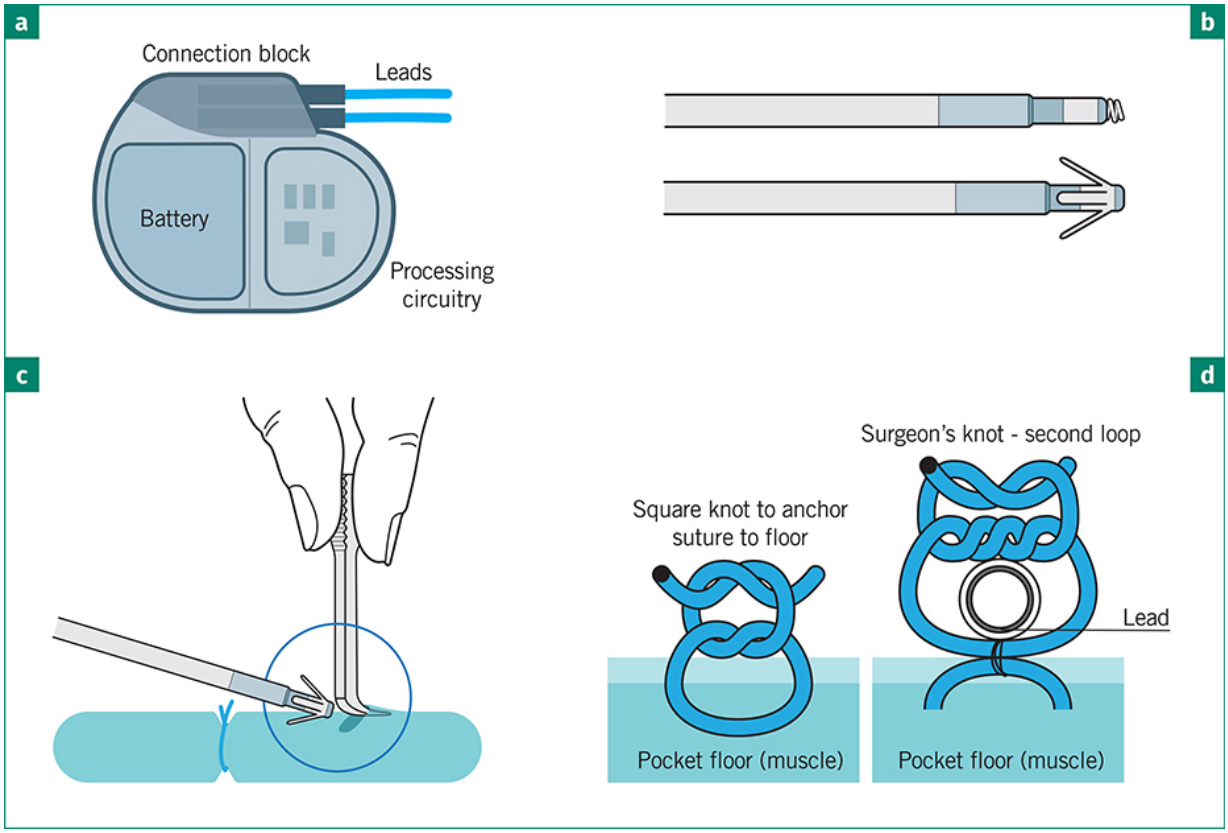


FIGURE 10.2. a) Pulse generator. Approximately half of the volume is taken by the battery. The connection block has one to three ports to accommodate the leads. b) Active fixation leads use a screw-in mechanism; passive fixation leads rely on tines to grasp the tissue. c) Vein lifter. The jugular vein is first ligated cranially. A small incision is made in the vessel wall and the vein lifter is inserted into opening to elevate the vein and facilitate lead insertion. d) Anchor knot. First, a nonslip knot is tied on the muscle under the lead, then a loop is tied in the groove of the suture sleeve.

Position	I	II	III	IV	V
Category	Chamber(s) paced	Chamber(s) sensed	Response to	Rate modulation	Multisite pacing
Letters used	O = none A = atrium V = ventricle D = dual (A+V)	O = none A = atrium V = ventricle D = dual (A+V)	O = none T = triggered I = inhibited D = dual (T+I)	O = none R = rate modulation	O = none A = atrium V = ventricle D = dual (A+V)

FIGURE 10.3. Pacemaker codes and modes. A standardized letter-code system has been developed to describe pacemaker function. The letter in the first position describes the chamber(s) paced. The second letter indicates where intrinsic cardiac electrical activity is sensed. The third letter describes what the pacemaker will do if it senses an intrinsic beat from the patient. For example, a sensed impulse can trigger (T) a paced stimulus, or instead inhibit (I) a paced stimulus. In dual (D) mode, it inhibits in one chamber and triggers in another chamber. The fourth letter indicate if there is a rate

modulation (“rate response”) function activated. The fifth letter is almost never used. For instance, a VVIR pacemaker signifies that it is programmed to pace the ventricle, inhibit pacing output upon sensing a spontaneous impulse, and activate the sensor for rate response.

Lead

Choosing leads involves various options. Leads are available as either unipolar or bipolar. Unipolar leads feature a single insulated wire leading to a lone electrode at the tip (cathode), with the generator serving as the opposite pole (anode) in the electrical circuit. The extensive distance covered by the circuit results in a prominent pacing spike on the electrocardiogram (Fig. 10.4). Typically, unipolar leads exhibit smaller diameters and greater flexibility compared to their bipolar counterparts. Conversely, bipolar leads comprise two insulated wires leading to two electrodes at their distal end; current flow is facilitated between the tip (usually the cathode) and a metallic ring positioned slightly above the tip. Currently, most implanted leads are of the bipolar type. These electrodes serve the dual purpose of sensing intrinsic electrical activity and providing pacing at their implantation sites. However, specific leads (VDD leads) designed for right ventricular implantation incorporate a second floating sensing electrode positioned more proximally to detect atrial activity. Leads designed for surface attachment to the heart are termed epicardial. Various fixation options are available, with the suture-based epicardial button being the preferred choice.[13] Leads implanted within the cardiac chambers are known as endocardial, featuring two types of fixations. Passive fixation leads incorporate small plastic tines at the tip to anchor within the intracardiac trabeculae. Active fixation leads possess a helix at the tip, which is screwed into the myocardium. The helix is often extendable and retractable through a tool at the lead’s proximal end (Fig. 10.2b). Typically, the lead tip includes a silicone rubber collar housing a steroid agent, aimed at reducing postimplantation inflammation and alleviating threshold increases associated with inflammatory responses. Lead connections to generators have been standardized (IS-1 type) across all pacemaker manufacturers. Therefore, a lead from one company is fully compatible with the pulse generator from another company. Each lead type is characterized by its impedance, which represents the resistance it opposes to the current, measured in ohms. Manufacturers provide an acceptable

range of values for each lead model, and significant variations below or above this range may indicate structural integrity issues with the lead.[17]



FIGURE 10.4. VVI ventricular pacing in a 12-year-old female Chihuahua with sick sinus syndrome. Notice, after the first two sinus beats, the occurrence of a sinus pause longer than the pacing interval, followed by a unipolar high voltage spike (arrow) and ventricular capture. After the paced beat, sinus rhythm recurs and since sensed by the pacemaker no further spikes appear. Lead II; speed, 50 mm/s; calibration, 5 mm/1 mV.

Accessories

The pacemaker programmer is a specialized laptop-sized computer exclusive to each pacemaker manufacturer. It functions as a pacing system analyzer to verify proper lead placement during surgery. Following implantation, it is utilized to fine-tune pacemaker settings and monitor the pulse generator. Additionally, the programmer features a magnet that, when placed atop the generator, activates the "magnet mode". This mode enables the collection of data from the device and the adjustment of programmable parameters.

A torque-limiting wrench is packaged with the pulse generator to tighten set screws to secure the leads in place in the ports of the device. The torque-limiting wrench prevents overtightening.

Endocardial pacemaker leads come with a disposable vein lifter—a small, pointed tool designed to be inserted into the vein's lumen after opening. This tool lifts the vein, facilitating easier insertion of the lead (Fig. 10.2c). Each lead is accompanied by a set of straight and curved stylets, which are inserted into its lumen to provide rigidity and shape its tip during the placement process.

IMPLANTATION PROCEDURE

Implantation checklist

It is advisable to employ a surgical checklist systematically when performing pacemaker implantation to minimize the likelihood of

significant complications and prevent the oversight of crucial procedural steps.[18] Notably, the implantation team should anticipate the potential need for emergency temporary pacing after anesthesia induction. In their institution, the authors employ external transthoracic pacing as the emergency pacing method. It is recommended to use a neuromuscular blocker to reduce muscle twitching during transthoracic pacing.[19,20] Transvenous temporary pacing using a peripheral vein access is also a viable option. Given the seriousness of potential device infections, it is imperative that animals are devoid of any ongoing infections, and antibiotic prophylaxis must be administered in all instances.[21]

Transvenous pacemaker implantation

Typically, a pacing lead is implanted through a right jugular venotomy, with the animal in left lateral recumbency. While lead placement from the left jugular vein is usually uncomplicated, the presence of a persistent left cranial vena cava can occasionally pose challenges, making it difficult or even impossible to reach the right ventricle with the lead.[22,23] The subsequent stage involves guiding the lead tip into the targeted cardiac chamber under fluoroscopic guidance, although it can also be done using transthoracic echocardiographic monitoring only.[24] This step involves thin metallic wires called stylets that can be shaped and inserted into the lead's lumen. In the case of right ventricular pacing, an initial straight stylet guides the lead into the right atrium. Subsequently, a slightly curved stylet replaces it, facilitating the lead's passage across the tricuspid valve. Once the lead tip reaches the right ventricle, it is swapped for a straight stylet to guide it against the endocardium of the right ventricular apex. Alternate pacing sites can be selected, such as the right ventricular outflow tract or the interventricular septum, but they are not routinely used in veterinary patients. For an active fixation lead, it is screwed directly into the myocardium with consistent gentle pressure applied to the lead. In contrast, a passive lead is guided towards the apex of the right ventricle, where its small tines anchor passively into the ventricular trabeculae without the necessity of screwing (Fig. 10.5). The stylet is then withdrawn at a slow and steady pace, and the lead tip position is visually monitored with fluoroscopy to ensure there are no signs of displacement. At that time, intraoperative testing is conducted with the pacing system analyzer. It is not uncommon

that the lead must be repositioned until satisfactory testing values are obtained. Lead slack is subsequently fine-tuned with fluoroscopic guidance to prevent undue tension on the lead tip or unnecessary lead redundancy within the cardiac chambers and minimize the risk of interference with valve function. To limit further movement of the lead, the anchoring sleeve is slid over the lead near the venous insertion site. Sutures (the authors use 2-0 nonabsorbable suture) are tied snugly but not too tightly around the grooves of the sleeve to secure the lead to the subcutaneous tissue. When three knot tying techniques were tested, the anchor knot provided the greatest lead stability and could contribute to decrease the risk of lead dislodgement (Fig. 10.2d).[25] During this step, a stylet can be left partially inserted in the lead to provide support and limit the risk of damage if excessive force is applied during suturing. To limit the risk of lead insulation damage, ligatures should not be tied directly onto the lead.

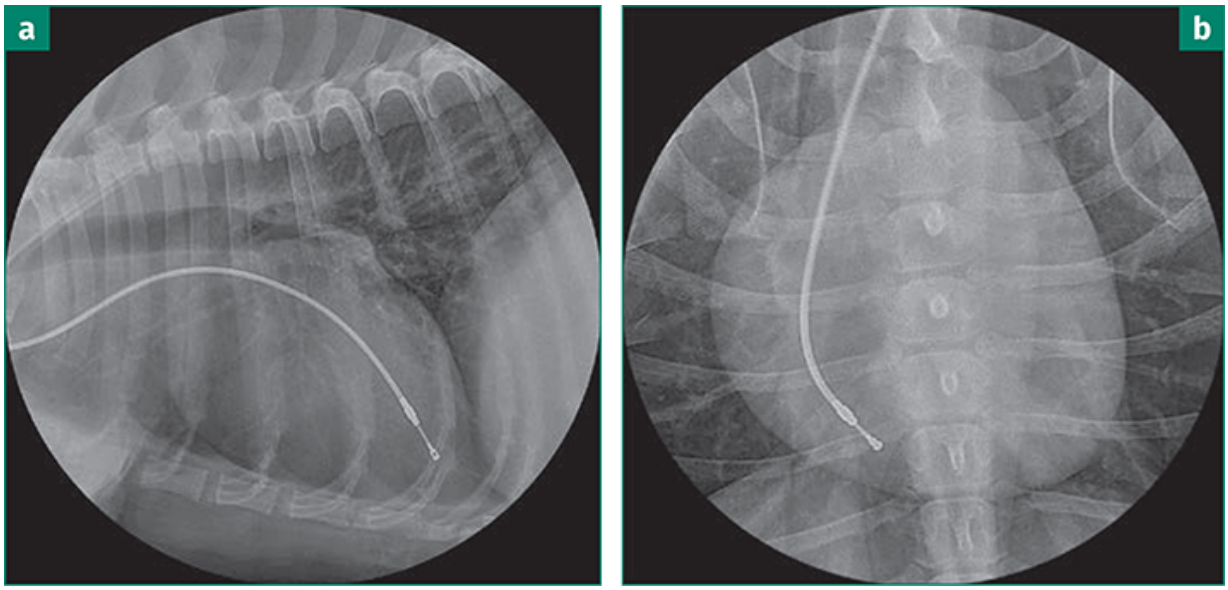


FIGURE 10.5. Right ventricular apical pacing. Lateral (a) and dorsoventral (b) thoracic radiographs of a dog with a single pacemaker lead implanted in the right ventricular apex. On the dorsoventral view, the lead tip is pointing towards the interventricular septum.

The procedure for atrial lead implantation follows similar initial steps. Initially, a straight stylet is employed to access the right atrium. When utilizing a preformed J-lead, withdrawing the stylet causes the lead tip to reassume its curved configuration. Alternatively, for a straight lead, a stylet pre-curved in a J shape is inserted into the lead. Subsequently, the lead is drawn cranially to reach the conventional implantation location in the right

auricle (Fig. 10.6). Active fixation leads are favored over passive leads due to the less trabeculated nature of the endocardial surface in the atrium compared to the ventricular apex.[26,27]

For dual-chamber pacemaker implantation, the ventricular lead is typically placed first, so that pacing support can be provided in case of emergency.

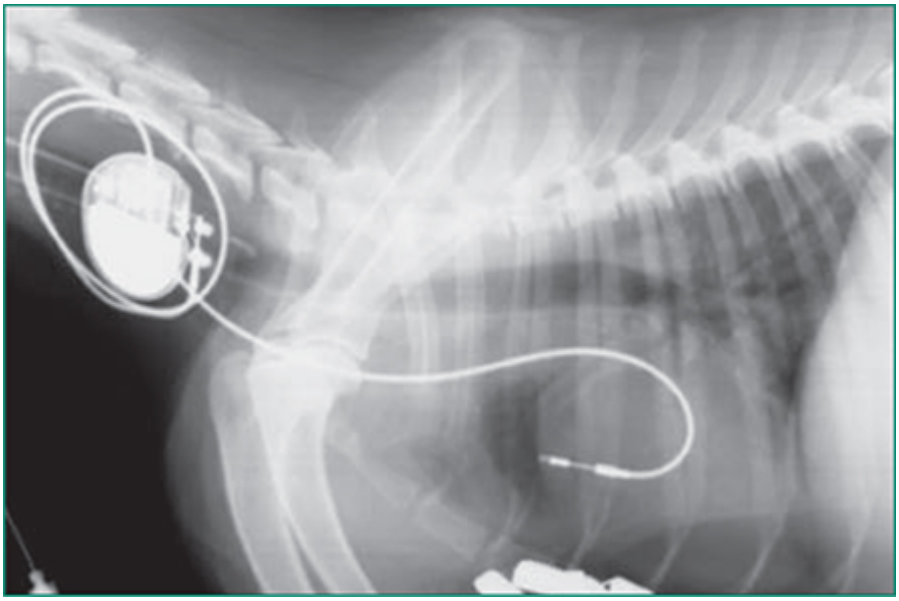


FIGURE 10.6. Atrial pacing. Lateral thoracic radiograph of a dog with a J-shaped atrial active fixation lead. The tip of the lead is situated in the right auricle. The lead is connected to a pulse generator placed in a subcutaneous pocket in the cervical region. Excess lead is coiled beneath the generator.

A subcutaneous pocket is created for the pulse generator just dorsal to the initial incision. Alternatively, the option exists to choose a thoracic site situated caudal to the right scapula; however, this alternative may necessitate the use of an extended lead or a lead extension. A cervical site for the pulse generator might be associated with a higher occurrence of seroma.[28] The lead is then tunneled subcutaneously between the two incisions, and rapidly connected to the generator. Excess lead is coiled and placed under the generator inside the pocket. Finally, the generator is sutured to the underlying muscle and both incisions are closed.

Epicardial pacemaker implantation

The pacing site for epicardial leads is typically the left ventricular apex, although epicardial atrial and epicardial dual-chamber pacing have been reported.[29] Access to the cardiac apex is achieved via an abdominal transdiaphragmatic approach or a minithoracotomy.[13,30] In large deep-chested dogs, a minithoracotomy should be preferred. The pulse generator is secured in the lateral abdominal wall (Fig. 10.7).[13]

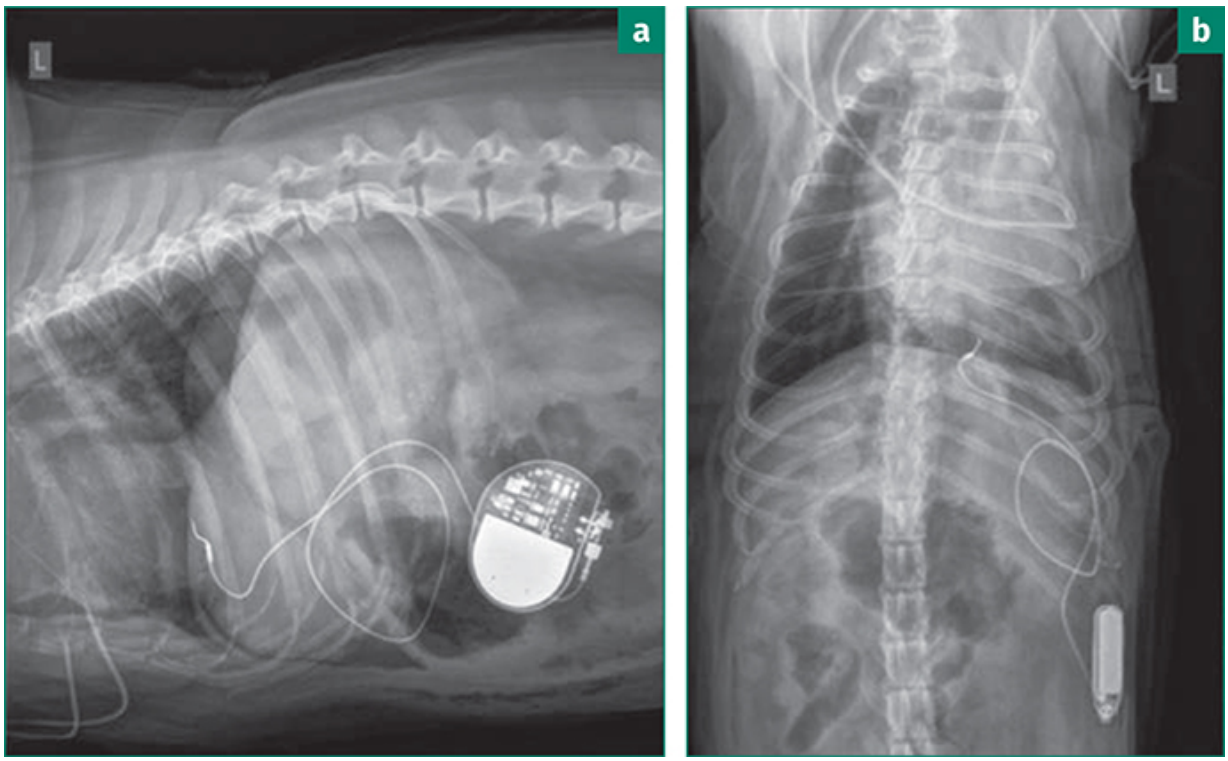


FIGURE 10.7. Epicardial pacing. Lateral (a) and dorsoventral (b) radiographs of a dog with an epicardial pacemaker. The lead is surgically secured to the epicardial surface of the left ventricle. The pulse generator is placed in a pocket in the lateral abdominal wall.

Intraoperative testing

The pacing system analyzer is utilized to verify the adequacy of the pacing site and ensure proper functioning of the lead in pacemaker lead testing. Additionally, the pacing system analyzer can serve as an external pacemaker if the patient requires chronotropic support. Several parameters must be evaluated, including the capture threshold, sensing threshold, lead impedance, and slew rate. Adequate lead placement is determined by a maximum capture threshold below 1.0 V for a ventricular lead and 1.5 V for an atrial lead at a pulse width of 0.5 ms. A crucial consideration is a low

initial threshold, which is expected to double within 1 to 4 weeks post-implantation, before settling to approximately 1.5 times its intraoperative value. The minimum sensing threshold for a ventricular lead is the patient's sensed R wave at 5.0 mV, while for an atrial lead, it is the sensed P wave at 2 mV. The signal slew rate should exceed 0.5 V/s, and lead impedance, indicative of lead structural integrity, should fall within the manufacturer's recommended range, typically between 500 and 2000 ohms. Lead impedance measurement is feasible only during pacing, and it plays a critical role in assessing lead structural integrity. The current of injury, indicative of local damage by the lead tip to the myocardium, appears as an ST segment elevation (at least 25% of the intrinsic atrial or ventricular electrogram amplitude in human patients) and prolongation of the sensed intracardiac electrogram (by 50 ms in human patients) right after lead placement.[31] It is another parameter that is useful as a marker of adequate lead fixation (Fig. 10.8). For active fixation leads and to a smaller extent passive fixation leads, the presence of a current of injury may also explain an initial high capture threshold, which decreases within 5 to 10 minutes as the electrogram morphology normalizes. Finally, although it is a rare complication with bipolar leads and standard pacing output values, the absence of diaphragmatic/phrenic nerve stimulation during pacing is achieved by confirming that there is no diaphragmatic movement when a high voltage stimulus (10 V) is delivered.[17,22]

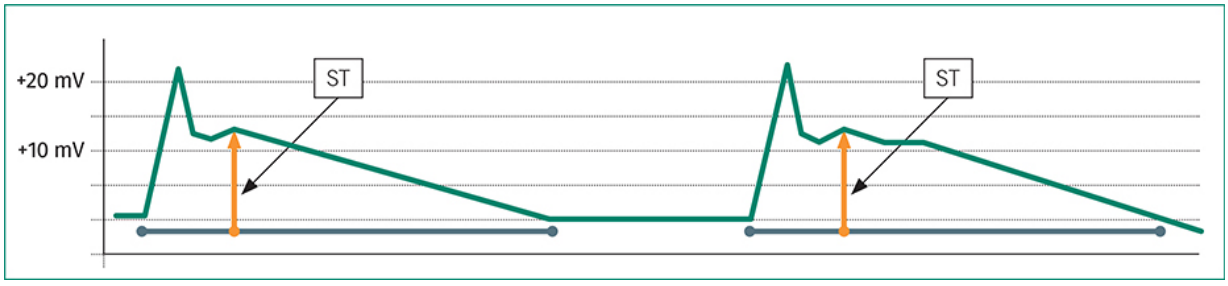


FIGURE 10.8. Electrograms recorded from the endocardial pacemaker lead. The current of injury reflects the transient endocardial damage that occurs during pacemaker lead placement. It is more pronounced with active fixation leads and appears as an elevation of the ST segment and a prolongation of the electrogram recorded from the pacemaker lead. Typically, the current of injury lasts 5 to 10 minutes. It can result in a higher pacing threshold immediately after lead implantation. It is therefore recommended to repeat the threshold test after resolution of the current of injury.

DEVICE PROGRAMMING

Programming of the pacemaker device involves choosing the pacing mode and then establishing the pacing protocol, including the rate of pacing, voltage and duration of the pacing stimulus, sensitivity to intrinsic cardiac activity, and refractory periods.

Programming single chamber modes: VVI(R) and AAI(R)

Pacing rate

In VVI or AAI pacing, a single pacing rate is chosen as the lower or base pacing rate. Factors to consider when programming the base rate in dogs include activity level, breed, age, size, temperament, and noncardiac comorbidities.[32] The base rate is often chosen to equal the average heart rate that is found on 24-hour Holter monitors in dogs, which is typically around 70 beats per minute. An important consideration, though, is that this can result in pacing at heart rates that are higher than necessary for times of low activity and that may be inadequate to meet perfusion demand during times of high activity. Thus, other features can be programmed to adjust the pacing rate.

Pacing at a lower rate can be accomplished through setting a sleep rate or using the hysteresis feature. *Sleep rate* can be programmed to lower the pacing rate during specific hours of expected sleep. A bedtime and wake time are programmed. *Hysteresis* is a feature that promotes intrinsic activity below the programmed base rate. The hysteresis rate is chosen at a lower rate than the base rate. When an intrinsic beat is sensed during normal pacing intervals, the next pacing interval is prolonged to the hysteresis rate to prioritize an intrinsic rhythm slightly slower than the base rate. If the intrinsic rate falls below the set hysteresis rate, normal pacing at the base rate will resume.

Changing the mode to VVIR or AAIR allows programming of higher heart rate during activity. This is termed *rate response* or *rate adaptive* pacing and uses an activity sensor (generally an accelerometer) within the generator to adapt the pacing rate to changes in the patient's physical activity. A maximum rate that can be achieved is set (termed the *maximum* or *upper sensor rate*), and Medtronic generators also set an intermediate rate associated with moderate activities (activities of daily living, or ADL). In addition, programming is used to set a threshold for the sensor, which is the lowest amount of activity to trigger an increase in the rate and the slope

or gain of the rate response, which determines how quickly the rate will rise to the maximum rate with the sensed activity (Fig. 10.9).

An exercise test can also be performed at the time of programming to assess optimization of rate response to activity. For Medtronic generators, choosing the "Exercise Test" feature will open a test screen that starts a 2-minute period when the dog can be exercised to varying degrees and then assessed to see how well the rate response feature triggered an increased pacing rate. Generators from other manufacturers do not have this specific test, though an exercise test can still be performed. Particularly for dogs with third-degree atrioventricular block, assessing the ratio of the atrial and ventricular rates after exercise can determine if the pacing rate is keeping up with the sinus rate in response to activity. This is described using a treadmill in dogs and assessing both atrial rate and ventricular paced rate over 10 minutes with increasing speeds.[33]

There is little available information about pacing rate setting for cats. Retrospective evaluation of pacemaker implantation in cats describe base pacing rates within a large range between 70 and 180 bpm, with one study showing a median of 110 bpm.[34,35] VVIR pacing was only reported in one cat, and there is no information about the use of a sleeping rate or hysteresis.

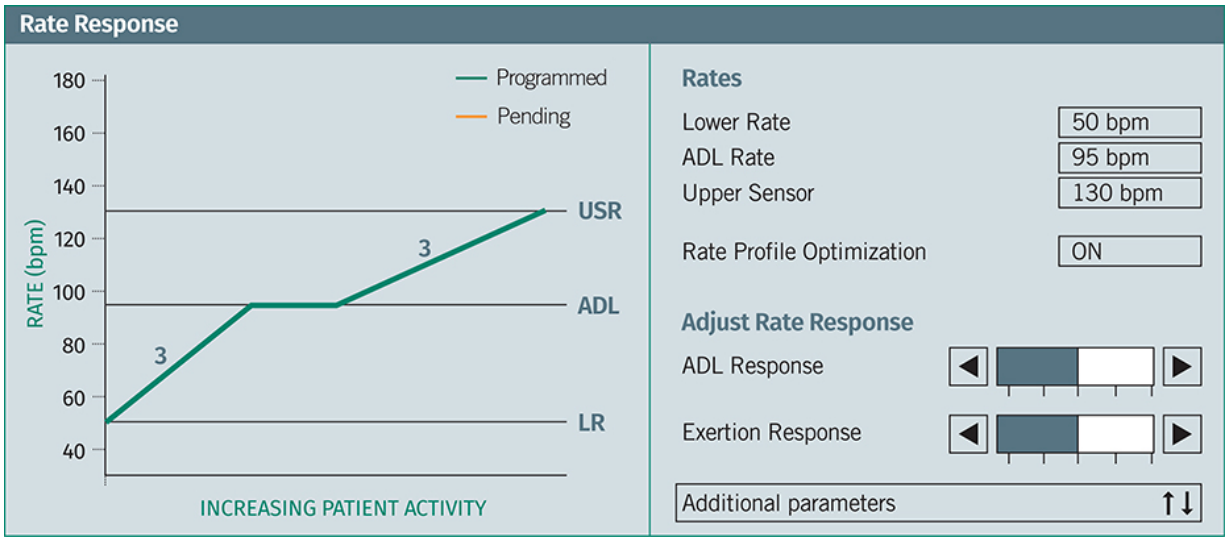


FIGURE 10.9. Example of rate response programming on a Medtronic generator. Lower rate, activities of daily living (ADL) rate, and upper sensor rate are programmed. ADL response controls the slope of the line from lower rate to ADL rate and exertion response controls the slope of the line from ADL rate to upper sensor rate. An increased slope will result in increased rates with lower patient activity.

Pacing stimulus

The pacing stimulus is programmed to have a specific voltage (or amplitude) and duration (or pulse width). The amplitude is determined though threshold testing, which is performed by gradually decreasing the pacing stimulus amplitude until there is loss of capture. The amplitude should be chosen to be at least two times greater than the measured threshold (i.e., a safety margin of greater than 2:1). A threshold test can also be performed for pulse width, though this parameter is more typically held constant.

Programming can be set up for the device to self-monitor pacing stimulus thresholds at periodic intervals. This is termed differently based on the manufacturer: Capture Management for Medtronic, AutoCapture for Abbott/St. Jude, and Capture Control for Biotronik. A minimum amplitude and safety margin are set during programming. This feature can also be programmed to perform the threshold test for monitoring, but not change the programmed amplitude.

Sensitivity

Sensitivity is set to be high enough to appropriately sense intrinsic cardiac activity but low enough to ignore low voltage noise, repolarization, and far-field sensing of either atrial or ventricular activity depending on the lead placement. To ensure there is appropriate sensing, testing the amplitude of inherent cardiac activity is performed. In some cases, particularly patients with third-degree atrioventricular block that are completely reliant on pacing, the pacing rate will need to be lowered to assess the underlying intrinsic rhythm during the test. The sensitivity should then be set to a number lower than the amplitude of the intrinsic activity. Oversensing of T waves or far-field sensing can be positional and may not be detected during a programming session; 24-hour Holter monitoring can be used as a tool to assess for oversensing, as rates lower than the base rate will result. If oversensing is noted, the sensitivity should be lowered (setting a higher number).

In a similar manner to the self-testing of thresholds described above, devices can be set to perform testing of inherent ventricular amplitude and automatically adjust programmed sensitivity in response to the results. This

feature is called Sensing Assurance for Medtronic, AutoSense for St. Jude/Abbott, and Automatic Sensitivity Control for Biotronik.

Refractory period

After each pacing stimulus, there is a period of time during which the pacemaker does not sense intrinsic activity (blanking period), followed by a period of time during which the pacemaker senses activity but does not respond by delaying the next paced beat (refractory period). The refractory period is programmable on all devices, while the blanking period may be fixed. The ventricular refractory period should be set to include the entirety of ventricular repolarization (QT interval).

Reviewing nonprogrammable data

During programming, it is also possible to assess data regarding the battery life, battery and lead impedance, and electrograms that have been stored from high-rate episodes. Lead impedance is often assessed automatically by the device at regular intervals and will display a trend line over time.

Programming dual chamber modes: VDD, DDI(R) and DDD(R)

Pacing rate

The base rate is set to the lower rate of pacing, but an upper tracking rate must also be programmed. The upper tracking rate will be the maximum rate of ventricular pacing in response to triggering from an atrial paced or atrial sensed beat. This range defines the range of ventricular pacing rates that can occur. The Rate Response feature can also be programmed for pacemakers that have an atrial pacing lead, to allow for an increase in the atrial pacing rate with activity when the sinus node is not functioning normally.

Programmable intervals

Dual chamber pacemakers have the added complexity of programming the relationship between atrial and ventricular activity. The first programmable interval that defines this relationship is the atrioventricular interval, which

determines the amount of time after an atrial beat to wait for either a sensed ventricular beat or a paced ventricular beat to occur. This is programmed for both atrial sensed beats and atrial paced beats. In addition, many devices allow programming of a rate adaptive atrioventricular interval, whereby the interval will become shorter with faster rates to mimic the physiological shortening of the PR interval. There are also programmed features to promote intrinsic atrioventricular conduction. Search AV+ is a feature that will periodically prolong the atrioventricular interval and analyze if atrioventricular conduction occurs at an appropriate interval; if yes, it will adjust the programmed atrioventricular intervals to allow for increased intrinsic conduction. Managed Ventricular Pacing provides atrial-based pacing with ventricular backup. It begins in AAI(R) mode, but if atrioventricular conduction is lost, it will switch to DDD(R) to allow for ventricular pacing. Periodic conduction checks are then performed, and if atrioventricular conduction resumes, the device switches back to an atrial pacing mode. Managed ventricular pacing modes appear as AAI(R)↔DDD(R) on the programmer.

The blanking and refractory periods also need to be set to account for the relationship between the leads. After an atrial paced stimulus, the atrial lead will have blanking and refractory periods as normal, but following the subsequent ventricular beat, it will have an additional refractory period, termed postventricular atrial refractory period. Likewise, the ventricular lead will have ventricular blanking and refractory periods, but it will also have a refractory period that occurs after an atrial stimulus called the postatrial ventricular refractory period.

The total atrial refractory period is equal to the postventricular atrial refractory period plus the programmed atrioventricular interval. The total atrial refractory period must be shorter than the upper tracking rate interval to prevent detrimental upper rate behavior for the pacemaker.

Upper rate behavior

The paced rhythm that occurs when the atrial rate increases above that of the upper tracking rate is termed upper rate behavior. Some examples of upper rate behavior include pacemaker Wenckebach response, 2:1 atrioventricular block, and automatic mode switching.[36] During pacemaker Wenckebach response, the atrioventricular interval is prolonged so the

paced ventricular rate does not exceed the upper tracking rate; this causes each successive atrial event to be closer to the preceding ventricular beat until the atrial event falls into the postventricular atrial refractory period and does not trigger a ventricular paced beat. This is a desirable response, as it aligns closely with normal decremental behavior of the atrioventricular node. Conversely, if the upper rate limit is programmed to be shorter than the total atrial refractory period, 1:1 atrioventricular tracking will occur until the total atrial refractory period is reached, at which point there will be a sudden drop to 2:1 block. Automatic mode switching describes a change in pacemaker mode to a nontracking mode (VVI, DVI or DDI) in response to detection of an atrial tachyarrhythmia. This is beneficial, as it prevents rapid ventricular pacing in response to a rapid atrial arrhythmia, though it can result in an abrupt change to a lower rate that can result in clinical signs.

COMPLICATIONS

Perioperative complications

Perioperative survival rates for dogs and cats undergoing pacemaker implantation surgery are high, ranging between 94% and 100% in various studies,[3,9,30,35,37–39] but perioperative complications, including those that are fatal, can occur. Perioperative complications are reported to be more frequent when the implantation is performed after normal business hours.[40] Ventricular fibrillation was the complication most commonly associated with death during the operative period[30,35,39] and was also reported in some dogs that were defibrillated and survived.[3,37,39] This may be due to the induction of mechanical ventricular arrhythmias during lead placement, as evidenced by one case in which fibrillation occurred immediately after suturing an epicardial lead to the heart.[30] It can also be caused by bradycardia-induced triggered arrhythmias (early afterdepolarizations). There are also reports of death due to cardiac tamponade caused by right ventricular wall perforation.[38]

Short-term complications

Many analyses of short- and long-term complications following pacemaker placement have been performed (Table 10.1). Lead dislodgement leading to

loss of capture is the most common major complication for transvenous and epicardial pacemakers; it can result in clinical signs and may require subsequent procedures to reposition the lead or replace the entire pacing system (Fig. 10.10). Lead dislodgement is typically reported between one day and one month after surgery.[37,39] Seroma formation in the pocket where the generator is placed is a common minor complication. Following implantation, instructions are provided to the owner that include monitoring the heart rate, activity restriction to limit chance of dislodgement, and bandaging around the generator surgical site to prevent seroma formation during the first month. Moreover, dogs with a pacemaker generator placed in the cervical region should not wear a neck collar.

TABLE 10.1. Nonexhaustive list of pacemaker complications reported in the veterinary literature from 1991 to 2023.

Study	Sisson 1991	Oyama 2001	Wess 2006	Johnson 2007	Hildebrandt 2009	Estrada 2012	Visser 2013	Ward 2015	Noszczyk-Nowak 2019	Swanson 2018	LeBlanc 2019	Franz 2021	Koster 2023
Total cases	40	154	105	104	33	16 Ap	33 28 dogs 5 cats	79	31	130	134	20 20 cats Ep	82 30 Ep 52 Tv
Loss of capture or rising thresholds (no cause identified)	–	–	–	–	–	5	3	–	–	–	4	5	11 7 Ep 4 Tv
Lead dislodgement	13	15	7	5	2 Ap	3	5 4 dogs 1 cat	5	–	3	3	1	14 4 Ep 10 Tv
Lead perforation	–	3	–	–	–	2	–	1	2	2	1	–	2 1 Ep 1 Tv
Lead fracture	–	1	–	2	–	–	–	–	–	–	1	–	1 Ep
Exit block	3	2	–	1	–	–	–	1	–	–	–	–	2 Ep
Seroma	4	18	3	17	4	–	1	6	–	–	–	–	1 Ep
Infection	6	7 6 G 1 L	1	–	–	–	–	5 2 G 3 L	2	1	1	–	1 Tv
Lead thrombus	–	–	–	–	2	–	–	1	–	–	–	–	3 Tv
Battery depletion	–	9	1	–	–	–	1	–	1	–	2	2	–
Sensing problems	–	2	6	–	–	9	2	–	–	–	–	8	6 1 Ep 5 Tv
Muscle twitching	5	17	–	–	–	3	2 1 dog 1 cat	2	–	–	–	2	2 Ep
Twiddler's syndrome	–	1	–	2	–	–	–	–	–	–	–	–	–
Lead prolapse/looping	–	–	–	2	–	–	–	–	–	–	–	–	–

Ap, atrial pacing; G, generator; L, lead; Ep, epicardial pacing; Tv, transvenous. Cases are dogs unless otherwise specified to be cats.



FIGURE 10.10. VVI ventricular pacing in an 8-year-old male English Bulldog with third-degree atrioventricular block and VVI pacemaker with endocardial lead dislodgement. Notice the presence of four unipolar high voltage spikes (arrows), of which only the first one is followed by a ventricular capture, which confirms the presence of a pacemaker malfunction due to loss of capture. After the third spike, a ventricular escape beat appears (*), which does not change the pacing interval due to pacemaker undersensing. The combination of loss of capture and undersensing is commonly caused by lead detachment and dislodgement. Lead II; speed, 50 mm/s; calibration, 5 mm/1 mV.

Long-term complications

Obstructions of various structures from transvenous pacemaker lead looping due to redundant lead or lead prolapse has been reported at the level of the tricuspid valve,[41] right-ventricular outflow tract,[42] and caudal vena cava,[43] often leading to severe consequences such as tricuspid valve stenosis or congestive heart failure. Cranial vena cava syndrome is due to fibrotic and/or thrombotic obstruction of venous blood flow to the right atrium from the cranial vena cava, where the pacemaker leads are placed (Fig. 10.11).[44–46] Pacemaker lead–associated thrombi, even when they do not lead to cranial vena cava syndrome, can cause significant morbidity and are associated with reduced survival times.[47]

Pacing of noncardiac structures can also occur as a complication. Muscle twitching was reported as a common complication due to pacing of skeletal muscles. Synchronous diaphragmatic contractions have been reported as a complication and can occur due to pacing of the phrenic nerve. This has been reported in a dog with a dual chamber pacemaker, in which it was determined to be caused by pacing of the atrial lead,[48] and has also been reported in dogs after dislodgement of a ventricular lead.[3] Diaphragmatic stimulation can cause no adverse clinical signs but has been reported in at least one dog to be the cause of episodic dyspnea.[38] Epicardial pacemaker placement in the right abdominal body wall was found to pace the pyloric cells in one case report, resulting in pyloric outflow obstruction.[49]

Changes in lead impedance are often a sign of pacemaker lead complications. Decreases in impedance can be seen with pacemaker lead insulation break,[50] while increases in impedance are seen with lead fracture or mechanical failure of the lead-header interface.[51]

Runaway pacemaker refers to a generator malfunction that results in sudden pacing at rapid, erratic, nonphysiological rates.[52] As a response to the sudden acceleration of rate output, a decrease in the amplitude of the

pacing stimulus may occur, which can result in loss of capture. Alternatively, if the pacing stimulus is at an amplitude that will depolarize the heart, the ventricle may be paced at the rapid rate and result in severe tachycardia, which can be fatal.

Twiddler's syndrome, which is typically caused by scratching of the neck or rolling on the back, can lead to excessive coiling of the lead within the pacemaker generator.[9] This can result in lead dislodgment.

Finally, pacemaker syndrome can occur as a complication when long-term asynchronous atrioventricular contractions leads to structural heart disease.[53] This is likely to be exacerbated by single ventricular lead pacing compared to dual chamber pacing.

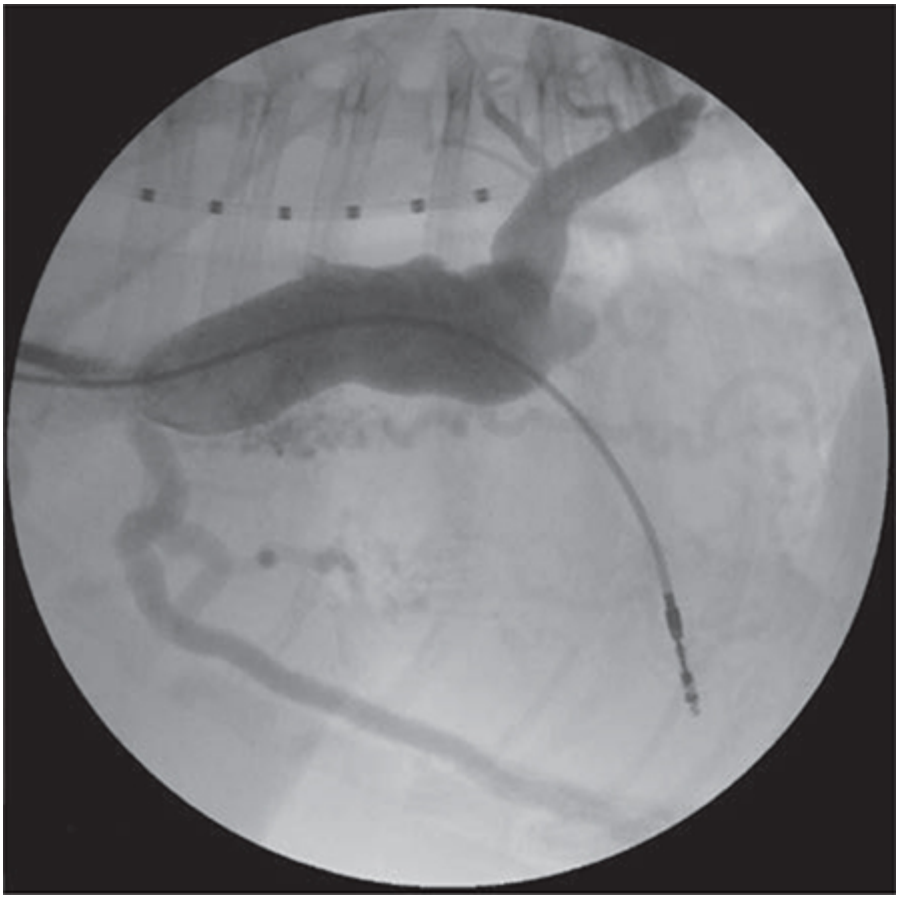


FIG 10.11. Nonselective venogram from the left jugular vein in a dog with cranial vena cava syndrome secondary to central venous obstruction just proximal to the right atrium associated with ventricular pacemaker lead implantation. The cranial vena cava, the azygous vein, and the internal thoracic vein are markedly distended. Tortuous acquired collateral veins are also visible ventral to the vena cava. No flow could be seen entering the right atrium.

IMPLANTABLE CARDIOVERTER DEFIBRILLATOR

Implantable cardioverter-defibrillators are electronic devices designed to detect and terminate ventricular tachycardia and ventricular fibrillation.[1] The pacing system analyzer offer three primary therapies:[1]

- *Antitachycardia pacing (ATP):* This therapy involves the delivery of short bursts of low-energy pacing pulses to correct reentrant ventricular tachycardia. Antitachycardia pacing attempts to terminate fast arrhythmias by pacing the heart at a slightly faster rate, aiming to restore a normal rhythm without the need for a shock.
- *Cardioversion:* Implantable cardioverter-defibrillators can administer low- to moderate-energy shocks synchronized with the ventricular rhythm to interrupt arrhythmias that do not respond to antitachycardia pacing.
- *Defibrillation:* In cases of life-threatening arrhythmias, such as ventricular fibrillation, or arrhythmias that do not initially respond to antitachycardia pacing and cardioversion, high-energy shocks are swiftly delivered to reset the heart's electrical activity.[1]

EQUIPMENT

Implantable cardioverter-defibrillators comprise a programmable generator and a transvenous lead placed within the right ventricular apex. This lead detects ventricular electrograms, while the generator's electronic circuitry is tasked with identifying and treating ventricular arrhythmias. When utilized as one of the defibrillation electrodes, the generator is referred to as the "active can", and the transvenous lead contains a shocking coil near its tip, which serves as the second defibrillation electrode (Fig. 10.12).[54] More recently, subcutaneous implantable cardioverter-defibrillators have been developed, but they lack some programming features.[55]

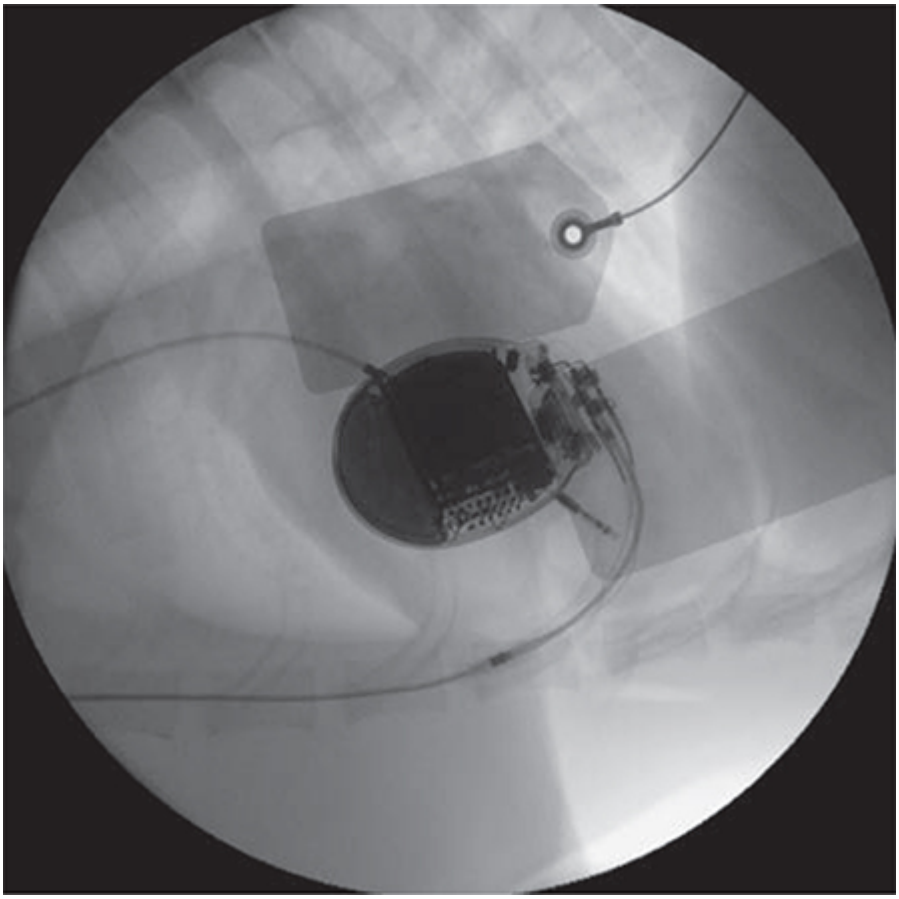


FIGURE 10.12. Implantable cardioverter-defibrillator lead and device placement in dogs. Lateral thoracic radiograph. The implantable cardioverter-defibrillator lead is secured in the right ventricle in an apical position. The lead is then tunneled from the jugular vein incision to the left lateral thorax and connected to the device. The implantable cardioverter-defibrillator can is positioned over the cardiac apex and the most distal defibrillation coil.

DEVICE PROGRAMMING

The defibrillation threshold represents the minimal energy or voltage needed to effectively defibrillate the heart.[56] The defibrillation threshold value is primarily influenced by various factors such as the shock vector—defined by the generator and the lead shocking coil—along with the configuration of the shock waveform, the underlying cardiac condition, body size and positioning, metabolic factors, and the use of antiarrhythmic medications. Determination of the defibrillation threshold occurs during the implantation procedure.

Implantable cardioverter-defibrillators utilize two programmable parameters—rate and duration—to detect arrhythmias. Consequently, a configurable ventricular fibrillation detection zone is established based on

its lower rate limit, typically capped at 300 beats per minute (corresponding to a cycle length of 200 milliseconds) but potentially higher in more recent models of implantable cardioverter-defibrillators. Treatment is administered when the number of sensed ventricular electrograms within the ventricular fibrillation zone reaches a predetermined count of intervals, usually up to a maximum of 100.[54] Programming a long detection time decreases the occurrence of unnecessary or inappropriate therapies.[57] Similarly, a therapy zone can be configured for antitachycardia pacing and cardioversion (Fig. 10.13).

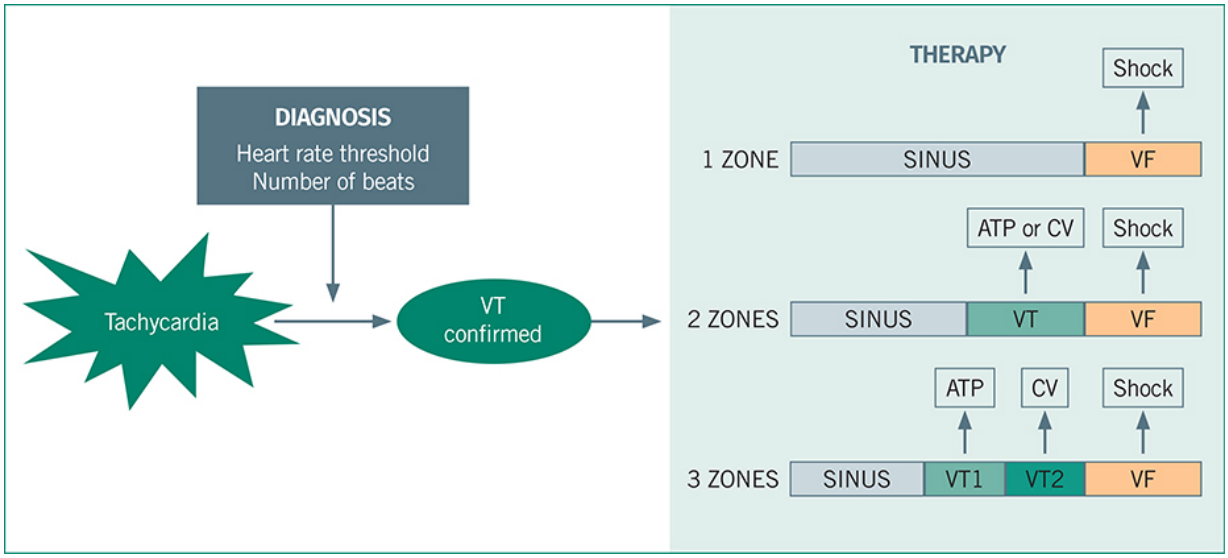


FIGURE 10.13. Principles of arrhythmia detection and treatment by an implantable cardioverter-defibrillator. VF, ventricular fibrillation; ATP, antitachycardia pacing; CV, cardioversion.

ROLE OF IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS IN DOGS WITH VENTRICULAR ARRHYTHMIAS

For human patients experiencing severe ventricular arrhythmias, implantable cardioverter-defibrillator therapy has demonstrated a noteworthy reduction in mortality by 23–55% when compared to antiarrhythmic medications. Additionally, a substantial amount of medical evidence strongly advocates for the utilization of implantable cardioverter-defibrillators in individuals affected by nonischemic cardiomyopathy coupled with left ventricular dysfunction and severe ventricular arrhythmias. In cases of arrhythmogenic cardiomyopathy in which

documented syncope persists due to ventricular arrhythmias despite optimal medical therapy, device implantation becomes a necessary course of action.[58]

Implantable cardioverter-defibrillator implantation was documented in a Boxer with arrhythmogenic cardiomyopathy by Nelson et al.,[59] and the author's team[60] proceeded to place implantable cardioverter-defibrillators in a young German Shepherd dog affected by inherited ventricular tachycardia and in a Doberman Pinscher diagnosed with dilated cardiomyopathy. Although the animals recovered uneventfully from the implantation procedure, major complications were subsequently encountered in all three dogs: 1) the maximal energy output of the device had to be programmed to successfully terminate induced episodes of ventricular fibrillation during device testing, which is in contrast with the 10-J safety margin that is recommended for defibrillation threshold;[56] 2) inappropriate therapies occurred in all three dogs. In dogs, inappropriate therapy commonly arises due to oversensing of a ventricular repolarization (T wave) or when the sinus tachycardia rate exceeds the threshold, thus triggering defibrillation.[60] Finally, in the case of the Doberman Pinscher, high-energy defibrillation therapy was triggered by a hemodynamically-stable episode of sustained ventricular tachycardia 36 hours after implantation, but the device failed to terminate the arrhythmia, which ultimately degenerated into ventricular fibrillation. In this example, inappropriate therapy was triggered by the high rate of ventricular tachycardia, which was above the maximal programmable rate of 300 bpm for the lower boundary of the ventricular fibrillation zone. Thus, these initial experiences have revealed two major obstacles to the use of implantable cardioverter-defibrillators in dogs: a high defibrillation threshold, defined as a safety margin of <10 J below the maximum output of the device, likely caused by inadequate device placement and shock configuration; and failure to discriminate between ventricular tachycardia and ventricular fibrillation using available programmable rate cutoffs for detection zones. The authors' group subsequently developed a protocol for implantable cardioverter-defibrillator implantation in dogs and studied various shock configurations in healthy research dogs to reliably achieve low defibrillation threshold values.[61] In this study, the mean defibrillation threshold with a fixed-pulse or fixed-tilt waveform configuration was approximately 9 J, way below the maximal

output of 35 to 40 J for current devices. Currently, cardioverter-defibrillators are not routinely implanted in dogs.

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CHAPTER 11

Catheter ablation

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Catheter ablation is considered the method of choice for the treatment of arrhythmias documented during electrophysiological mapping.[1] The energy released by the ablation catheter (radiofrequency or cryoablation) damages the tissue and eliminates automaticity and conduction, thereby abolishing the arrhythmia.[2]

The first use of percutaneous catheter ablation of myocardial tissue with radiofrequency energy dates to 1987, when successful ablation of the atrioventricular node in a closed-chest canine model with a conventional 2 mm–tipped electrode catheter was performed.[3] In the following years, multiple studies demonstrated the safety and efficacy of radiofrequency catheter ablation of different cardiac tissues such as the ventricle, the coronary sinus, the atrium, and the tricuspid valve annulus in experimental animal models.[4,5] Nowadays, radiofrequency catheter ablation is considered a class I indication for the treatment of many tachyarrhythmias in human cardiology, and in the last decades its clinical use has also been described in dogs with supraventricular and ventricular arrhythmias.[6–10]

INDICATIONS FOR CATHETER ABLATION

Catheter ablation is the treatment of choice for rhythm control in most supraventricular and ventricular arrhythmias.[1] When ablation of the arrhythmic substrate is not possible, catheter ablation or modification of the atrioventricular junction for ventricular rate control of supraventricular

arrhythmias can be performed (ablate and pace).[1] Catheter ablation should always be considered in patients with symptomatic arrhythmias, arrhythmic disorders not responsive to antiarrhythmic drugs, or as an alternative to long-term drug therapy.[1]

The most common supraventricular arrhythmias treated with radiofrequency catheter ablation in veterinary medicine are accessory pathway–mediated tachycardias, atrial flutters, and focal atrial tachycardias.[6–11] Recently, radiofrequency catheter ablation has been performed in ventricular tachycardia, most frequently when associated with primary myocardial disorders, such as arrhythmogenic cardiomyopathy.[12]

TYPES OF CATHETER ABLATION PROCEDURE

Two principal energy sources can be used for catheter ablation: radiofrequency or cryoablation. While radiofrequency delivers heat, cryoablation delivers extreme cold to the cardiac tissue.[2,13]

RADIOFREQUENCY CATHETER ABLATION

Radiofrequency is a form of alternating current in the range of 0.1–100 MHz. Radiofrequency is the most common energy used for catheter ablation in veterinary medicine. When radiofrequency is used to ablate cardiac arrhythmias, unmodulated, continuous sine wave outputs are delivered to the tissue with a wavelength that ranges from 100 kHz to 750 kHz. The voltage applied induces a current that flows between a small electrode inside the cardiac cavity to a large, grounded, dispersive electrode on the body surface. Once radiofrequency energy reaches the tissue, electromagnetic energy is converted into thermal energy by the absorption of microwave radiation in the tissue. At a temperature of approximately 48 °C, the heating of the cells draws water out of them, leading to desiccation and coagulative necrosis. Damage to the myocardium is induced by resistive heating in the superficial layers closer to the electrode-tissue interface, where the current flows result in an acceleration of ions, and by a passive conductive heating in the deeper layers (Fig. 11.1).

Thermal injuries vary according to the temperature reached: abnormal automaticity has been observed at temperatures >45 °C, while conduction

block at temperatures comprised between 51.7 °C and 54.4 °C. Temperatures above 50 °C induce an irreversible loss of cellular excitability. The size of the lesion can be predicted based on the electrode diameter, power, contact level, temperature of the catheter tip, time of delivery, and impedance. Depending on these variables, the width of a lesion can vary from 5 to 9 mm and is achieved within 30–40 seconds, while its depth varies from 4 to 8 mm and requires up to 90 seconds to develop. Most radiofrequency generators used to perform catheter ablation have controlled temperature (range, 60–70 °C) to impede boiling of the tissue and potential perforation. These damages are prevented by an abrupt rise in impedance when a high temperature is reached at the tip, which limits current flow and further expansion of the lesion. A cooled-tip system can be used to increase the size of the lesion. Saline forced through the catheter lumen cools the electrode tip, which reduces overheating of the electrode–tissue interface and leads to increased impedance, thus allowing delivery of higher levels of energy for longer.

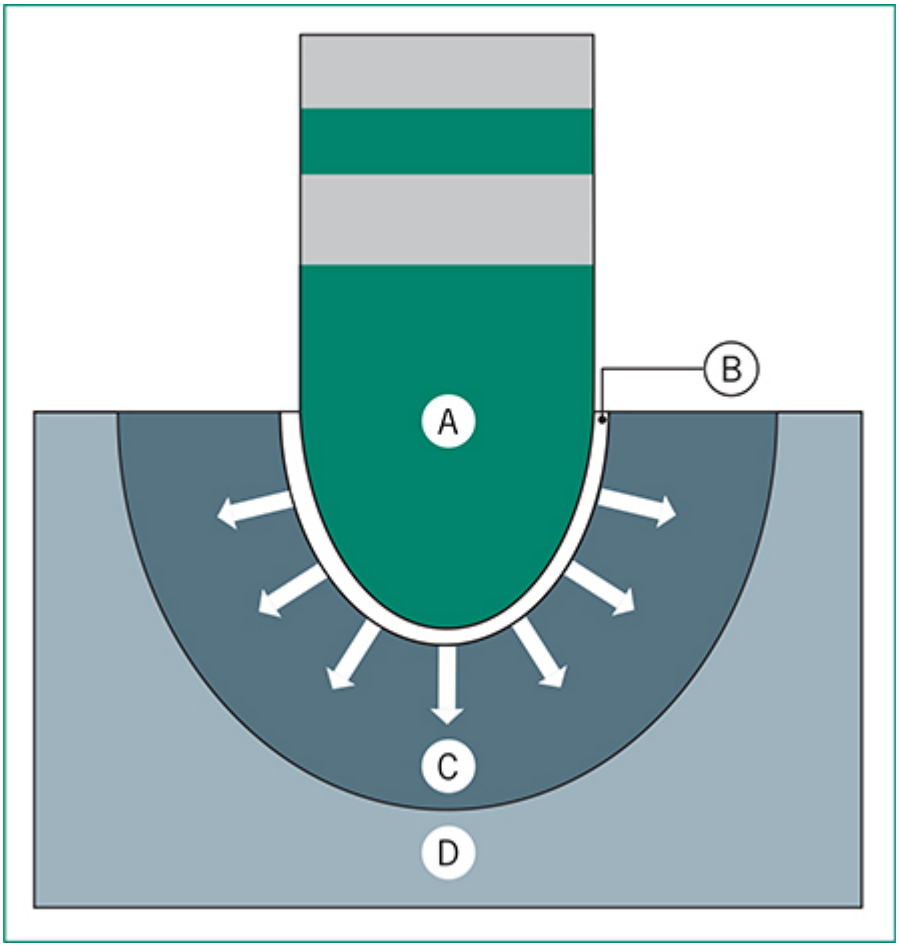


FIGURE 11.1. Schematic representation of radiofrequency current delivery from the tip of the ablation catheter (A) to the adjacent tissue. Damage to the endocardium or epicardium is induced by resistive heating in the thin rim of muscle closer to the electrode–tissue interface (B) and by passive conductive heating in the deeper layers (C). The portion of myocardium unaffected by the radiofrequency current is labelled D.

Radiofrequency catheter ablation is performed in a controlled temperature environment with a thermocouple-tipped steerable 7 Fr catheter (length, 105 mm). The radiofrequency current is generated by a conventional generator that monitors catheter tip temperature, power output, and impedance. To ablate atrial ectopic foci, accessory pathways, and ventricular circuits, radiofrequency energy is delivered to the atrial or ventricular endocardium or epicardium, depending on the technique used, at a maximum of 65 °C and 75 W for 60 seconds. In case of ablation of the isthmus area to treat atrial flutter, 65 °C and 100 W for at least 45 seconds are used. In case of anteroseptal or midseptal accessory pathways, with a location, respectively, next to the bundle of His or compact atrioventricular node, low energy ablation (<20 W) with a reduced duration of delivery (<40 seconds) should be performed. Current delivery is terminated immediately in the event of an increase in impedance or displacement of the catheter. Energy is usually applied during tachycardia to ensure interruption of the arrhythmia with no recurrence for at least 45 minutes postablation.[6,8–11,14–16]

CRYOABLATION

Cryoablation works by lowering molecular movement and stored kinetic energy, which results in tissue cooling and ice formation.[13] It is performed with two types of catheters: traditional-tip ablation catheters used for focal ablation (4–8 mm) and cryoballoon catheters for higher tissue contact (24–28 mm).[13] The tip of the cryoablation catheter balloon contains an expansion chamber to produce the Joule–Thomson effect, by which the temperature of a gas (e.g., nitrogen, argon, or nitrous oxide) falls when it is allowed to expand into an insulated environment.[13] The liquefied gas returns to gas form in the expansion chamber, which results in heat absorption to produce tissue cooling and freezing.[13] In comparison to radiofrequency energy, cryoablation induces less endothelial and connective tissue damage, thus limiting thrombi generation as well as the risk of cardiac perforation and tamponade.[19]

RADIOFREQUENCY CATHETER ABLATION OF SUPRAVENTRICULAR TACHYCARDIAS

ACCESSORY PATHWAYS

To ablate accessory pathways responsible for orthodromic atrioventricular reciprocating tachycardia or permanent junctional reciprocating tachycardia, the ablation catheter is placed around the tricuspid valve annulus or within the coronary sinus using a 30-degree oblique fluoroscopic view.[6,7,14–18] When the distal pair of electrodes are placed at the optimal position, an annular signal, characterized by balanced atrial and ventricular intracardiac electrograms, is obtained. The position of the accessory pathway is defined using a clockwise analogy, looking at the tricuspid and the mitral annuli from the ventricular side (Fig. 11.2). In dogs, most accessory pathways are posteroseptal (at 5 o'clock when viewing the tricuspid annulus [TA] as a clockface: TA 5), right posterior (TA 6), right lateral (TA 8–10) and less frequently midseptal (TA 4). They are very rarely anterior (TA 11–12) or anteroseptal (TA 1–3).[18] In case of left-sided accessory pathways, a transseptal puncture should be performed.

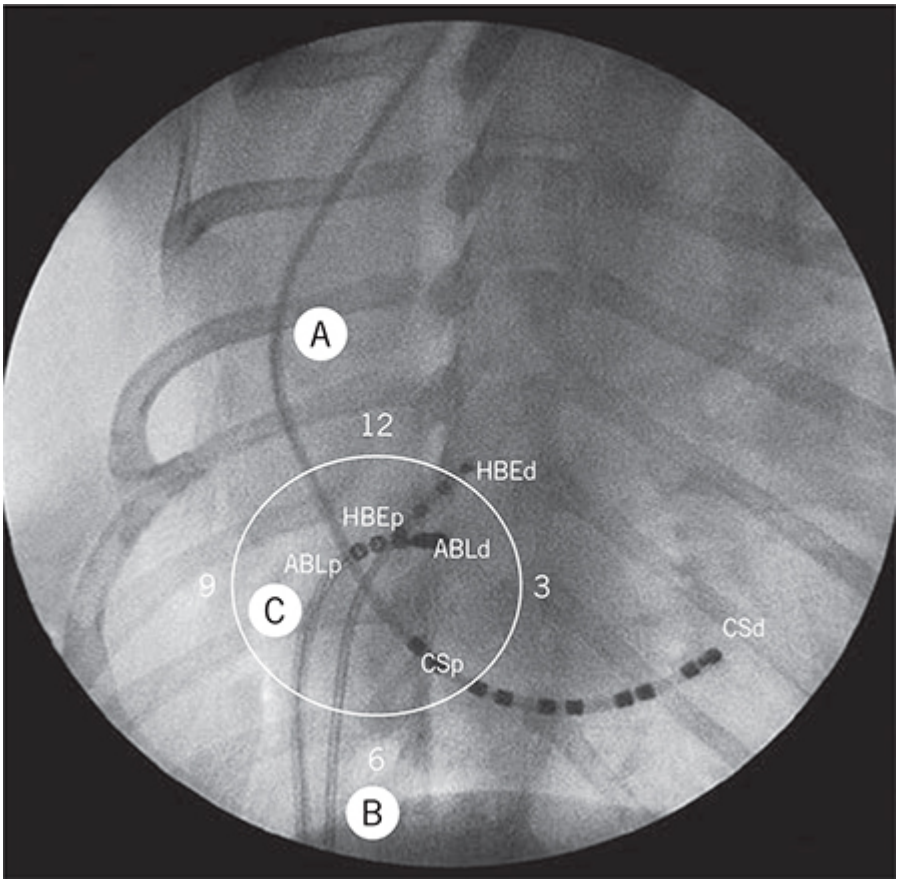


FIGURE 11.2. Thirty-degree oblique fluoroscopic view showing the anatomical location of the accessory pathways around the tricuspid valve annulus using a clockwise analogy. The anteroseptal area is located between 1 and 3 o'clock, the midseptal area at 4 o'clock, the posteroseptal area at 5 o'clock, the right posterior area between 6 and 7 o'clock, the right lateral area between 8 and 10 o'clock, and the right anterior area between 11 and 12 o'clock. A decapolar catheter (A) is introduced through the right jugular vein into the coronary sinus to record left atrial potentials with the distal electrode pair (CSd) and coronary sinus ostium potentials with the proximal electrode pair (CSp); a quadripolar catheter (B) is placed through the femoral vein at the anteroseptal aspect of the tricuspid valve annulus to record His potentials (HBEp, HBEd); and an ablation catheter (C) is introduced through the femoral vein and advanced through the caudal vena cava to reach the right atrium, the right ventricle, or the tricuspid valve annulus (ABLp, ABLd).

Ablation procedures are guided by intracardiac bipolar recording, searching for the earliest site of ventricular activation during antegrade conduction (shortest or negative His–ventricular [HV] interval) in case of ventricular preexcitation (sinus rhythm or atrial pacing) (Fig. 11.3) and the earliest site of ventricular activation (shortest ventriculoatrial [VA] interval) during tachycardia or ventricular pacing (Fig. 11.4). In both cases, a simultaneous unipolar recording with a sharp and negative waveform should be obtained to locate the pole closest to the bypass tract.[6,7,18] The

goal of the ablation procedure is to induce a loss of accessory pathway conduction for at least 45 minutes postablation. Posteroseptal accessory pathways are often located within the coronary sinus; in this case, a cooled-tip system should be used to increase the power and reduce the tip temperature.

The reported acute success rate is 95–100%, with a recurrence rate of 8%. The success rate with a second attempt reaches 98.8%. The rate of major complications, including death during anesthesia and iatrogenic atrioventricular block, varies from 4.5 and 7%, while that of minor complications (e.g., hematoma in the regions of access) is around 3%.[6,7,14–18]

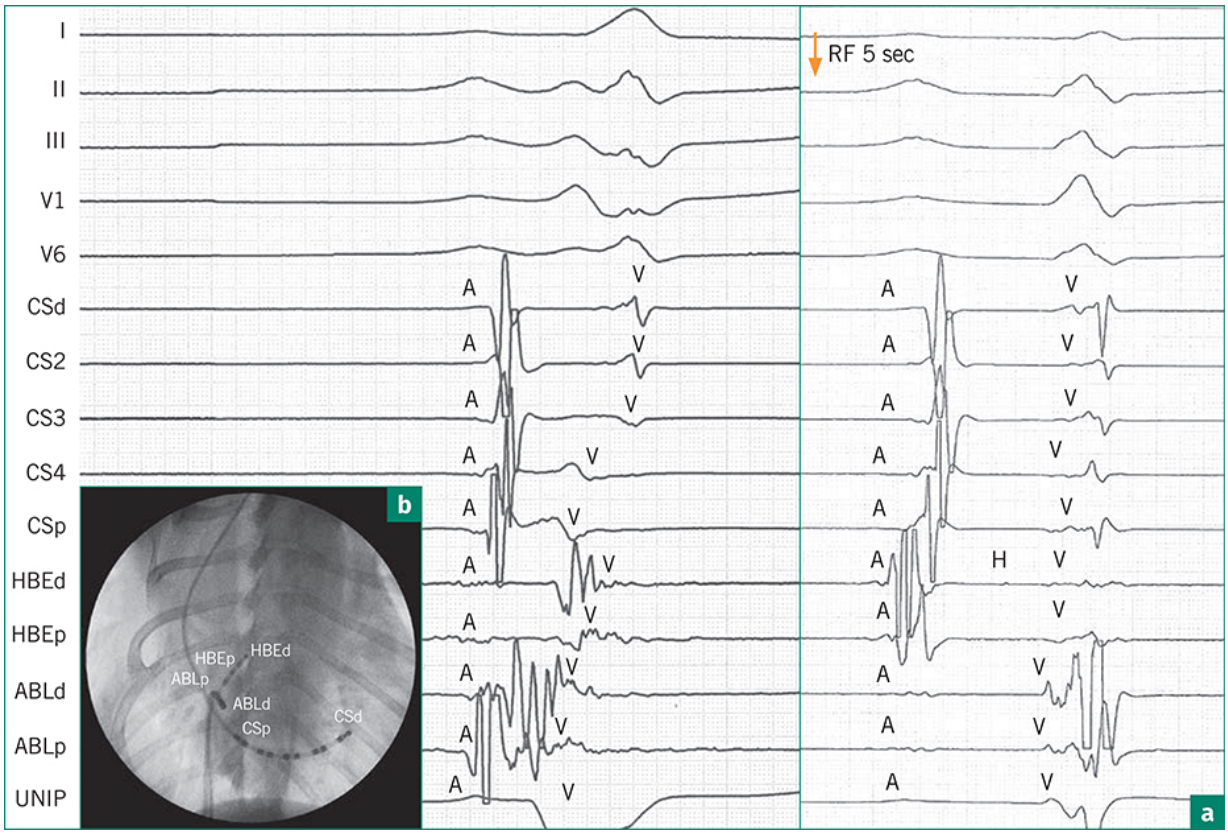


FIGURE 11.3. Radiofrequency catheter ablation of a posteroseptal accessory pathway during sinus rhythm with ventricular preexcitation. a) Five lead-surface electrocardiogram (I, II, III, V1, V6); nine intracardiac electrograms: from the proximal (CSp) to the distal (CSd) coronary sinus, from the proximal (HBEp) and distal (HBEd) His bundle region, from the proximal and distal electrode pairs (ABLp, ABLd) of the ablation catheter placed at the coronary sinus ostium; and unipolar recording (UNIP). Notice the sequence of atrial (A) and ventricular (V) activations with the shorter AV interval recorded by the ABLd electrode pair. Five seconds after the delivery of radiofrequency (RF) energy (arrow), a progressive prolongation of the AV and PQ intervals occurred, which confirmed the abolition of antegrade accessory pathway conduction. The ABLd recording noise and UNIP

saturation are induced by the radiofrequency current (speed, 150 mm/s; calibration, 22.8 mV/cm). b) Dorsoventral fluoroscopic view of the same dog as in a), with the catheters in place: a decapolar catheter in the great cardiac vein (CSp-CSd), a quadripolar catheter at the His bundle region (HBEp-HBEd), and a steerable ablation catheter at the coronary sinus ostium (ABLp-ABLd).

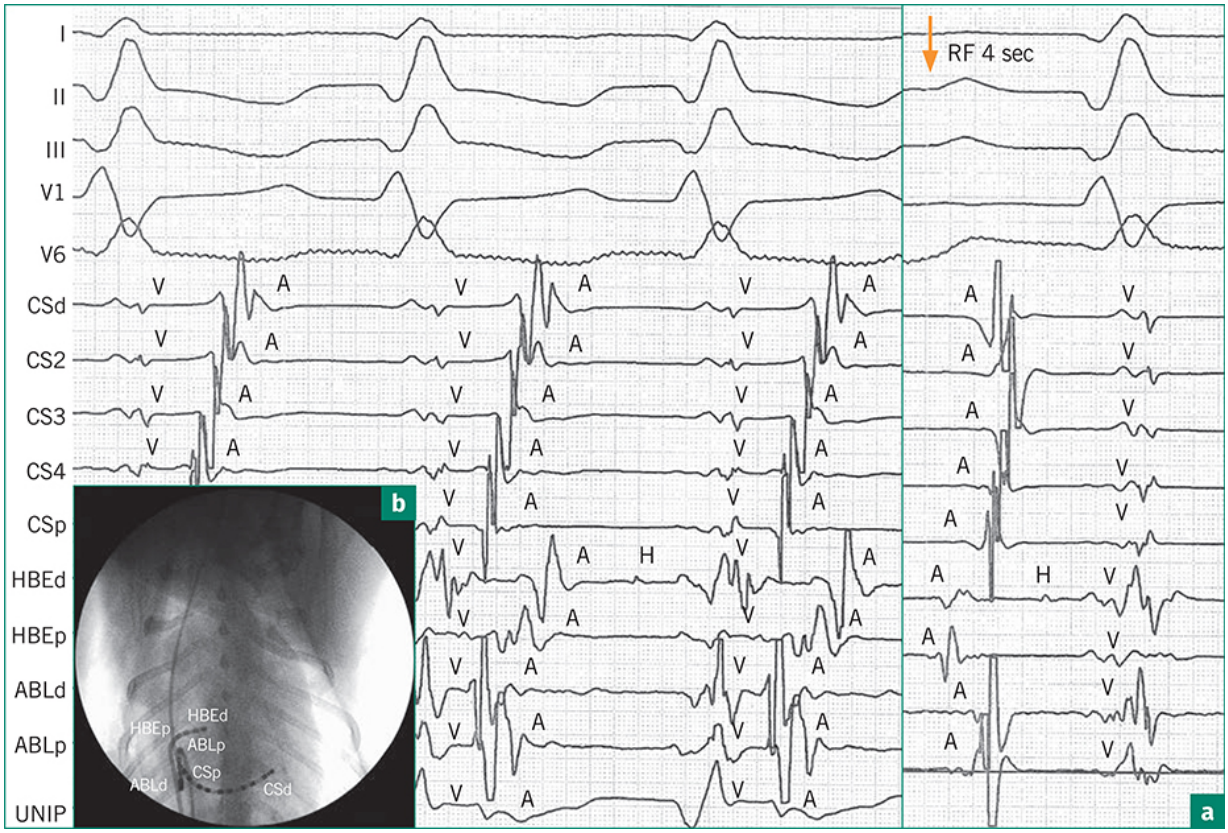


FIGURE 11.4. Radiofrequency catheter ablation of a right posterior accessory pathway during orthodromic atrioventricular reciprocating tachycardia. a) Five lead-surface electrocardiogram (I, II, III, V1, V6); nine intracardiac electrograms: from the proximal (CSp) to the distal (CSd) coronary sinus, from the proximal (HBEp) and distal (HBEd) His bundle region, from the proximal and distal electrode pairs (ABLp, ABLd) of the ablation catheter placed at the posterior aspect of the tricuspid valve annulus; and unipolar recording (UNIP). Notice the sequence of atrial (A) and ventricular (V) activations with the shorter VA interval recorded by the ABLd pair. Four seconds after the delivery of radiofrequency (RF) energy (arrow), the tachycardia stopped and sinus rhythm resumed. UNIP saturation is induced by the radiofrequency current (speed, 300 mm/s; calibration, 22.8 mV/cm). b) Dorsoventral fluoroscopic view of the same dog as in a) with the catheters in place: a decapolar catheter in the great cardiac vein (CSp-CSd), a quadripolar catheter at the His bundle (HBEp-HBEd), and a steerable ablation catheter at the posterior tricuspid valve annulus (ABLp-ABLd).

FOCAL ATRIAL TACHYCARDIA

Radiofrequency catheter ablation of focal atrial tachycardias should be performed during tachycardia using a 30-degree oblique fluoroscopic view searching for the site of earliest presystolic activity relative to the onset of

the P wave (–39.9 ± 17.7 ms) where a sharp and negative unipolar recording, with a QS pattern, can be recorded.[10] The location of ectopic foci can also be determined by applying pressure to the focus with the ablation catheter to achieve mechanical interruption of the tachycardia, or by searching for the presence of fractionated, long-duration, low-amplitude electrograms. Fractionated potentials consist of three or more consecutive negative deflections with a low peak-to-peak amplitude (Fig. 11.5). In the dog, 57% of atrial potentials at the ectopic focus are fractionated and 31% are low amplitude.[10] Based on detailed endocardial mapping, 63% of dogs with focal atrial tachycardia had right-sided foci (crista terminalis, 41%; triangle of Koch, 25%; tricuspid valve annulus, 16 %; right interatrial septum, 9%; and right auricle, 9%), and 37% presented with focal atrial tachycardia arising from the pulmonary veins (right superior pulmonary veins, 57%; left superior pulmonary veins, 28%; right inferior pulmonary veins, 15%). Twelve percent of dogs had multiple ectopic foci. The objective of the procedure is the abolition of tachycardia with no reinduction of the arrhythmia with programmed atrial stimulation in case of nonautomatic focal atrial tachycardias, or with isoproterenol infusion in case of automatic focal atrial tachycardias.[10]

In the author's laboratory, the acute success rate of radiofrequency catheter ablation of focal atrial tachycardia is 79%. In one third of cases, the arrhythmias cannot be induced with programmed or incremental atrial stimulation, atrial bursts, or isoproterenol infusion. The recurrence rate is 2%, while the complication rate is around 5.2%. The complications include anesthesia-related death, self-limiting stroke with spontaneous resolution during ablation of a pulmonary vein ostium focus, and iatrogenic atrioventricular block in a dog with Koch's triangle tachycardia unresponsive to the pharmacological treatment.

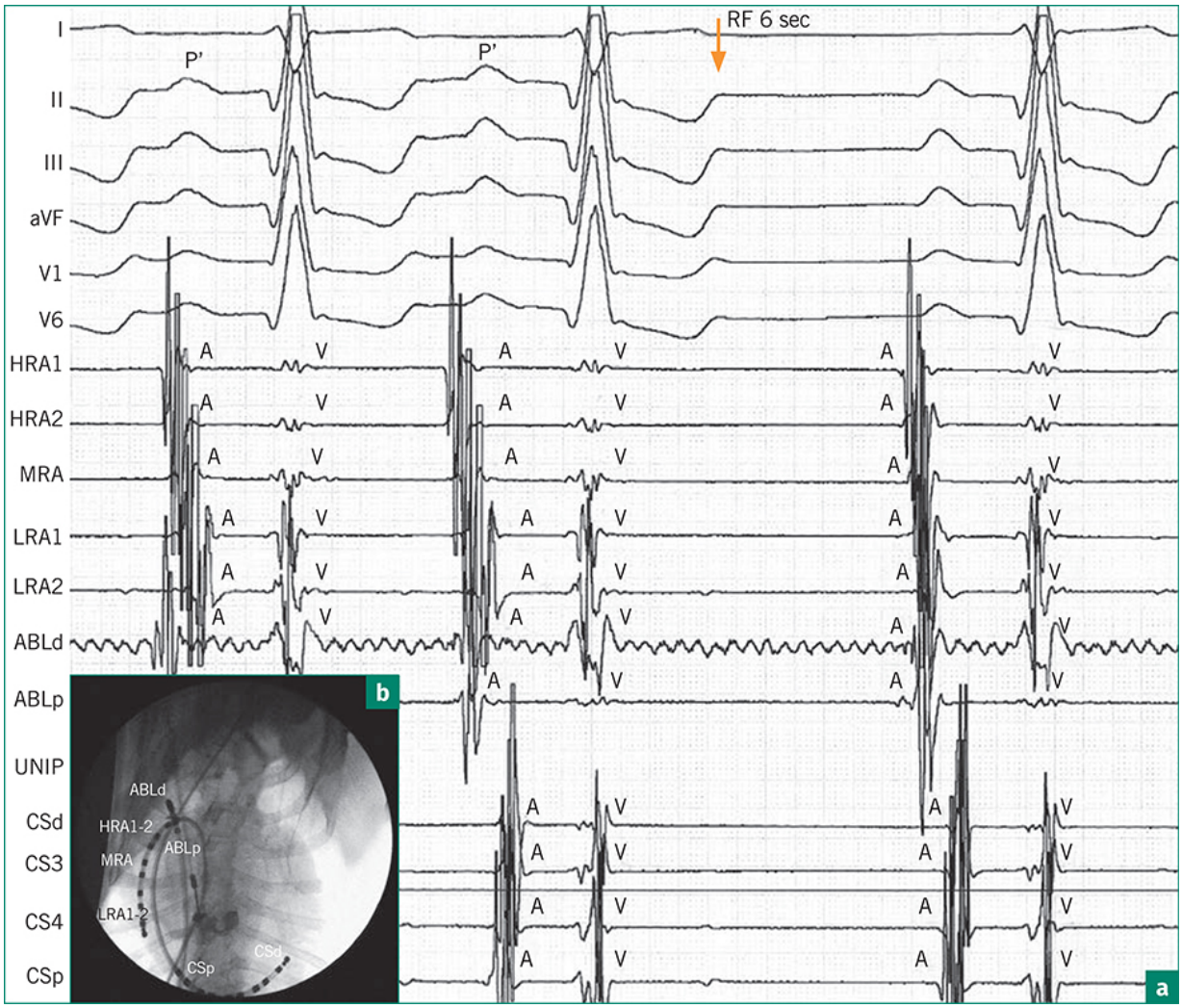


FIGURE 11.5. Radiofrequency catheter ablation during focal atrial tachycardia arising from the high crista terminalis. Six lead-surface electrocardiogram (I, II, III, aVF, V1, V6) and twelve intracardiac electrograms: at the high right atrial wall (HRA 1-2), medium right atrial wall (MRA), and low right atrial wall (LRA 1-2); from the proximal and distal electrode pairs (ABLp, ABLd) of the ablation catheter placed at the superior part of the crista terminalis; unipolar recording (UNIP); and from the proximal (CSp) to the distal (CSd) coronary sinus. Notice the atrial potentials (A) recorded by the ablation catheter, which are fractionated and presystolic (–35 ms) relative to the onset of the P' wave of the surface electrocardiogram. Six seconds after starting the delivery of radiofrequency (RF) energy (arrow), the tachycardia stopped and sinus rhythm resumed (P), which confirmed the abolition of the abnormal automaticity of the ectopic focus. The ABLd recording noise and UNIP saturation are induced by the radiofrequency current (speed, 300 mm/s; calibration, 22.8 mV/cm). b) Dorsoventral fluoroscopic view of the same dog as in a) with the catheters in place: a decapolar catheter in the great cardiac vein (CSp-CSd), a decapolar catheter along the right atrial wall (HRA 1-2, MRA, LRA 1-2) and a steerable ablation catheter at the superior part of the crista terminalis (ABLp-ABLd).

ATRIAL FLUTTER

The target of ablation in atrial flutter is the critical isthmus, which is located in the cavotricuspid area in typical and typical reverse atrial flutter, and in the interatrial septum or the right atrial free wall in atypical atrial flutter.[8,9] Recently, a case of atypical atrial flutter was also described in which the isthmus of the macroreentrant circuit was located within the distal portion of the cranial vena cava.[11]

To interrupt atrial flutter, a bidirectional conduction block should be achieved by applying radiofrequency energy to the critical isthmus. This is performed using an anatomical and an electrophysiological approach, guided respectively by the right lateral fluoroscopic view and by the presence of concealed entrainment with a first postpacing interval shorter than 30 ms at the target site.[8,9,11]

Radiofrequency is applied during macroreentrant atrial tachycardia by positioning the catheter in the midportion of the isthmus area to induce a linear lesion. The endpoints of ablation are flutter termination and impossibility to reinduce the arrhythmia with programmed atrial stimulation from both the coronary sinus ostium (CSp) and the low right atrium (LRA) to confirm the bidirectional block. The presence of a bidirectional block can be assessed by pacing both areas and measuring a prolongation of the conduction time, with double potentials at the site of ablation and a variation in the activation pattern of the atrial wall (Fig. 11.6).[8,9,11] In case of cranial vena cava flutter, before delivering radiofrequency, high-output pacing should be performed at the targeted site of ablation to assess right phrenic nerve stimulation and avoid the area in case of positive results.[11]

In the author's electrophysiology laboratory, the acute success rate of induction of a bidirectional block of the critical isthmus is 100% for both typical and atypical atrial flutter, with a recurrence rate of 15% (5% typical atrial flutter and 10% atypical atrial flutter). A bidirectional conduction block is more difficult to achieve in atypical atrial flutter since the boundaries of the critical isthmus are less defined. So far, no complications during radiofrequency catheter ablation of atrial flutter have been encountered.

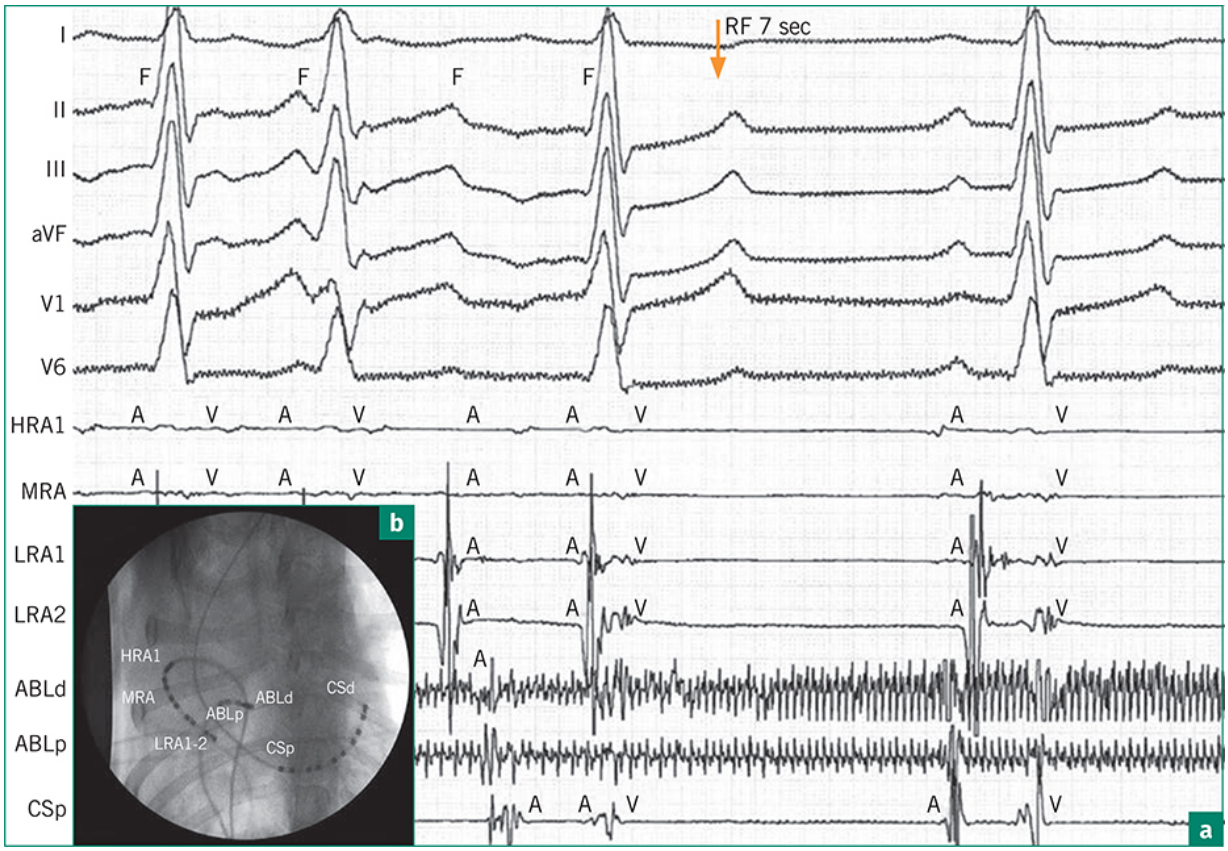


FIGURE 11.6. Radiofrequency catheter ablation during atypical right septal atrial flutter. Six lead-surface electrocardiogram (I, II, III, aVF, V1, V6) and seven intracardiac electrograms: at the high right atrial wall (HRA 1), medium right atrial wall (MRA), and low right atrial wall (LRA 1-2); from the proximal and distal electrode pairs (ABLp, ABLd) of the ablation catheter placed at the right interatrial septal isthmus; and at the proximal coronary sinus (CSp). Notice the sequence of atrial activation (A) that rotates clockwise around the tricuspid valve annulus from the LRA to the HRA1, to the ABLd and ABLp, to the CSp, and back to the LRA. Seven seconds after starting the delivery of radiofrequency (RF) energy (arrow), the tachycardia stopped and sinus rhythm resumed (P), which confirmed the abolition of conduction along the critical isthmus. The surface electrocardiogram, ABLp and ABLd recording noise is induced by the radiofrequency current (speed, 300 mm/s; calibration, 22.8 mV/cm). b) Dorsoventral fluoroscopic view of the same dog with the catheters in place: a decapolar catheter in the great cardiac vein (CSp-CSd), a decapolar around the tricuspid valve annulus (HRA 1, MRA, LRA 1-2), and a steerable ablation catheter at the right interatrial septum, where the flutter isthmus was located (ABLp-ABLd).

RADIOFREQUENCY CATHETER ABLATION OF VENTRICULAR TACHYCARDIAS

Radiofrequency catheter ablation of ventricular arrhythmias is used in human medicine to treat monomorphic ventricular tachycardias associated with ischemic disease, different cardiomyopathies, bundle branch reentry,

and various forms of idiopathic ventricular tachycardia in the absence of structural heart disease.[19]

In veterinary medicine, most ventricular tachycardias are associated with degenerative structural heart disease such as dilated cardiomyopathy and arrhythmogenic cardiomyopathy, but on rare occasions and in some specific breeds they can also be found in the absence of structural heart disease.[12,20–27] Myocardial disorders are in most cases diffuse and radiofrequency catheter ablation is therefore often considered palliative since it does not eliminate the need for antiarrhythmic therapy.

Arrhythmogenic cardiomyopathy is a familial myocardial disease associated with ventricular arrhythmias that has been described in Boxers and English Bulldogs.[20–22,24,25,28] This myocardial disorder induces mechanical and electrical dysfunction, creating circuits for monomorphic ventricular tachycardias. It can be diffuse or segmental. The most common myocardial changes (fibrofatty infiltration) involve the right ventricular outflow tract (segmental form) and/or right ventricle (diffuse form), but extension of the changes to the left ventricle has been reported in Boxer dogs.[20–22,24,25,28]

The anatomical circuits responsible for sustained monomorphic ventricular tachycardia in English Bulldogs with segmental arrhythmogenic cardiomyopathy are usually located on the endocardial or the epicardial aspect of the right ventricular outflow tract aneurysm.[20,22] In these dogs, the targeted site of ablation is the critical isthmus of the circuit, which can be found by positioning the ablation catheter within the aneurysm or on its epicardial aspect via a transpericardial approach. The critical isthmus is located based on the presence of concealed entrainment with a first postpacing interval shorter than 30 ms.[22] Linear radiofrequency catheter ablation can be performed during tachycardia or, in case of a very rapid ventricular rate, the ablation site can be identified during sinus rhythm searching for fractionated diastolic potentials that suggest inhomogeneous and slow conduction within the circuit (Fig. 11.7).[22] The endpoints of the procedure are the abolition of fractionated diastolic potentials and the induction of a bidirectional block with no reinduction of the tachycardia with programmed ventricular stimulation.

The acute success rate of radiofrequency catheter ablation of ventricular tachycardia in arrhythmogenic cardiomyopathy depends on the size of the

aneurysm and location of the circuit; this rate ranges from 60% to 75%. The recurrence rate is around 15%, and in the authors' experience, these arrhythmias can be controlled with low-dose amiodarone or sotalol. The complication rate in the authors' electrophysiology laboratory is 3%, with some procedure-related deaths due to the presence of ventricular tachycardia refractory to medical treatment that caused advanced congestive heart failure.

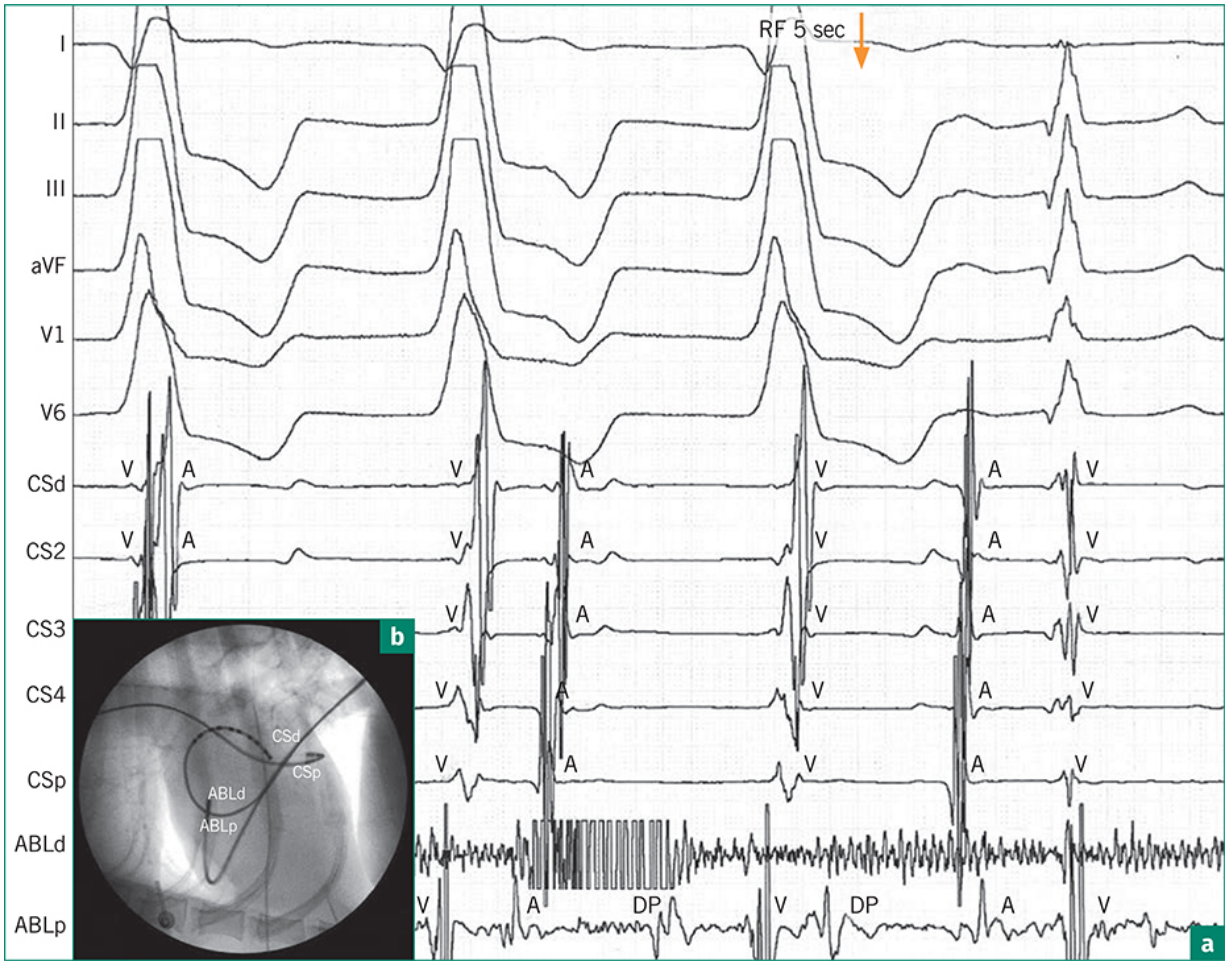


FIGURE 11.7. Epicardial radiofrequency catheter ablation during ventricular tachycardia in an English Bulldog with segmental arrhythmogenic right ventricular cardiomyopathy. Six lead-surface electrocardiogram (I, II, III, aVF, V1, V6) and seven intracardiac electrograms: from the proximal (CSp) to the distal (CSd) coronary sinus and from the proximal and distal electrode pairs (ABLp, ABLd) of the ablation catheter placed on the endocardial aspect of the right ventricular outflow tract. Notice the presence of mid-diastolic potentials (DP), which are characteristic of an area of slow conduction of the isthmic area. Ventricular (V) and atrial (A) potentials are dissociated. The atrial electrograms coming from the decapolar catheter placed in the right atrium are not displayed. Five seconds after starting the delivery of radiofrequency (RF) energy (arrow), the tachycardia stopped and sinus rhythm resumed (P), which confirmed the abolition of conduction along the critical isthmus. The ABLp and ABLd recording noise was induced by the radiofrequency current (speed,

300 mm/s; calibration, 22.8 mV/cm). b) Right lateral fluoroscopic view of the same dog with the catheters in place: a decapolar catheter in the great cardiac vein (CSp-CSd), a decapolar catheter along the right atrial wall, and a steerable ablation catheter at the right ventricular outflow tract area where the tachycardia isthmus was located (ABLp-ABLd).

Radiofrequency ablation guided by three-dimensional mapping was recently described in Boxers with ventricular arrhythmias associated with arrhythmogenic cardiomyopathy[12] and in a dog with no structural heart disease.[27] Catheter ablation was performed successfully, and abnormal low-voltage areas were located at the level of the right ventricular outflow tract[12] and cranial right ventricle, and at the basal anterior left ventricular septum.[27]

RADIOFREQUENCY CATHETER ABLATION OF THE ATRIOVENTRICULAR NODE

Atrioventricular nodal ablation is a nonpharmacological strategy to treat patients with permanent atrial fibrillation refractory to medical therapy. In humans, two techniques have been described: complete interruption of atrioventricular nodal conduction followed by pacemaker implantation (ablate and pace therapy) and transcatheter modification of the atrioventricular node. The ablate and pace therapy yielded a clinical benefit in 63% of human beings with permanent atrial fibrillation paced only from the right ventricular apex and in 83% of the cases treated with biventricular pacing.[29] Transcatheter modification of the atrioventricular node is achieved through ablation of the nodal region and induction of a first- or second-degree atrioventricular block. Although this technique had a 66% success rate in experimental animal models, in a clinical study reported in dogs, a stable incomplete atrioventricular block was obtained only in one case, while in the remaining dogs a complete atrioventricular block developed within 100 hours of ablation.[15,30]

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SECTION IV

TACHYCARDIAS

CHAPTER 12

Sinus tachycardia

Manuela Perego

DEFINITION

Sinus tachycardia is defined as an increased sinus node discharge rate (>180 bpm in the adult dog and >220 bpm in puppies and cats) in response to physiological and pathological stimuli.[1] Heart rate is a physical sign that is easily and noninvasively measured with no specific training or equipment, although precise cutoff values cannot be provided for human or veterinary patients. Still, the lack of official normal resting heart rate values should not discourage clinicians from evaluating this parameter.[2]

ELECTROPHYSIOLOGICAL MECHANISM

Heart rate, heart rate variability, and heart rate recovery time following a stressor event are influenced by intrinsic and extrinsic factors.[3–6] Intrinsic factors include automaticity of the pacemaker (P) cells located at the level of the sinus node, while extrinsic factors are related to the activation of the sympathetic and parasympathetic branches of the autonomic nervous system.[6] Automatic depolarization of P cells leads to the generation of

action potentials, mainly as a result of calcium ion movement into the sarcoplasmic reticulum.[5] P cell automaticity is a self-regulating process, with changes in calcium, potassium, and sodium ion concentrations as action potentials are generated during the spontaneous depolarization phase.[5] Spontaneous depolarization of P cells is induced by the "membrane clock" mechanism. This mechanism is mediated by voltage-sensitive membrane currents (hyperpolarization-activated current, also called funny current, I_f), which are regulated by cyclic adenosine monophosphate (cAMP).[7] An additional mechanism to explain spontaneous P cell depolarization involves the spontaneous release of Ca^{2+} ions from the sarcoplasmic reticulum. This mechanism is referred to as the "Ca^{2+} clock".[7] Increased Ca^{2+} release followed by activation of the Na^{+}–Ca^{2+} exchange current could play a role in the positive chronotropic effect of β-adrenergic stimulation in latent pacemaker cells. The involvement of the Ca^{2+} clock in spontaneous depolarization suggests that automaticity and delayed afterdepolarizations, which occur when there is sarcoplasmic reticulum Ca^{2+} overload, share a similar mechanism.[7]

Concerning extrinsic factors, an increased sympathetic tone leads to an augmented heart rate as it increases the slope of phase 4 of the action potential (also named spontaneous depolarization) and reduces the action potential duration (Fig. 12.1).[8] The catecholamines released by the sympathetic neurons of the autonomic nervous system bind to the α- and β-adrenergic receptors. Stimulation of the β1-adrenergic receptors modulates the activity of various intracellular targets, leading to an increased sinus node discharge rate.[8] In particular, binding with β1-adrenergic receptors, which are coupled to the Gs protein, has been shown to be essential for the increase in heart rate during adrenergic stimulation.[9]

Heart rate can be influenced by physiological processes; in this case, an increased heart rate is named physiological sinus tachycardia.[1] Physiological sinus tachycardia is considered an appropriate response to pain, restraint, excitement, anxiety, or fear and is also present during exercise.[1,10] In dogs subjected to intense exercise protocols, the maximum heart rate increases to reach a mean value of 246 ± 14.3 bpm (range, 229–291 bpm).[10] The increase in heart rate is attributed to the increased

sympathetic drive in conjunction with glycogenolysis and increased blood lactate levels subsequent to high-intensity exercise.[10]

Physiological sinus tachycardia should be distinguished from inappropriate sinus tachycardia, which is described as a persistent increase in the sinus node discharge rate in the absence of an identifiable cause and a further exaggerated increase in heart rate with minimal physiological stimuli.[1,14] Inappropriate sinus tachycardia is correlated with different conditions such as intrinsic sinus node hyperactivity, sympathetic hypersensitivity, vagal hyposensitivity, familiar/genetic causes, and central sympathetic stimulation.[14] Inappropriate sinus tachycardia has been suspected in one dog in veterinary medicine.[15]

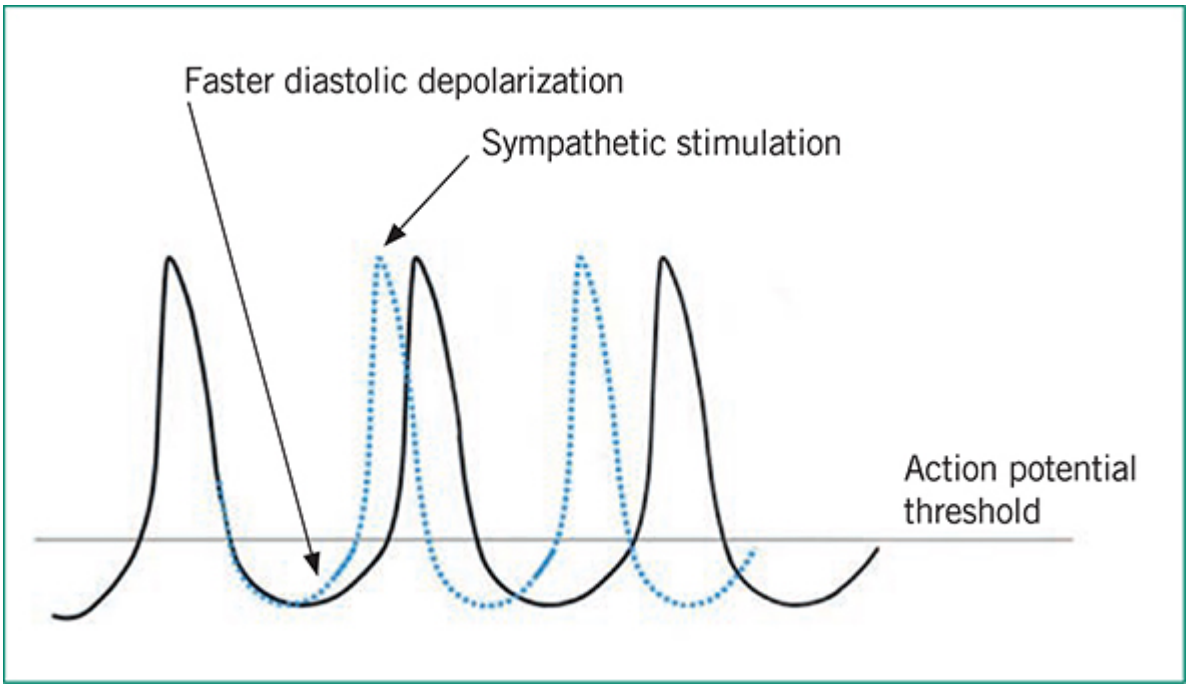


FIGURE 12.1. Effects of sympathetic stimulation on the sinus node action potential. Note the increase in the slope of the spontaneous depolarization phase (phase 4) and the decreased action potential duration.

Pathological processes can influence the physiological mechanisms governing heart rate, heart rate variability, and heart rate recovery time. Abnormalities in these parameters have been observed in different conditions such as fever, dehydration, sepsis, anemia, heart failure, pulmonary embolism, hypoxia, myocardial infarction, β-blocker

withdrawal, or cardiac stimulants. In this case, the increased heart rate is defined as pathological sinus tachycardia.[1,16–18]

Heart rate itself can be an important factor in the progression of a disease because it is a determinant of myocardial oxygen demand and coronary blood flow. Heart rate thus reflects cardiac performance and plays a pivotal role in the adaptation of stroke volume and cardiac output to metabolic requirements.[19]

Because coronary arterial blood flow is phasic and most of it occurs during the diastolic phase, an increased heart rate leads to a reduced diastolic time, which thus decreases the amount of time for coronary perfusion.[2] In addition, variations in heart rate also have effects on vascular shear stress, shear frequency, endothelial function and systemic vascular resistance.[19–21] Based on that, it can be said that heart rate is an effective biomarker in different conditions such as chronic heart failure. In fact, chronic heart failure is associated with autonomic nervous system dysregulation characterized by a sustained increase in sympathetic tone and withdrawal of parasympathetic activity. Parasympathetic and sympathetic activities are regulated through baroreflex mechanisms. Therefore, the baroreflex plays a key role in short-term cardiovascular regulation and also acts as a buffer system in blood pressure control.[22]

ELECTROCARDIOGRAPHIC FINDINGS

During sinus tachycardia, the electrocardiogram shows a heart rate greater than 180 bpm in dogs and 220 bpm in cats, with a mean atrial cycle length of 291± 31 bpm.[23] Atrial deflections are positive in the inferior leads (II, III, aVF), negative in aVL and aVR (with maximum negativity in aVR), and slightly positive or isodiphasic in lead I. The median electrical axis of the P waves is + 66° (range, + 52 to +73°) (Figs. 12.2 and 12.3).[23] Their amplitude is usually greater during sinus tachycardia than during sinus rhythm because sympathetic activation drives atrial depolarization out of the sinus node through the superior exit pathway. The median duration of the P waves is 41 ms (range, 35–45 ms).[23] The QRS complexes are usually narrow (median duration, 52 ms; range, 48–60 ms)[23] and have a normal morphology, unless preexisting intraventricular conduction disturbances are

present. The median duration of the QT interval in dogs presenting with sinus tachycardia is 167 ms (range, 159–178 ms).[23]

Sinus tachycardia is associated with a long RP interval with a median duration of 215 ms (range, 192–222 ms).[23] The mean PR interval, which represents atrioventricular conduction time, is 81 ± 16 ms.[23] The median RP/PR ratio was reported to be 2.68 (range, 2.25–3.08). The electrocardiogram of patients with focal atrial tachycardia arising from the roof of the right atrium (cristal focal atrial tachycardia) may show atrial deflections similar to those of sinus tachycardia. The RP interval and the RP/PR ratio can help to distinguish sinus tachycardia from cristal focal atrial tachycardia. An RP interval >201 ms (sensitivity, 70%; specificity, 90%) and a RP/PR ratio >2.01 (sensitivity, 86%; specificity, 96%) are suggestive of sinus tachycardia.[23]

CLINICAL PRESENTATION

Patients with sinus tachycardia are usually asymptomatic.[1] If clinical signs are present, they are usually related to the underlying diseases causing sinus tachycardia. A detailed history is important to decide on the most appropriate diagnostic and therapeutic approach for the patient and should include precipitating factors such as fever or exercise, recent drug administration, toxic exposures, and a history of disease (including heart disease).[1]

THERAPY

The identification and treatment of the underlying etiology of sinus tachycardia is the cornerstone of management.[1] Causes such as physical activity or stress often do not require any specific antiarrhythmic treatment.[1] If sinus tachycardia is due to a disease that puts the patient at risk of sepsis, shock, hypoxia, or congestive heart failure, the animal should be admitted for urgent evaluation, and treatment should focus on the underlying cause.[1]

Because a rapid heart rate decreases the ventricular diastolic filling time and stroke volume, esmolol has been used in dogs and cats to lower the heart rate in cases of sinus tachycardia due to intoxication.[24,25]

Ivabradine is a heart rate lowering drug recommended in human medicine in the latest European Society of Cardiology guidelines[1] to reduce mortality and hospitalization in heart failure patients with a reduced ejection fraction and sinus tachycardia and in symptomatic patients with inappropriate sinus tachycardia. Additionally, ivabradine has been associated with reduced cardiac remodeling, reduced heart rate variability, improvement in exercise tolerance, improved heart failure class (New York Heart Association classification), and better quality of life.[26]

In addition, interesting effects of ivabradine on endothelial and myocardial function and on oxidative stress and inflammation pathways are progressively emerging.[26]

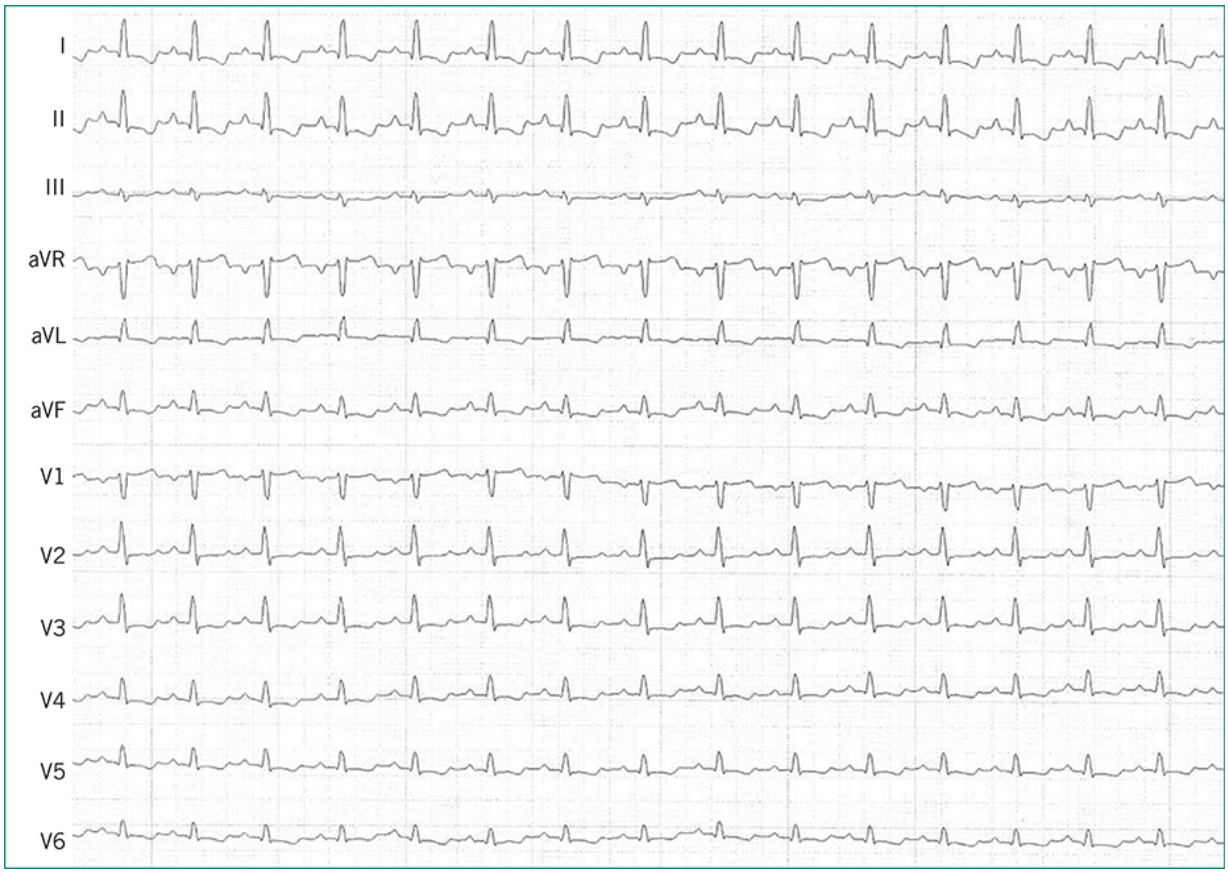


FIGURE 12.2. Sinus tachycardia in a 7-year-old male Chihuahua. Note the presence of atrial deflections that are positive in the inferior leads (II, III, aVF), positive in lead I, and most negative in aVR, with a rate of 200 bpm. P waves are followed by narrow QRS complexes with a normal

morphology, a normal mean electrical axis in the frontal plane (+ 60°), a normal atrioventricular conduction time (100 ms). Twelve leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6); speed, 50 mm/s; calibration, 5 mm/1 mV.



FIGURE 12.3. Sinus tachycardia in a 2-year-old male Maine Coon. Note the presence of atrial deflections that are positive in the inferior leads (lead II, III, aVF), positive in lead I, and most negative in aVR with a rate of 230 bpm. P waves are followed by narrow QRS complexes with a normal morphology, a normal mean electrical axis in the frontal plane (+60°), and a normal atrioventricular conduction time (80 ms). Six limb leads (I, II, III, aVR, aVL, aVF); speed, 50 mm/s; calibration, 10 mm/1 mV.

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CHAPTER 13

Focal atrial arrhythmias

Roberto Santilli

DEFINITION

Focal atrial arrhythmias include atrial ectopies or atrial ectopic beats (singlet, couplets, triplets, and allorhythmias), atrial rhythm, focal atrial tachycardia, and multifocal atrial tachycardia. The term *focal* refers to the fact that these arrhythmias originate from a discrete area of the atria or tributary veins. They then spread to and activate the rest of the atrial myocardium with a centrifugal pattern but no endocardial activation for a significant portion of the cycle length.[1,2] No precise cutoff values exist to separate an atrial rhythm from atrial tachycardia in dogs or cats; however, since the focal atrial tachycardia rates documented during electrophysiological mapping range from 195 to 260 bpm, any rate below 180 bpm with ectopic atrial activation should be considered an ectopic atrial rhythm.[3,4] Multifocal atrial tachycardia is a rapid and irregular rhythm that presents at least three different atrial activation waves with different rates and atrioventricular conduction times.[1,5]

The reported prevalence of premature atrial ectopic beats in normal dogs ranges from 2.9% to 25.4%.[6] In a study conducted in a larger population of dogs[7], this prevalence was 4.1%, while the prevalence of atrial rhythm was 0.7%, and that of focal atrial tachycardia was 1.6%. In dogs with cardiac diseases inducing atrial dilation, the prevalences of atrial ectopies, atrial rhythm, and focal atrial tachycardia rose to 10.3%, 1.7%, and 4%, respectively.[7] Focal atrial arrhythmias are also a common feature in dogs during the perioperative period: atrial ectopies are observed in 32% and

focal atrial tachycardia in 7.6% of cases.[8] Premature ectopic beats are rarely reported in normal unsedated cats (4%, 17 ± 18 in 24 hours) but rise to 53.8% (361 ± 1287 in 24 hours) in cats with cardiomyopathy, with the appearance of atrial bigeminy (16%), couplets (58%), and triplets (47%).[9–11]

The anatomy of the right and left atria, right and left auricles, interatrial septum, and tributary veins plays a crucial role in the occurrence of focal atrial arrhythmias.[12–17]

Four key right atrial structures should be considered as possible sources of focal atrial arrhythmias or parts of reentrant circuits responsible for macroreentrant atrial tachycardia, and therefore as possible targets for ablation: the crista terminalis, the right auricle, the cavotricuspid isthmus, and the coronary sinus ostium (Fig. 13.1).[12]

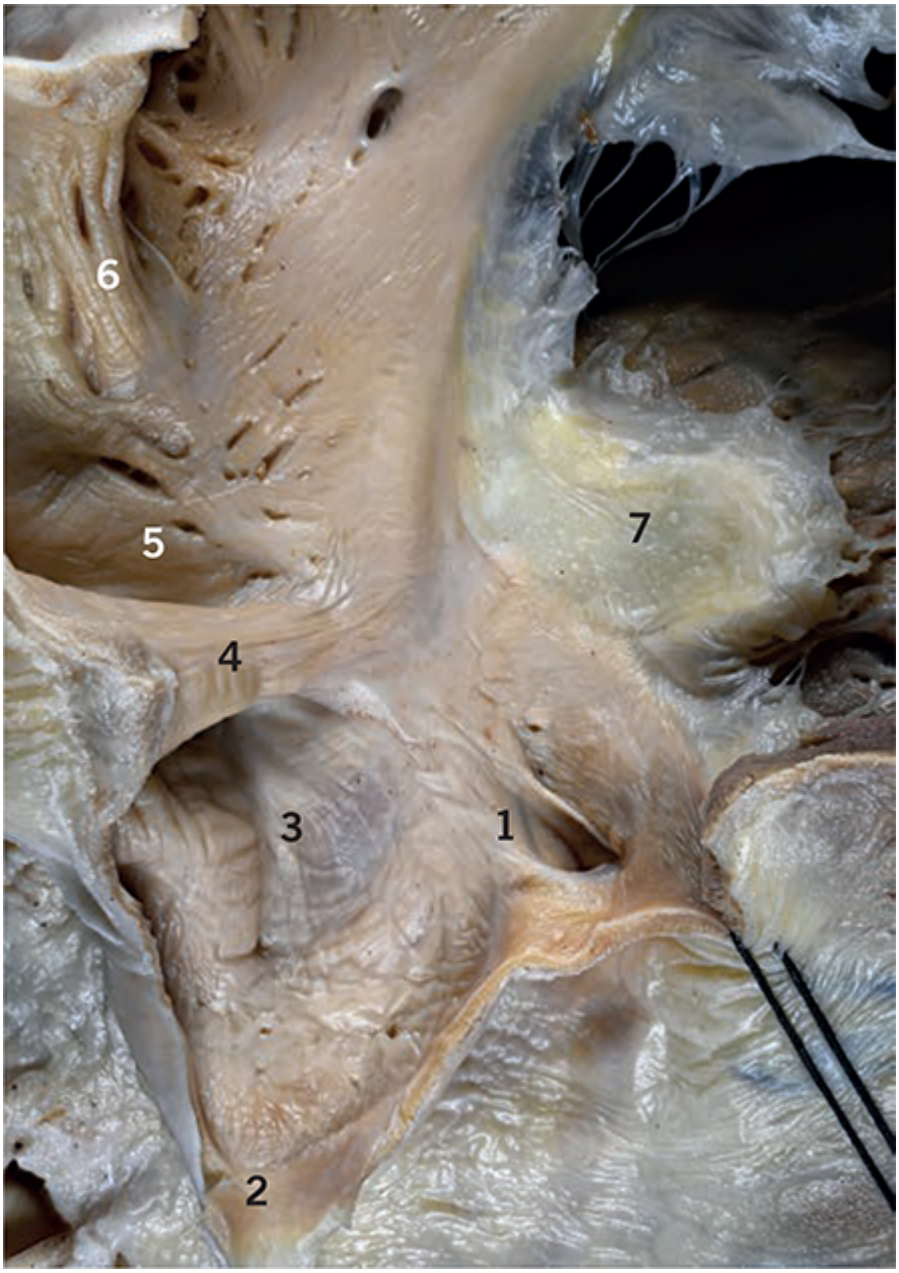


FIGURE 13.1. Right atrial anatomy in the dog; right cranial view after cutting the right atrial wall. 1, Ostium of the coronary sinus; 2, opening of the caudal vena cava; 3, fossa ovalis; 4, intervenous tubercle or tubercle of Lower; 5, opening of the cranial vena cava; 6, crista terminalis; 7, septal leaflet of the tricuspid valve. Picture courtesy of Dr. Massimiliano Tursi, Department of Veterinary Sciences, University of Turin (Italy).

The crista terminalis is a muscular structure that extends between the cranial and the caudal venae cavae (high and low crista terminalis). The cardiomyocytes that make up the crista terminalis are longitudinally aligned, forming a preferential conduction pathway during macroreentrant

atrial tachycardias, while the subendocardial and subepicardial regions present an irregular arrangement of myocardial fibers promoting nonuniform anisotropic conduction, which is the electroanatomical basis for atrial ectopies and focal atrial tachycardia in 26.3% of dogs.[3,12]

The *right auricle* forms the anterolateral part of the right atrium and consists of a complex arrangement of pectinate muscles that spread from the crista terminalis and give to the auricle an irregular and corrugated appearance. The right auricle is the source of focal arrhythmias in 5.3% of the dogs studied.[3,12]

The *cavotricuspid isthmus* is a complex area between the entrance of the caudal vena cava and the septal leaflet of the tricuspid valve; it is part of the reentrant circuit in typical atrial flutter in dogs (see p. 233).[15,18]

The *coronary sinus* drains in the posteromedial area of the right atrium, between the ostium of the caudal vena cava and the ostium of the tricuspid valve. It constitutes the base of Koch's triangle, a landmark situated in the vestibule of the right atrium that is used to locate the compact atrioventricular node. Atrial ectopies, ectopic atrial rhythms, and focal atrial tachycardias commonly originate from the coronary sinus in the dog (15.7%).[3,12]

The interatrial septum is a fibromuscular area interposed between the two atria. The anterosuperior part of the septum is in proximity of the transverse pericardial sinus and the aortic root, while the true atrial septum comprises the floor of the fossa ovalis and the anteroinferior part of the muscular rim that surrounds it. The rest of the rim is a fold of atrial myocardium (interatrial groove). The fossa ovalis is the landmark to perform transseptal puncture (see p. 71), while the interatrial septum is a source of focal arrhythmias in 5.3% of dogs, and the site of the right and left septal isthmuses in atypical atrial flutters (see p. 233).[3,15,19,20]

The *left atrium* can be divided into five components: the venous part (with the ostia of the pulmonary veins), the vestibule close to the mitral valve area, the body of the left atrium, the left auricle, and the left side of interatrial septum (Fig. 13.2).

In dogs, the venous part of the left atrium is the site of confluence of seven veins into three ostia: [21]

1. The cranial right ostium drains the right cranial and right middle pulmonary lobe veins.
2. The caudodorsal ostium drains the right caudal, accessory, and left caudal pulmonary lobe veins.
3. The cranial left ostium drains the left cranial and left caudal veins of the left cranial pulmonary lobe.

The left atrium is connected electrically to the pulmonary veins through muscular sleeves of ordinary atrial myocardium.[22] The venous wall is composed of thin endothelium, a smooth muscle media, and a thick fibrous adventitia. The extension of the atrial myocardial tissue into the venous wall is variable, and these sleeves lie between the smooth muscle and the adventitia. They can extend 1 to 2 cm into the vein, with a variable thickness (Fig.13.3).[17,22,23] Pacemaker cells can be found embedded in the pulmonary working myocardium and can act as subsidiary pacemakers or as ectopic foci upregulated by atrial dilation and congestive heart failure. These cells have a high density of I_f channels compared to the slow pacemaker cells of the atrial working myocardium.[24] The arrangement of myocardial fibers within the sleeves is complex, with an alternation of circular-oriented and longitudinal fibers and interconnections between the different veins, a possible substrate for microreentry and focal trigger activity.[17,23] In addition, the veins are rich in epicardial ganglia, from which intrinsic nerves extend to the venous endothelium.[23] The source of atrial ectopy and tachycardia in the dog is frequently found in the pulmonary veins (37% of cases); triggered atrial fibrillation is seen in 36.8% of cases of pulmonary vein firing.[3] Myocardial sleeves have also been found in the cranial vena cava in a canine model, and their interaction with the cranial vena cava–aorta ganglionated plexus can induce firing from this area, thereby initiating atrial fibrillation during sleep apnea.[25]

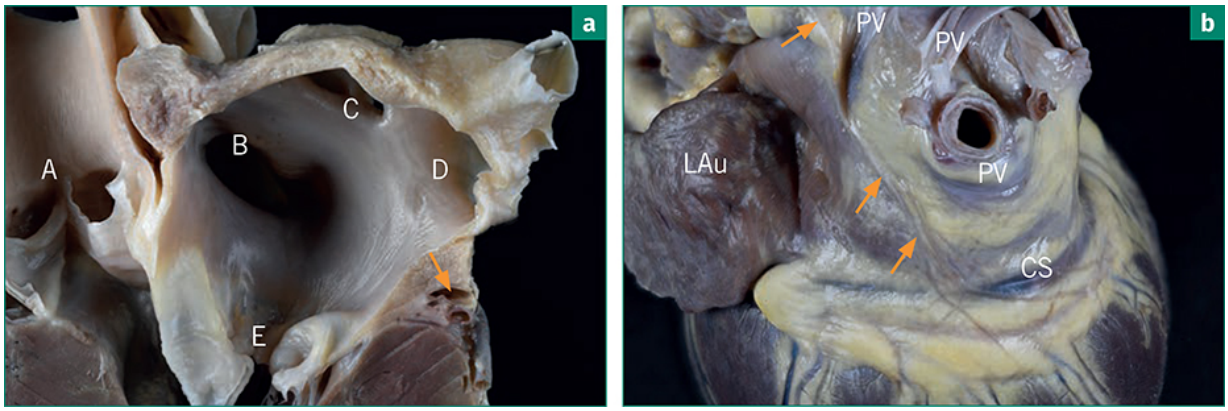


FIGURE 13.2. Left atrial anatomy in the dog: a) cavity of the left atrium and outflow tract of the left ventricle. A, aortic valve; B, left auricle; C, opening of the cranial left pulmonary vein; D, outflow tract of the caudal left pulmonary vein; E, mitral valve; arrow, coronary sinus. b) Ligament of Marshall anatomy: left and caudal gross pathology view. The ligament of Marshall is recognizable (arrows) on the epicardial surface of the caudal left atrial wall, with an oblique course between the left caudal pulmonary lobe vein (PV) and the coronary sinus (CS). LAu, left auricle. Pictures courtesy of Dr. Massimiliano Tursi, Department of Veterinary Sciences, University of Turin (Italy).

The *body of the left atrium* is located in between the vestibule and the venous part of the atrium. A functional line of block is present in its posteroinferior area (left atrial isthmus or mitral isthmus), starting from the roof of the left atrium and passing between the ostia of the pulmonary veins. It is an area of slower conduction, particularly in case of left atrial enlargement, and favors the breakup of the wavefront arising from the pulmonary vein foci, thus initiating atrial fibrillation.[26]

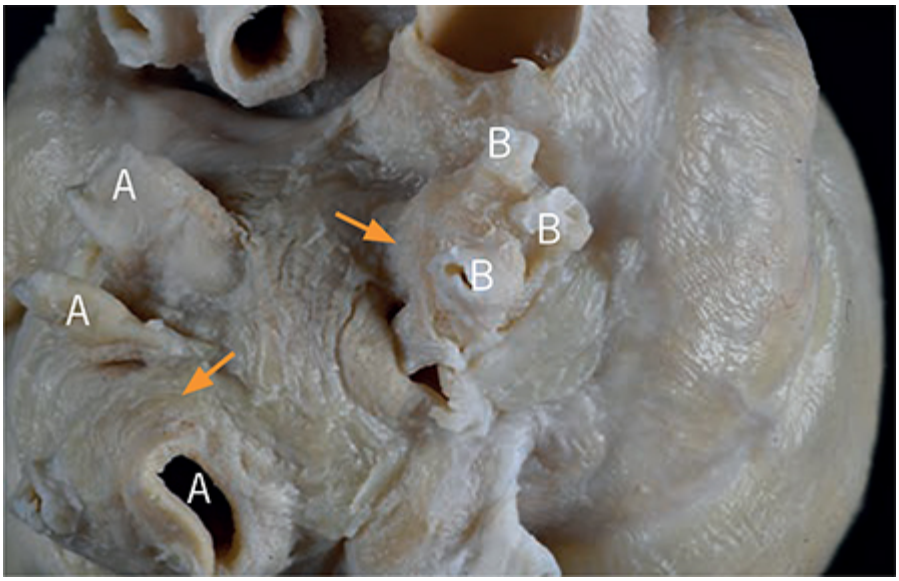


FIGURE 13.3. Pulmonary venous sleeves in the dog: base of the heart after removal of the pericardial sac and epicardium. Extension of the atrial myocardium (myocardial sleeves) in the terminal portion of the pulmonary veins (arrows). A, left pulmonary veins; B, right pulmonary veins. Courtesy of Dr. Massimiliano Tursi, Department of Veterinary Sciences, University of Turin (Italy).

Between the left pulmonary vein ostium and the entrance of the left auricle, it is possible to observe an infolding of the atrial wall that forms an endocardial prominence called *left lateral ridge*. The oblique vein of Marshall, a remnant of the left cranial vena cava, can be found on the lateral and inferior epicardial aspect of the left lateral ridge. This vein can obliterate, forming in most cases the ligament of Marshall. These structures run together with several autonomic nerve bundles (both vagal and sympathetic) and end in the great cardiac vein in close proximity to the coronary sinus ostium. The vein or ligament of Marshall has muscular connections with the left pulmonary veins, which provides a substrate for atrial fibrillation triggered by pulmonary vein firing (Fig. 13.2b).[16,23]

The *left auricle* has a multilobulated appearance and a very thin wall. In humans, its pectinate muscle trabeculations vary with its morphology. It is in close contact with the circumflex artery, which runs on the epicardial side of the atrial wall, and with the left phrenic nerve.[14,23,27]

ELECTROPHYSIOLOGICAL MECHANISM

Focal atrial arrhythmias can be caused by three different arrhythmogenic mechanisms or a combination of them: enhanced abnormal automaticity, triggered activity, and microreentry.[2] Histological stains of arrhythmogenic foci in humans have shown either normal myocardium or myocyte hypertrophy with extensive myocardial fibrosis, mononuclear infiltration, and fibrofatty replacement. These abnormalities are the substrate for abnormal automaticity and microreentry.[28] Some ectopic foci contain many pacemaker cells, with their relative currents playing a major role in automatic arrhythmias.[24]

An arrhythmogenic mechanism can be defined based on its response to a variety of pacing and pharmacological maneuvers. Automatic tachycardias can be initiated only under isoproterenol hydrochloride (0.04–0.1 mg/kg/min IV as a constant rate infusion); programmed stimulation cannot induce or terminate them. They can be suppressed with overdrive pacing or β-blockers, but not with carotid massage or calcium antagonists. Triggered

activities can be induced with pacing when the critical cycle length is achieved. Either early or delayed afterdepolarizations can be recorded in the monophasic action potential before the onset of triggered arrhythmias. They cannot be entrained, but they can be terminated with overdrive pacing or postpacing acceleration, or with carotid massage, β-blockers, and calcium channel blockers. Microreentry tachycardias can easily be initiated and terminated with programmed stimulation. They can also be concealed entrained (the coupling interval between the atrial ectopy and the first tachycardia beat is inversely related to the pacing cycle length) and terminated with calcium channel blockers.[2]

Abnormal automaticity can arise from any area of the atrial myocardium and tributary veins, since primary or secondary pacemaker cell activity can also be found in nonpacemaking regions of the atria and ventricles and act as subsidiary pacemakers or ectopic foci.[24] The automaticity of these regions depends mainly on the membrane clock, and therefore on the I_f current.[29] The lower crista terminalis, in particular, may generate a stronger I_f current despite its minimal HCN4 concentration, because it has a more negative diastolic potential than the sinus node.[29]

Some atrial subsidiary ectopic pacemaker cells are in intermediate position in the hierarchy of cardiac pacemakers when the sinus node fails to depolarize; however, in 50% of the dogs studied, an escape junctional rhythm predominated.[30] Atrial ectopic rhythms have a faster rate compared to junctional rhythms (average 150 bpm vs. 100 bpm) and they arise from the crista terminalis, the coronary sinus, and the interatrial septum.[30]

Age, atrial stretch, and autonomic balance also play an important role in the development of focal atrial arrhythmias. The aging process induces anatomical and electrical atrial remodeling that is mainly due to interstitial fibrosis and is characterized by a longer P wave and PQ interval duration and a reduced conduction velocity and action potential duration.[31] Increased fibrosis in the pulmonary veins is also a potential aggravating factor for arrhythmia inducibility and maintenance.[32] Atrial remodeling during chronic atrial stretch alters direction-dependent conduction, which promotes ectopic triggers.[33] Adrenergic stimulation, particularly in case of congestive heart failure, can promote abnormal automaticity and triggered activity of nonpacemaking regions of the atrium and tributary veins by shifting I_f

current activation to more positive potentials and increasing the Ca^{2+} transient with calcium overload, thereby inducing, respectively, enhanced automaticity and delayed afterdepolarizations.[2,29] The same mechanism, combined with vagal activation, induces shortening of the pulmonary vein action potential, particularly at the level of the left atrium–pulmonary vein junction, where the action potential duration is the shortest, and constitutes the theory behind pulmonary vein firing (Ca^{2+} transient triggering hypothesis).[34]

The arrhythmogenic mechanisms of focal atrial arrhythmias are largely descriptive and different overlaps exist. A new three-dimensional noncontact mapping technique now allows visualization of activation maps to identify a centrifugal activation pattern and low-voltage zones, which are characteristic of focal atrial arrhythmias.[35]

In dogs, most focal atrial tachycardias are considered automatic (63%), while a minority result from either microreentry or triggered activity (21%).[3,36]

ELECTROCARDIOGRAPHIC FINDINGS

Focal atrial arrhythmias are characterized by an abnormal atrial activation (P' wave), abnormal atrial repolarization (T_a wave), various degrees of atrioventricular conduction delay, and a normal QRS duration and polarity, unless an aberrancy, bundle branch block, or intraventricular conduction delay is present.

The polarity and duration of the P' wave vary depending on the site of origin, as does its position relative to the QRS complex. Depending on the depolarization rate of the focus, the site of origin and the atrioventricular conduction time, the P' wave can appear in previous ST segment, or different degrees of fusion with the previous T wave may be observed.[3]

ATRIAL ECTOPIC BEATS

Atrial ectopic beats can arise from different areas of the atrial myocardium and from the tributary veins. Based on the time of occurrence in relation to the basal sinus rhythm rate, they can be premature or escape beats. Ectopic

atrial depolarizations usually have a P' wave with a longer duration, and an evident and discordant Ta wave. The longest, negative, and bimodal P' waves (up to 80 ms) with a prominent positive Ta wave can be found in cases of atrial ectopic beats arising from the posterior right atrial area (coronary sinus ostium or posterior tricuspid valve annulus) (Fig. 13.4). The polarity of the P' wave is a valuable parameter only in the frontal plane and depends on the site of origin:

1. Right atrial roof ectopies (originating from the crista terminalis, cranial vena cava, right pulmonary veins or right auricle) have an axis between –20° and +90°. In case of atrial ectopies originating from the low crista terminalis, a left axis deviation is observed (± 0°).
2. Right atrial floor ectopies (originating from the coronary sinus, posterior tricuspid valve annulus, or lower interatrial septum) have an axis between –20° to –80°.
3. Left atrial roof ectopies (originating from the left pulmonary veins or left auricle) have an axis between +90° to +180° with negative leads I and aVL.
4. Left atrial floor ectopies (originating from ligament or vein of Marshall, great cardiac vein, mitral annulus or anterior and posterior left atrial wall) have an axis between –100° to –180° and a negative lead I (Fig. 13.5).[3,37]



FIGURE 13.4. Coronary sinus atrial ectopy in a 10-year-old German Shepherd with chronic myocarditis. Note the presence of a prolonged P' wave (100 ms) (arrow) followed by an elevation of the PQ segment (Ta). A giant discordant atrial depolarization then occurs, followed by a normal QRS complex. Lead II; speed, 50 mm/s; calibration, 10 mm/1 mV.

The P' wave shows different degrees of fusion with the previous T wave depending on the rate of depolarization of the ectopic focus, the site of origin, and the atrioventricular conduction time. The P' wave in case of pulmonary vein firing is usually located in the ST segment of the previous QRS complex, that is, when ventricular systole and maximal atrial stretch during the reservoir phase of the left atrium occur (Fig. 13.6).[38]

Depending on their prematurity, atrial ectopic beats can have a normal or slightly increased PQ interval or, in case of venous ectopic beats, they can be blocked.

Atrial ectopic beats usually have QRS complexes with a normal duration and axis, unless a phase 3 or 4 aberrancy, anatomical bundle branch block, or intraventricular conduction delay is present.[3]

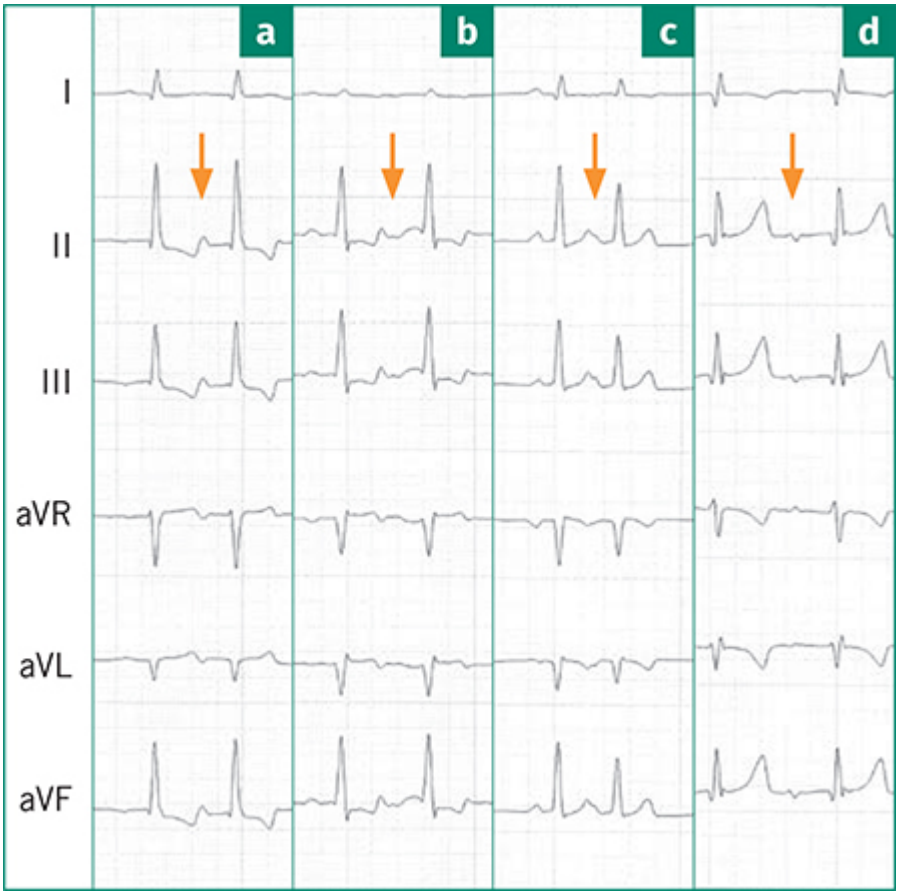


FIGURE 13.5. Atrial premature ectopic beats arising from different foci in the atria or tributary veins. a) Right atrial roof ectopy with a P' wave (arrow) with a superior-to-inferior, right-to-left axis (+60°). b) Right atrial floor ectopy with a P' wave (arrow) with an inferior-to-superior, right-to-left axis (–80°). c) Left atrial roof ectopy with a P' wave (arrow) with a superior-to-inferior, left-to-right axis (+120°). d) Left atrial floor ectopy with a P' wave (arrow) with an inferior-to-superior, left-to-right axis (–150°). Six limb leads (I, II, III, aVR, aVL, aVF). Speed, 50 mm/s; calibration, 5 mm/1 mV.

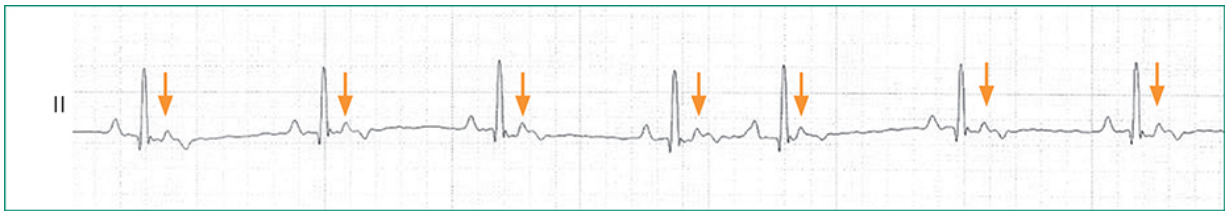


FIGURE 13.6. Pulmonary vein firing in a 5-year-old female Newfoundland. Note the presence of positive atrial deflections (arrows) in each ST segment. During ventricular systole, atrial stretch occurs, inducing depolarization of the pulmonary vein sleeves. Lead II; speed, 50 mm/s; calibration, 10 mm/1 mV.

Atrial ectopic beats can also be organized in couplets, triplets, and allorhythmias. In the author's experience, atrial bigeminy is a particular feature in dogs with ectopic foci in either the vein or ligament of Marshall or the pulmonary veins (Fig. 13.7).



FIGURE 13.7. Atrial bigeminy originating from the ligament of Marshall in a 1-year-old male Golden Retriever. Note the presence, every other sinus beat, of P' waves (arrows) with an inferior-to-superior, left-to-right axis (–150°). Six limb leads (I, II, III, aVR, aVL, aVF); speed, 50 mm/s; calibration, 10 mm/1 mV.

ATRIAL PARASYSTOLE

Atrial parasystole is an arrhythmia that occurs very rarely in dogs and cats. It is the result of the interaction between two rhythms with different rates: one arising from the sinus node and a parasystolic rhythm arising from the atrial myocardium.[39] The parasystolic rhythm is protected from being overdriven by the sinus rhythm, which has a dominant rate, due to an intermittent or constant entrance block. The theory behind the cause of this entrance block is the level of depolarization of membrane potentials at which abnormal automaticity occurs.

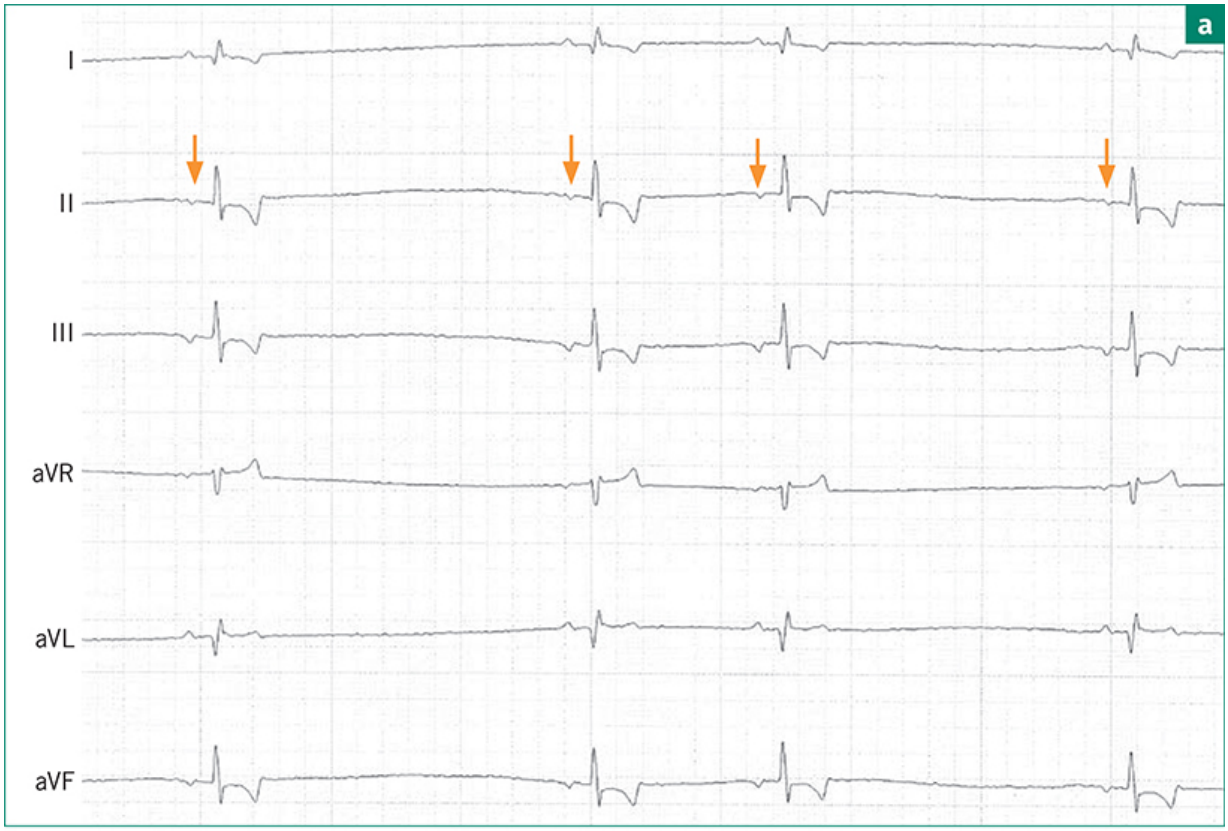
Fixed parasystole is characterized by a P' wave with a variable coupling interval, interectopic intervals that are a multiple of a common denominator, and the possible presence of fusion beats.

In case of modulated parasystole, the rate is variable due to the electrotonic influences of the tissues surrounding the parasystolic focus. If these occur early in diastole, they delay the parasystolic focus rate, and they accelerate it if they occur late in diastole.[39]

ATRIAL RHYTHMS

Atrial rhythms can be generated by subsidiary pacemakers in case of sinus node dysfunction or secondary to enhanced automaticity due to any cardiac or extracardiac causes triggering sympathetic activation. The most common sites of origin of atrial rhythms are the lower crista terminalis, the coronary sinus (Fig. 13.8a), or the ligament or vein of Marshall (Fig. 13.8b), and more rarely the interatrial septum.[29,30,40]

The reported average atrial rate ranges from 100 to 150 bpm. The P' wave axis in the frontal plane varies according to the site of origin as previously described; due to the slower rate, atrioventricular conduction is usually normal, as are the QRS complex duration and polarity.[29,30,40]


a
I
II
III
aVR
aVL
aVF

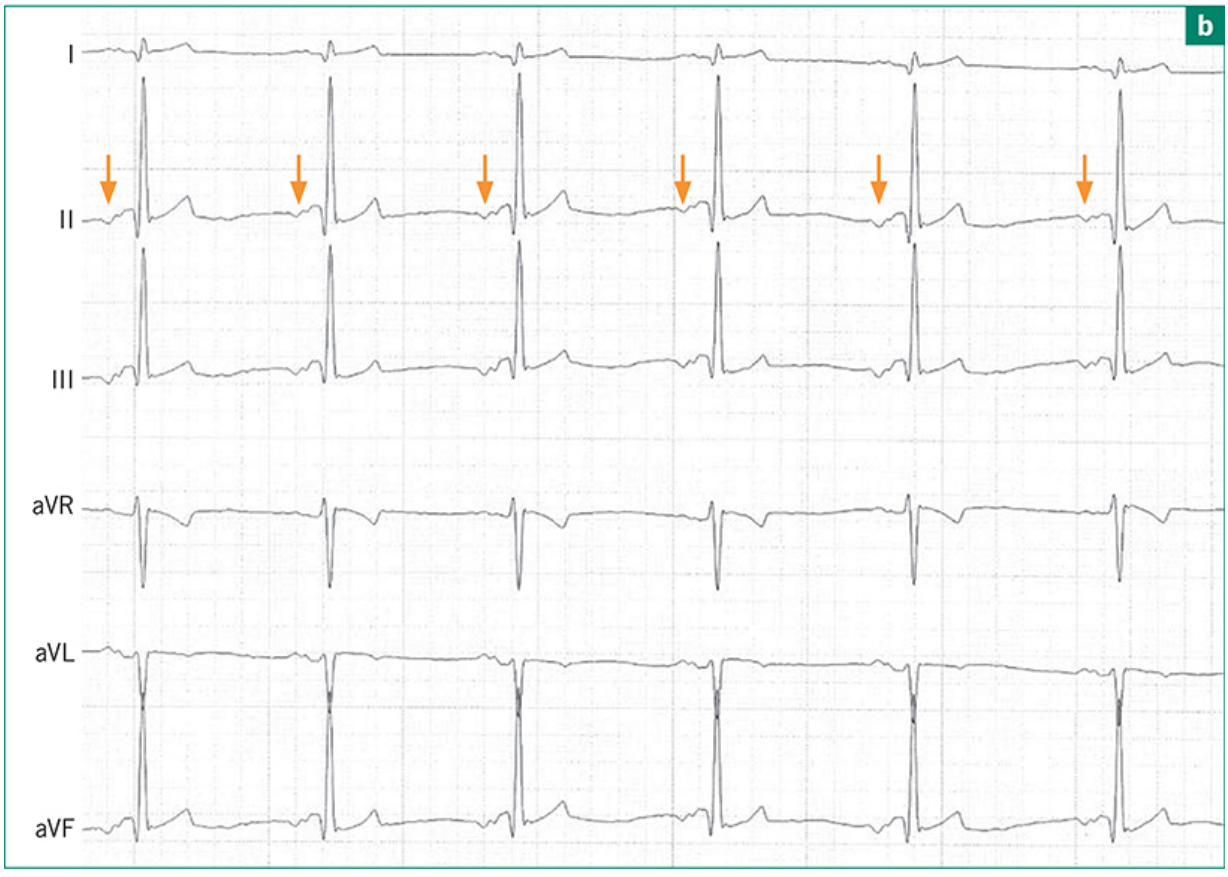

b
I
II
III
aVR
aVL
aVF

FIGURE 13.8. a) Atrial escape rhythm originating from the floor of the right atrium in a 11-year-old male mixed-breed dog with sinus node dysfunction. Note the presence of P' waves (arrows) with an inferior-to-superior, right-to-left axis (–30°) with a rate ranging from 40 bpm to 80 bpm in the absence of sinus activity. b) Atrial rhythm originating from the coronary sinus in a 1-year-old female Labrador Retriever. Notice the presence of bifid P' waves (arrows) with an inferior-to-superior, right-to-left axis (–30°) followed by a prominent positive discordant Ta inducing an elevation of PQ segment. The presence of prolonged (80 ms), bifid P' waves with a prominent Ta wave is a classic electrocardiographic finding in ectopies originating from the coronary sinus ostium. Six limb leads (I, II, III, aVR, aVL, aVF); speed, 50 mm/s; calibration, 10 mm/1 mV.

FOCAL ATRIAL TACHYCARDIAS

The focal atrial tachycardias reported in dogs are predominantly right sided (63%), arising from the crista terminalis (26.3%), coronary sinus ostium (15.7%), tricuspid valve annulus (10.5%), interatrial septum (5.3%), and right auricle (5.3%). They are less commonly left sided, arising from the right and left cranial or superior pulmonary veins (31.5%) and right caudal or inferior pulmonary vein (5.3%).[3] Multiple concomitant ectopic foci can be found in up to 10.5% of dogs. Single or multiple pulmonary vein foci can trigger atrial fibrillation in 36.8% of cases.[3]

Focal atrial tachycardia has a mean atrial cycle length of 270 ± 38 ms (195–260 bpm), which is statistically slower than in orthodromic atrioventricular reciprocating tachycardia and atrial flutter. This cycle length is regular in 55% of cases and irregular in 45% of cases. The atrioventricular conduction ratio in focal atrial tachycardia is 1:1 in 97% of the dogs studied and 2:1 in the remaining 3%. The ventricular cycle length characteristics are therefore similar to those described for atrial activations (240–300 ms, 200–250 bpm) during this type of arrhythmia.[4]

Cycle length irregularity is defined as a sudden variation of more than 20 ms in a regular RR interval tachycardia. This variation can either be due to changes in the focus discharge rate (initial warm-up and final cool-down phenomena in automatic focal atrial tachycardia) or to variations in the atrioventricular conduction time and ratio.[3,4]

In focal atrial tachycardia, the P' wave has a median duration of 41 ms (range, 35–45 ms), with the longest duration recorded at the level of the posterior right and left atria, and a very variable median electrical axis depending on the site of origin (49°; range, –72°/76°). The RP' interval is long in 52% of cases (160 ms; range, 120–200 ms); RP' interval variability is seen in 50% of dogs. The P' wave falls on the T wave (camel sign) in

33% of dogs. The RP' interval is short in 12% and variable in 3% of cases. The mean P'R interval is 125 ± 29 ms; its duration is variable in 24% of dogs. The median RP'/P'R ratio reported for focal atrial tachycardia is 1.45 (range, 0.92–1.67).[4]

A RP' interval >100 ms can differentiate focal atrial tachycardia from orthodromic atrioventricular tachycardia with a sensitivity of 89%, a specificity of 95%, a positive predictive value of 85% and a negative predictive value of 96%. A RP'/P'R ratio >0.85 also allows differentiation between these two arrhythmias with a sensitivity of 95%, a specificity of 79%, a positive predictive value of 93%, and a negative predictive value of 84%. Finally, a RP' interval >201 ms can differentiate sinus tachycardia from focal atrial tachycardia with a sensitivity of 70%, a specificity of 90%, a positive predictive value of 89%, and a negative predictive value of 71%. A RP'/P'R ratio >2.01 also allows differentiation between these two arrhythmias with a sensitivity of 86%, a specificity of 96%, a positive predictive value of 96%, and a negative predictive value of 85%.[4]

QRS complexes in focal atrial tachycardia are usually narrow (60 ms; range, 52–60 ms) and may rarely present alternans (12%), mainly in lead V3. The QT interval during focal atrial tachycardia is within normal limits (198 ms; range, 180–200 ms); this value can therefore be helpful in discriminating the location of the P' wave (Fig. 13.9).[4]

Depending on their electrocardiographic behavior and duration, focal atrial tachycardias can be classified as follows using a surface electrocardiogram or 24-hour Holter recording:

- Self-limiting focal atrial tachycardia: repetitive 6- to 12-beat runs, either paroxysmal or with warm-up and cool-down phenomena. This tachycardia is very common in chronic mitral valve disease cases (Fig. 13.10).
- Sustained focal atrial tachycardia: runs lasting more than 30 seconds, likely secondary to microreentry or triggered activity. It can be associated to different acquired and congenital heart disorders.
- Incessant focal atrial tachycardia. It lasts more than 12 hours and occurs as a complication of several acquired and congenital heart disorders. It can often be secondary to myocarditis. It is a common cause of arrhythmia-induced cardiomyopathy.

- Paroxysmal focal atrial tachycardia with atrioventricular block. In humans, it is usually secondary to digoxin toxicity.
- Pulmonary vein tachycardia. It arises from different pulmonary veins with a very rapid cycle length (150–180 ms), often as a repetition (firing) of atrial depolarizations across the QRS complex when ventricular systole and atrial filling occur. Because of the rapid rate, they are not conducted along the atrioventricular node (Fig. 13.11). As already explained, it often triggers paroxysmal atrial fibrillation (Figs. 13.12 and 13.13).[1–3,22,38] Similar electrocardiographic findings can be documented in cases of cranial vena cava or ligament of Marshall firing.

No data on focal atrial tachycardias are available in cats since endocardial mapping has not been performed in this species. A case series generically described the differences between supraventricular tachycardias and atrial fibrillation in cats and very likely included some focal atrial tachycardias.[41] The median heart rate for cats with supraventricular tachycardia is 300 ms (range, 150–380 ms), and it is usually faster than the one reported for atrial fibrillation (220 ms; range, 0–260 ms).[41]

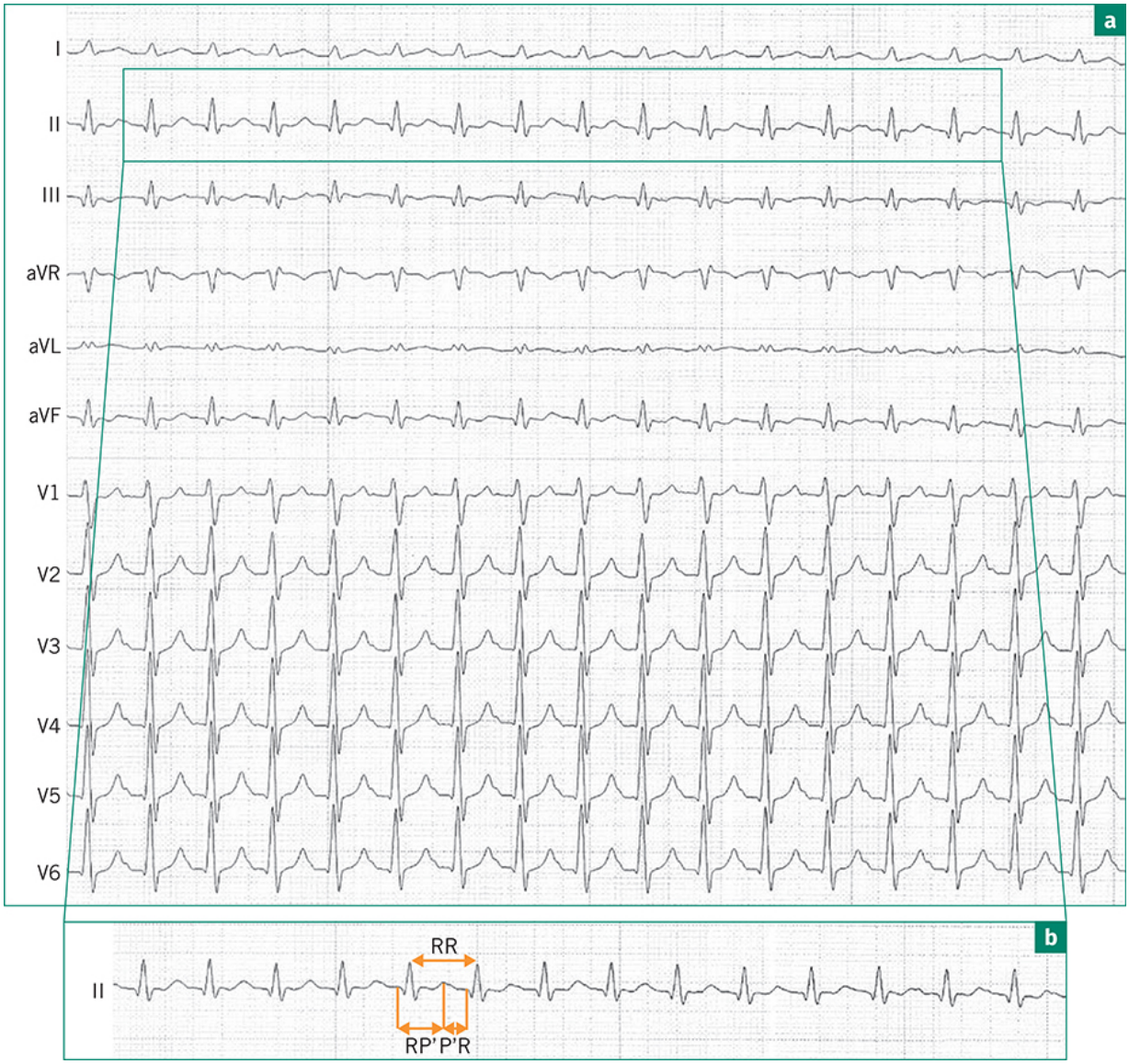


FIGURE 13.9. a) Cristal focal atrial tachycardia in an 8-year-old male Bull Mastiff. Notice the presence of a narrow QRS complex (60 ms) tachycardia with a ventricular rate of 250 bpm and the presence of a P' wave after the T wave (RP' of 160 ms) with a superior-to-inferior and right-to-left axis (+60°). Twelve leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6); speed, 50 mm/s; calibration, 10 mm/1 mV. b) Zoom of the previous lead II tracing to show the RP' and P'R intervals and RP'/P'R measurements. Focal atrial tachycardia is usually a long RP' interval tachycardia (RP' >50% of the RR interval). In this case, the RP' interval is 160 ms, the P'R interval is 100 ms, and the RP'/P'R ratio is 1.6. Lead II; speed, 50 mm/s; calibration, 10 mm/1 mV.

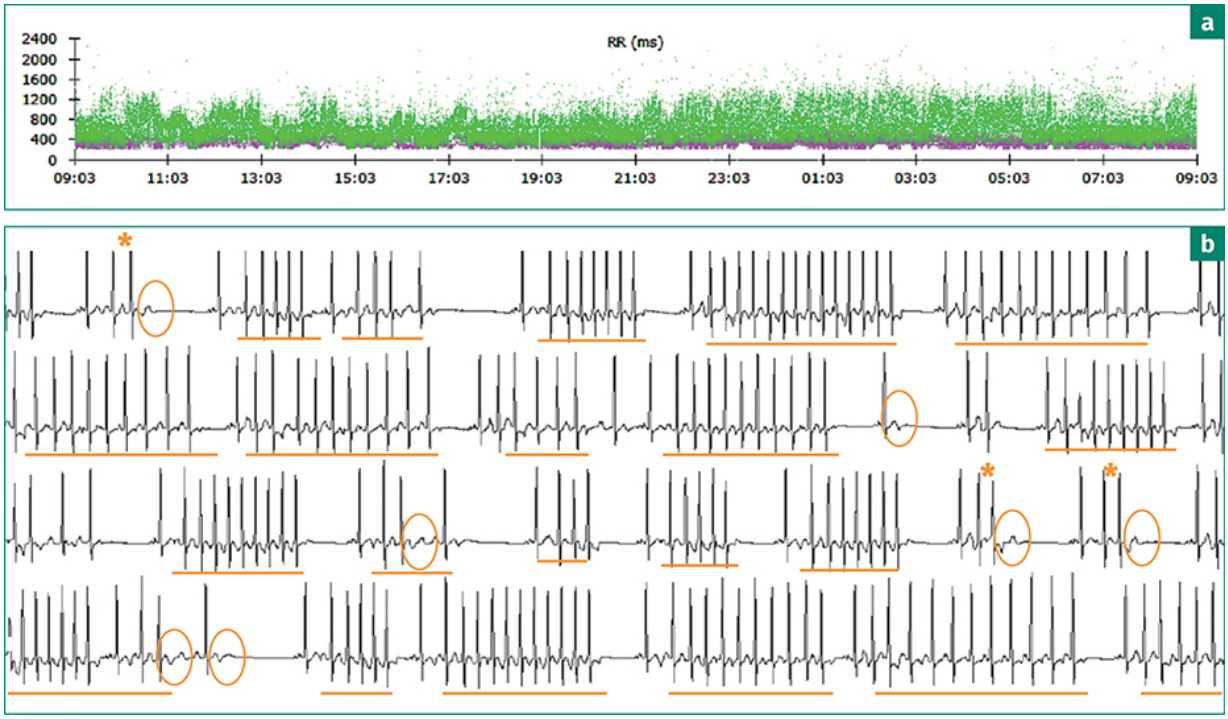


FIGURE 13.10. Ambulatory electrocardiographic recording from an 8-year-old male Cavalier King Charles Spaniel with chronic degenerative mitral valve disease and frequent supraventricular arrhythmias. a) Twenty-four-hour tachogram showing the distribution of normal RR intervals (green) and abnormal RR intervals during atrial arrhythmias (purple). Y-axis, RR interval duration; x-axis, hours of day and night. b) Electrocardiographic recording showing a dominant sinus rhythm interrupted by rare atrial couplets (*) and frequent self-limiting runs of focal atrial tachycardia (horizontal lines), some of which not conducted to the ventricle (circles). Lead Y; each line corresponds to 30 seconds. Speed, 7.5 mm/s; calibration, 2 mm/mV.

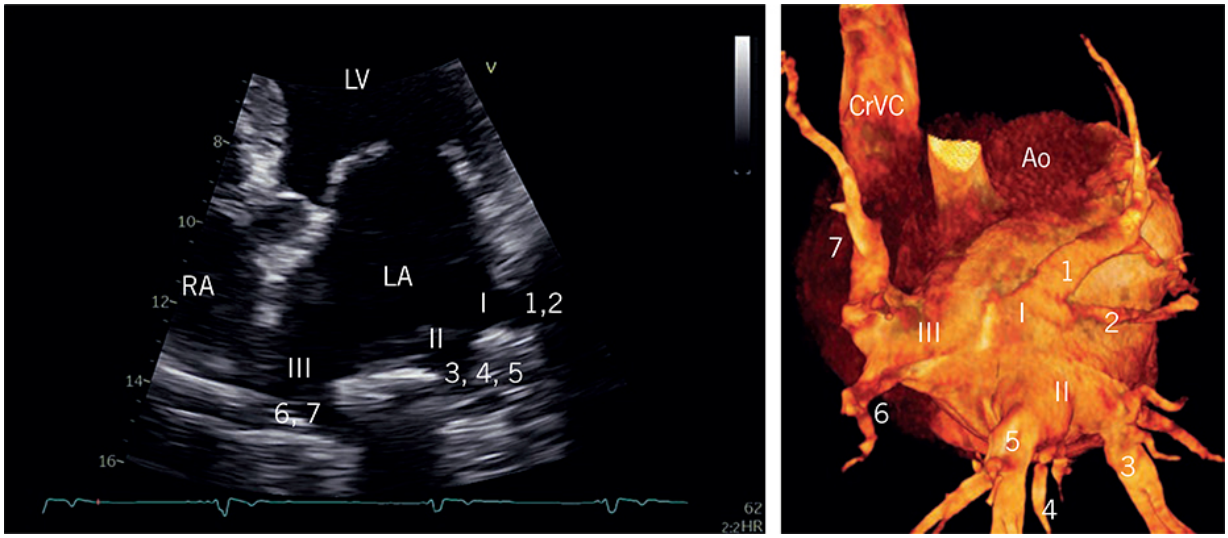


FIGURE 13.11. Pulmonary vein anatomy study using a four-chamber left parasternal apical echocardiographic view (a) and a three-dimensional computed tomography reconstruction (b). I, Left cranial ostium draining the left cranial (1) and left caudal (2) pulmonary lobe veins of the left cranial

lung lobe; II, caudodorsal ostium draining the left caudal (3), accessory (4), and right caudal (5) pulmonary lobe veins; III, right cranial ostium draining the right middle (6) and right cranial (7) pulmonary lobe veins. LA, left atrium; LV, left ventricle; RA, right atrium; CrVC, cranial vena cava; Ao, cut of the ascending aorta.



FIGURE 13.12. Ambulatory electrocardiographic recording from a 5-year-old female Newfoundland with a recent history of paroxysmal atrial fibrillation. a) Twenty-four-hour tachogram showing the distribution of normal RR intervals (green), which varies after around 1 hour from the beginning of the recording (yellow horizontal line). Y-axis, RR interval duration; x-axis, hours of day and night. b) Electrocardiographic recording showing, in the first part of the tracing, a dominant sinus rhythm interrupted by pulmonary vein firing (arrow) inducing paroxysmal atrial fibrillation, which lasts until the end of the recording. Lead Y; each line corresponds to 30 seconds. Speed, 7.5 mm/s; calibration, 2 mm/mV.

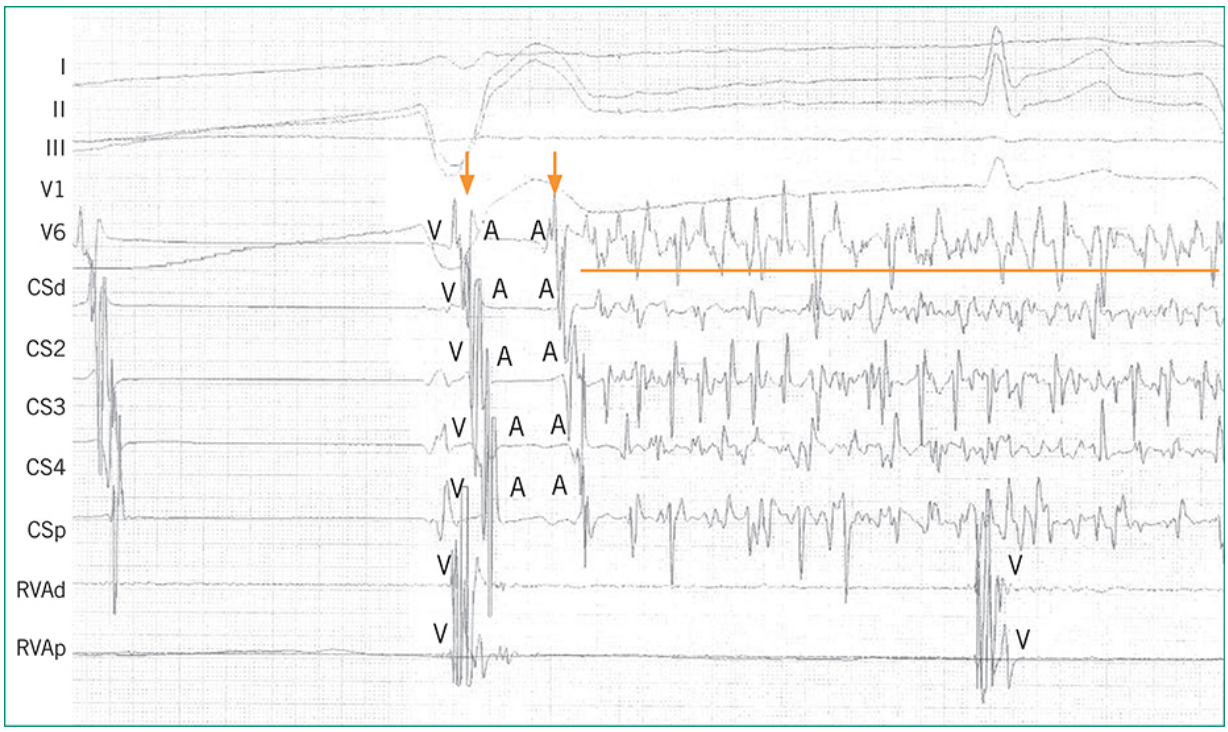


FIGURE 13.13. Pulmonary vein premature ectopy inducing paroxysmal atrial fibrillation in a 5-year-old female Dogue de Bordeaux after electrical cardioversion for persistent atrial fibrillation. Five-lead surface electrocardiogram (I, II, III, V1, and V6) and seven intracardiac electrograms from the posterior left atrium (CSd) to the posterior right atrium (CSp) and the right ventricular apex (RVAd-RVAp). A ventricular pause is interrupted by a ventricular escape beat, which stretches the atria promoting two early pulmonary vein ectopies (arrows), with a left-to-right activation (from CSd to CSp) that favors the initiation of paroxysmal atrial fibrillation (horizontal line). A, atrial electrogram; V, ventricular electrogram. Speed 150 mm/s; calibration, 22.8 mV/cm.

MULTIFOCAL ATRIAL TACHYCARDIA

Multifocal or chaotic atrial tachycardia is a rare arrhythmic disorder commonly found in elderly human patients with acute or chronic obstructive pulmonary disease, coronary artery disease, pulmonary hypertension, hypomagnesemia, and theophylline therapy. It occurs very rarely in infancy.[1,5,42]

Multifocal atrial tachycardia is a rapid and irregular rhythm with at least three different and distinct P' wave morphologies, three different atrial cycle lengths and P'Q intervals, and an isoelectric line between consecutive atrial depolarizations. No data regarding this rhythm disturbance has been reported in dogs and cats.[1,42]

CLINICAL PRESENTATION

Dogs with focal atrial tachycardias are usually males (64%), Boxers (18%), Labradors (15%), or Bernese Mountain Dogs (9%), with a median age of 4 years (interquartile range, 5.7 years), and a median body weight of 37 ± 7.7 kg. They are presented for weakness (68.4%) or congestive heart failure (15.8%), or they can be asymptomatic (15.8%).[3,4] In 15.7 % of cases, the reported focal atrial tachycardia is incessant and produces arrhythmia-induced cardiomyopathy (see p. 395); in 5.2 % of cases, it is associated with chronic mitral valve disease.[3]

No demographic data are reported in dogs for premature atrial ectopic beats or atrial rhythms; they can occur due to cardiac or extracardiac causes associated with an increased sympathetic drive and as a result of sinus node dysfunction with sinus standstill, respectively (see p. 271).[30]

Cats with generic supraventricular tachycardia including focal atrial tachycardias are prevalently males (72.7%), domestic shorthairs (65.9%) and domestic longhairs (11.4%). They are presented for respiratory distress (9.1%), lethargy (6.8%), collapse (13.6%), hindlimb paresis (4.5%), ascites (2.3%), and weight loss (4.5%), but they can also rarely be asymptomatic (4.5%).[41]

OTHER METHODS OF EVALUATION

ECHOCARDIOGRAPHY

A complete echocardiographic examination should be performed in all patients with focal atrial arrhythmias to assess for the presence of any concomitant acquired and congenital heart disease, and evaluate right and left ventricular systolic function over time, in case the atrial ectopy and focal atrial tachycardia burden is high, due to the possible occurrence of arrhythmia-induced cardiomyopathy.[3]

Preoperative echocardiography in conjunction with computed tomography is essential for proper evaluation of pulmonary vein anatomy, to assess the size of the ostia and draining veins, as these can be a possible site for ectopic foci if enlarged (see Figs. 13.11a and b).[21,43] Transesophageal echocardiography can guide ablation of these structures

and the execution of transseptal puncture to access the left atrium and tributary veins.[3]

Cats with supraventricular tachycardias, including focal atrial tachycardias, can have different degrees of left atrial enlargement (38.6%) and left ventricular hypertrophy (25%).[41]

ELECTROPHYSIOLOGICAL STUDY

An electrophysiological study is suggested in case of a high burden of premature atrial ectopic beats or focal atrial tachycardias in medium and large breed dogs when arrhythmias are considered primary, if antiarrhythmic therapy fails, or to prevent systolic dysfunction.

As already described in Chapter 9, three electrodes are used to map focal atrial arrhythmias: a decapolar catheter is placed into the great cardiac vein to record the right (CSp) and left (CSd) atrial potentials, and a decapolar catheter is positioned around the tricuspid valve annulus to record electrograms at the anterolateral aspect of the crista terminalis (high right atrial wall, HRA) with the proximal pair of electrodes, the middle lateral right atrial wall (MRA) with the middle pairs, and the low posterior right atrial wall (LRA) with the distal pairs. A steerable ablation catheter is then used to map different areas of the right atrium and tributary veins, or of the left atrium and tributary veins after transseptal puncture and placement of a transseptal sheath. A Lasso catheter can also be used for mapping of pulmonary vein firing foci.[3] Assessment of right pulmonary foci can also be performed from the right atrial roof through the identification of early double potentials. The recording at this site of a second potential greater than the first one suggests the presence of a pulmonary vein focus.[3]

Different electrophysiological tests are used to induce the arrhythmias and study their arrhythmogenic mechanisms. Automatic tachycardia can be induced with isoproterenol hydrochloride (0.04–0.1 μg/kg/min intravenously [IV] in a constant rate infusion [CRI], and can be suppressed with overdrive atrial pacing. Triggered activities can be induced with programmed atrial pacing or burst atrial pacing; they cannot be entrained, but they can terminated with overdrive atrial pacing with postpacing acceleration. Microreentrant focal atrial tachycardias can be initiated and terminated with programmed stimulation; they can also be concealed entrained. Pacing the atrial myocardium close to the arrhythmia isthmus

with a rate 10–20 ms faster than the tachycardia cycle length accelerates the tachycardia with the same sequence of activation and a short postpacing interval (0–30 ms longer than the tachycardia cycle length).[2] Pulmonary vein firing can be initiated with isoproterenol hydrochloride (0.04–0.1 μg/kg/min IV CRI) or with burst atrial pacing and, in some cases, by remifentanil or fentanyl (5–10 μg/kg/hour, variable rate IV infusion).[3]

Focal atrial tachycardia can be differentiated from reciprocating tachycardia through evaluation of the ventriculo-atrial interval after overdrive pacing. In focal atrial tachycardia, this interval is usually >10 ms from baseline. Microreentrant focal atrial tachycardia can be differentiated from macroreentrant atrial tachycardia based on the presence, in the former, of a significant portion of the cycle length without atrial activation and the impossibility to entrain focal arrhythmias from two sites more the 1–2 cm apart.[3]

Ectopic atrial foci are located at the site of earliest presystolic atrial activation relative to the onset of P' on the surface electrocardiogram (–39.9 ± 17.7 ms), where a sharp and negative unipolar recording with a QS morphology can be recorded, or when mechanical interruption of the arrhythmias is obtained by application of sufficient pressure on the focus with the ablation catheter. These areas also present fractionated potentials characterized by three or more consecutive negative deflections with a very low peak-to-peak amplitude, which reflects local slowing of atrial conduction due to nonuniform anisotropic properties of the focal area (Fig. 13.14). [3]

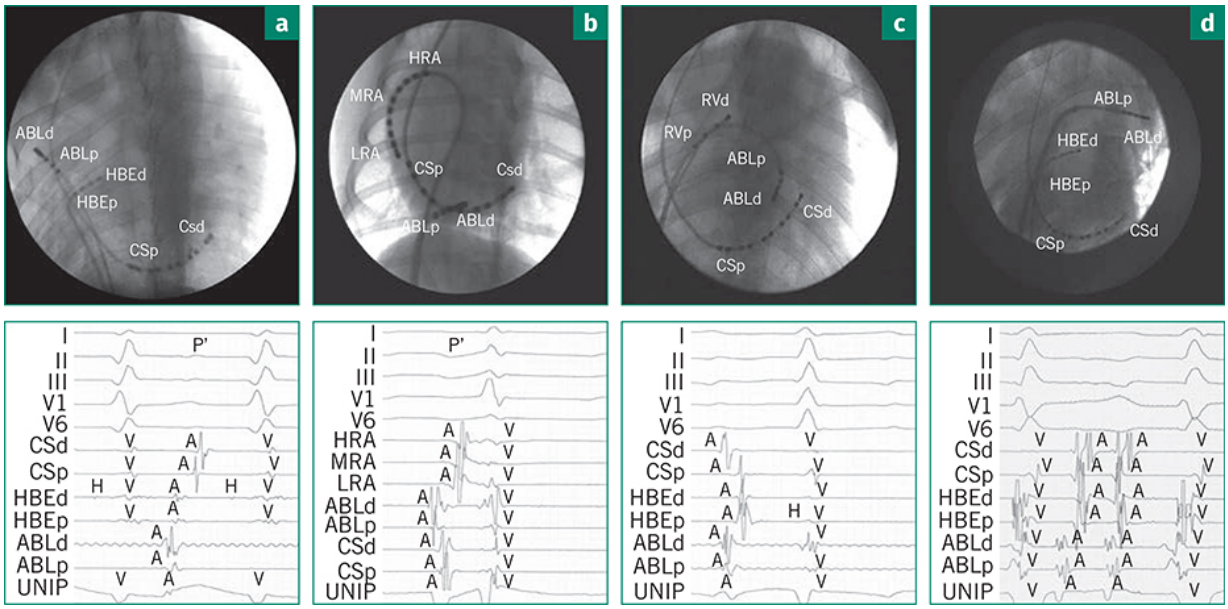


FIGURE 13.14. Dorsoventral fluoroscopic views and endocardial mapping tracings of four different ectopic foci: a) crista terminalis; b) coronary sinus ostium; c) ligament of Marshall; d) left cranial pulmonary vein. Five-lead surface electrocardiogram (I, II, III, V1, V6) and seven or eight intracardiac electrograms, depending on the case, from the posterior left atrium (CSd) to the posterior right atrium (CSp), the His bundle (HBEd-HBEp), the high right atrial wall (HRA), the medium right atrial wall (MRA), the low right atrial wall (LRA), and the ablation catheter (ABLd-ABLp) positioned on the target area, where a sharp and negative unipolar recording is visible (UNIP). A, atrial electrogram; H, His potential; V, ventricular electrogram. Speed, 150 mm/s; calibration, 22.8 mV/cm.

THERAPY

Little data have been reported for acute and chronic treatment of focal atrial arrhythmias in dogs and cats.[3,4,41–44] Acute treatment is rarely indicated in case of fast and incessant focal atrial tachycardias with hemodynamic instability. Endovenous boluses of diltiazem (dogs: 0.05–0.15 mg/kg in a slow IV infusion, which can be repeated every 5 minutes up to a total dose of 0.1–0.3 mg/kg; cats: 0.025 mg/kg in a slow IV infusion, which can be repeated every 5 minutes up to a total dose of 0.15–0.2 mg/kg), verapamil (dogs: 0.05 mg/kg in a slow IV infusion, which can be repeated every 5 minutes up to a total dose of 0.15–0.2 mg/kg; cat: 0.125–0.35 mg/kg in a slow IV infusion) or esmolol (dog: 330 µg/kg in an IV bolus, then 50 µg/kg/min in a CRI) can be used, but particular attention should be paid to right and left ventricular systolic dysfunction and a possible drop in the sinus rate after interruption of the tachycardia. Esmolol is efficacious in up

to 46% of cases, with a heart rate reduction by at least 20%.[44] Synchronized electrical cardioversion can be used as an alternative (see p. 137).[1]

Chronic management of focal atrial tachycardias can be achieved with antiarrhythmic therapy or catheter ablation.[1] In dogs, different antiarrhythmic drugs have been used, including oral metoprolol, quinidine, sotalol, propranolol, amiodarone, and digoxin.[3,4] In cats with generic supraventricular tachycardias (including focal atrial tachycardias), oral diltiazem, atenolol, or sotalol have been used.[41]

Experimental and clinical studies have evaluated the efficacy of ivabradine in the treatment of automatic focal atrial tachycardias, including that originating from the pulmonary vein.[24,45] Thanks to its effect on the nonpacemaking I_f current and Ca^{2+} transient currents, ivabradine is an efficacious option to treat focal atrial tachycardia.[24]

In the author's experience, ivabradine (0.4–0.6 mg/kg orally every 12 hours) or metoprolol (0.25–0.5 mg/kg orally every 12 hours) can successfully treat automatic focal atrial tachycardias, mainly those arising from the crista terminalis and pulmonary veins. For microreentrant or triggered focal atrial tachycardias, mainly those arising from the coronary sinus and sympathetically driven, sotalol (1–2 mg/kg orally every 12 hours) should be considered. In dogs, oral verapamil (0.5–2 mg/kg PO every 8 hours) and oral diltiazem (0.5–2 mg/kg PO every 8 hours) are rarely efficacious in terminating focal arrhythmias; they can only change the atrioventricular conduction ratio with a detrimental effect on ventricular contractility.[1]

Radiofrequency catheter ablation is the first-choice treatment in case of primary rapid focal atrial arrhythmias provoking arrhythmia-induced cardiomyopathy and when pharmacological treatment has failed. Once the ectopic foci (i.e., the targets of ablation) are found, radiofrequency energy is delivered to the atrial endocardium, at a maximum of 65° C and 75 watts (W) for 60 seconds when using nonirrigated catheters, or at 20 W for 60 seconds with 15–35g contact force when using irrigated catheters.[3,35] In case of ablation of pulmonary vein foci, a maximum of 20 W is usually used.[46] Current delivery should be terminated immediately in the event of an increase in impedance or displacement of the catheter. The energy is usually delivered during tachycardia to evaluate the interruption of the

arrhythmia, which should not recur for at least 45 minutes after ablation. The endpoint of the procedure is the abolition of the tachycardia with no reinduction of the arrhythmia with programmed atrial stimulation in cases of nonautomatic focal atrial tachycardias or with isoproterenol infusion in cases of automatic focal atrial tachycardias.

In the author's laboratory, the acute success rate of radiofrequency catheter ablation of focal atrial tachycardia is 79%. In one-third of cases, the arrhythmias cannot be induced with programmed or incremental atrial stimulation, atrial bursts, or isoproterenol infusion. The recurrence rate is 2%, while the complication rate is around 5.2% and includes anesthesia-related death, self-limiting stroke with spontaneous resolution during ablation of a pulmonary vein automatic focus, and iatrogenic atrioventricular block in a dog with Koch's triangle tachycardia unresponsive to pharmacological treatment.

The discovery of an atrial rhythm in conjunction with sinus standstill in dogs with sinus node dysfunction is one of the indications for permanent pacing.[47]

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CHAPTER 14

Junctional rhythms and junctional tachycardias

Manuela Perego

DEFINITION

Junctional arrhythmias include junctional ectopies (or junctional ectopic beats), junctional rhythms, accelerated junctional rhythms, focal junctional tachycardia, and nonparoxysmal junctional tachycardia. These rhythm disturbances arise from the atrioventricular junction.[1–9] This area comprises the atrioventricular specialized conduction system, which consists of the transitional cell zone, the atrioventricular node and its extensions, and the penetrating part of the His bundle.[3] A deep knowledge of the structure of the atrioventricular junction is crucial to understand the mechanisms of the different arrhythmias. The atrioventricular junction is the region of the heart where the distal portion of the atrial musculature inserts into the base of the ventricular mass and where the atrioventricular valves attach.[10] The areas surrounding the mitral and tricuspid valve annuli completely insulate the atrial myocardium from the ventricular myocardium, except at the site of penetration of the specialized system responsible for conduction of the electrical impulse.[10] The atrioventricular junction was first described in 1906 by Tawara,[11] who likened the axis responsible for electrical conduction to a tree, with roots located in the atrial myocardium, a trunk that penetrates the insulating atrioventricular plane at the aortic root, and branches at the crest of the muscular interventricular septum. The branches then descend as insulated branches on both sides of the interventricular

septum and ramify within the ventricular myocardium. A key part of this conduction system is the His bundle. In the human heart, because of the position of the subaortic outflow tract, the atrial muscle is close to the muscular interventricular septum, and the His bundle is thus correspondingly short. However, in dogs, the His bundle is appreciably longer.[10] The part of the right atrial wall containing specialized conduction tissue is known as Koch's triangle: its borders are delimited posteriorly by a fibrous extension of the Eustachian valve (called tendon of Todaro) and anteriorly by the line of attachment of the septal leaflet of the tricuspid valve. The apex of Koch's triangle is the membranous part of the interventricular septum and corresponds to the site of penetration of the His bundle.[10] Another clinically important area of Koch's triangle is the area between the coronary sinus ostium and the attachment of the septal leaflet of the tricuspid valve. This area is composed of working myocardium and devoid of insulating tracts. This is where the so-called *slow pathway* is located, and although its substrate has not yet been precisely defined, the nonanisotropic orientation of the working muscular fibers is probably a major determinant of slow conduction through this pathway.[10] The electrical impulse can also be transmitted from the atrial myocardium to the central part of the atrioventricular node through the *fast pathway*, which is located in the anterior portion of Koch's triangle.[10]

From the histological point of view, the atrioventricular junction is composed of different cell types: transitional cells and pacemaker (P) cells.[12] These transitional cells and P cells are similar to those present in the sinus node, but the latter has many more P cells. Almost 95% of the myocytes in the atrioventricular node are transitional cells, and most of the remainder are P cells.[12] P cells in the atrioventricular node, as in other locations of the heart, are small round or oval cells, with relatively few myofibrils. In general, P cells are connected with transitional cells through simple cellular junctions consisting of a few scattered desmosomes, and no junctions are present between two P cells.[12] Based on its histological features, the canine atrioventricular node can be divided into two different regions: a proximal one, which roughly corresponds to the proximal area of the atrioventricular node (atrionodal region) previously described in the rabbit, plus some parts of the central part (nodal region); and a distal part, which can be compared with the nodo-hisian region of the rabbit.[12]

Based on these anatomical and histological features, the most important electrophysiological functions of the atrioventricular node are:

1. To slow the conduction velocity.
2. To act as the main stable subsidiary pacemaker of the heart in case of sinus node failure. Normal slowing of the conduction velocity through the atrioventricular node provides a hemodynamic advantage by allowing optimal filling of the ventricles.[10]

No precise cutoff values exist in veterinary medicine to separate junctional rhythms from junctional tachycardias. However, studies in veterinary medicine have shown that the rate of junctional P cells was less than 66% of the sinus rate, while studies in human medicine have reported that the heart rate in focal junctional tachycardia should be more than the 95th percentile of heart rate for age and should otherwise be qualified as a junctional rhythm.[13,14] Based on these data, dogs can be considered to have a junctional rhythm with a heart rate <60 bpm, an accelerated junctional rhythm with a heart rate between 60 bpm and 100 bpm, and focal junctional tachycardia and nonparoxysmal junctional tachycardia with a heart rate between 100 bpm and 200 bpm. Junctional rhythms and junctional tachycardias are narrow QRS complex arrhythmias that may be regular or regular with cycle length irregularity.[3] In human beings, junctional tachycardias are differentiated into focal junctional tachycardia and nonparoxysmal junctional tachycardia.[1] Focal junctional tachycardia is common in children and may be congenital or postoperative.[3] Congenital focal junctional tachycardia is often refractory to medical treatment, and it is associated with high morbidity and mortality rates in the first 6 months of life due to its incessant behavior.[13,14] Postoperative focal junctional tachycardia is commonly seen in up to 5% of patients after cardiac surgery,[3] and it has been associated with ß1-receptor polymorphisms. The etiology of postoperative arrhythmias after pediatric and congenital cardiac surgery is multifactorial, even if adrenergic activation has been implicated in the pathogenesis of these arrhythmias.[15] Focal junctional tachycardia is a rare arrhythmia in adults and its pathogenesis is not completely understood.[1–9] Focal junctional tachycardia has also been described in humans in association with myocarditis as a result of edema and/or inflammation of the His bundle area.[16,17]

In dogs, focal junctional tachycardia has been described in Labrador Retrievers, with a median heart rate of 140 bpm in association with isorhythmic atrioventricular dissociation and different types of synchronization.[18]

Nonparoxysmal junctional tachycardia is a junctional rhythm of gradual onset and termination. In human medicine, it is considered a typical example of digitalis-induced delayed afterdepolarizations and triggered activity in the atrioventricular node.[1]

ELECTROPHYSIOLOGICAL MECHANISM

Automatic activity has been demonstrated deep in the distal canine atrioventricular node. Clusters of P cells have been found in this part of the atrioventricular node, which is therefore likely to be the main focus of secondary subsidiary escape pacemaking.[12] A series of experiments in dogs has shown that more than one pacemaker focus is active in the junctional area: the faster pacemaker cells possess a 66% rate relation to the original sinus rhythm and are responsible for the escape junctional rhythm, thus constituting a subsidiary pacemaker when the sinus node function is depressed.[12]

Normal enhanced automaticity has been postulated as the main mechanism inducing and maintaining focal junctional tachycardias.[19] Normal enhanced automaticity is described as an increased in P cell activity in the atrioventricular node. In dogs, P cells are scattered singly or in very small clusters of a few cells throughout the atrioventricular node. However, clusters of P cells are larger and more numerous near the junction between the distal atrioventricular node and the His bundle, and nerve tissue is also more abundant in this area.[20] In mice, it has been proven that spontaneous automaticity in the atrioventricular node depends on the presence of $Ca_v1.3$ channels, which constitute the predominant calcium channel isoform. In addition, HCN channels are considered to play a key role in both generation and regulation of atrioventricular node pacemaker activity. However, HCN channels are important for basal excitability of the P cells of the atrioventricular node and are not required for acceleration of pacemaker activity under ß-adrenergic stimulation.[21,22]

Under normal conditions, the sinus node has the fastest rate of firing, and the so-called subsidiary pacemakers fire at a slower rate, so the normal hierarchy is maintained. The discharge rate of a P cell is determined by three main factors: the maximum diastolic potential, the threshold value at which an action potential is initiated, and the slope of phase 4 of the action potential. A change in any of these three factors may alter the discharge rate of a P cell. P cell activity is also controlled by the autonomic nervous system and modulated by different mechanisms, such as metabolic and endogenous factors.[2,3] In particular, parasympathetic activity reduces the discharge rate of P cells by acetylcholine-induced hyperpolarization. The suppressive activity of the parasympathetic nervous system can be used in clinical practice for diagnostic and therapeutic goals. Indeed, tachycardias resulting from normal enhanced automaticity are expected to respond to vagal maneuvers.[2,3] Conversely, sympathetic activity increases the discharge rate of P cells by increasing the permeability of I_{CaL} channels and consequently the inward calcium current. Sympathetic activity also results in enhancement of the I_f current, thereby increasing the slope of phase 4 repolarization. Furthermore, metabolic abnormalities such as hypoxia and hypokalemia can lead to enhanced normal automatic activity as a result of sodium–potassium pump inhibition.[2,3]

Other mechanisms can be responsible for the development of junctional tachycardia, such as abnormal enhanced automaticity and triggered activities. The difference between normal and abnormal enhanced automaticity is that abnormal automaticity does not demonstrate overdrive suppression because of its reduced resting membrane potential (less than –60 mV). The sodium current and electrogenic pump are in a deactivated state and the abnormal automaticity depends on the slow inward calcium current.[2,3] In some cases of human medicine in which the etiology was uncertain, a correlation was observed between focal junctional tachycardia and viral myocarditis.[16,17] An association has also been established between other histological abnormalities (e.g., inflammation, fibrosis, or focal degeneration) and fibroelastosis involving the atrioventricular node and the His bundle region.[2,3]

The arrhythmogenic mechanism underlying nonparoxysmal junctional tachycardia is triggered activity due to delayed afterdepolarizations, which in human medicine has been correlated with increased blood levels of

digitalis. Myocardial ischemia, hypokalemia, and chronic obstructive pulmonary disease have also been reported to be associated with nonparoxysmal junctional tachycardia in human medicine.[1] In dogs, nonparoxysmal junctional tachycardia can also be observed in normal patients.

ELECTROCARDIOGRAPHIC FINDINGS

JUNCTIONAL BEATS AND RHYTHMS

Junctional beats are ectopic beats arising from the atrioventricular junctional area. A junctional beat is considered premature when it occurs earlier than the expected sinus beat and is considered an escape beat when it occurs at the end of a sinus pause. Junctional beats can have a negative P' wave preceding the QRS complex in the inferior leads (II, III, and aVF), with either concentric retrograde atrial activation with a superior axis shift with values between –80° and –100° (aVR and aVL with the same amplitude) and a short P'Q interval in case of an anterior exit site, or eccentric retrograde activation with a right or left superior axis shift and a long P'Q interval in case of a posterior exit site (Fig. 14.1a). In some cases, junctional beats have P' waves following the QRS complex, with a short RP' interval if retrograde conduction occurs along the fast atrioventricular nodal pathway (Fig. 14.1b), or with a long RP' interval if retrograde conduction takes place along the slow atrioventricular nodal pathway.

Junctional rhythms and junctional tachycardias are characterized by more than three consecutive junctional ectopic beats.

During a junctional rhythm, the heart rate is <60 bpm, and narrow QRS complexes are observed with regular RR intervals that can be associated with cycle length irregularity. Junctional rhythms occur when the sinus node discharge rate falls below the intrinsic rate of P cells in the atrioventricular junction or when the sinus node stops firing (sinus arrest or sinus standstill) (see p. 281). P waves are absent in junctional rhythms. After the narrow QRS complex, an atrial deflection is usually present and compatible with concentric retrograde atrial activation with an inferior-to-superior axis. This atrial deflection is negative in the inferior leads (II, III, and aVF), isodiphasic in lead I, and equally positive in leads aVR and aVL, with a mean electrical axis in the frontal plane of –80°/–100°. The P' wave

is more visible in the left precordial leads as a positive deflection. In junctional rhythms with concentric retrograde atrial activation along the fast atrioventricular pathway, atrial depolarization is visible close to the descending branch of the R wave or embedded in the first portion of the ST segment, with a short RP' interval and mimicking a S wave (pseudo-S wave) in the inferior leads (II, III, and aVF). If retrograde atrial activation occurs along the slow atrioventricular pathway, the RP' interval becomes longer. Electrocardiographic findings in cases of accelerated junctional rhythm are similar to those seen with junctional rhythms, except for the heart rate (60–100 bpm) (Fig. 14.2).


a
I
II
III
aVR
aVL
aVF

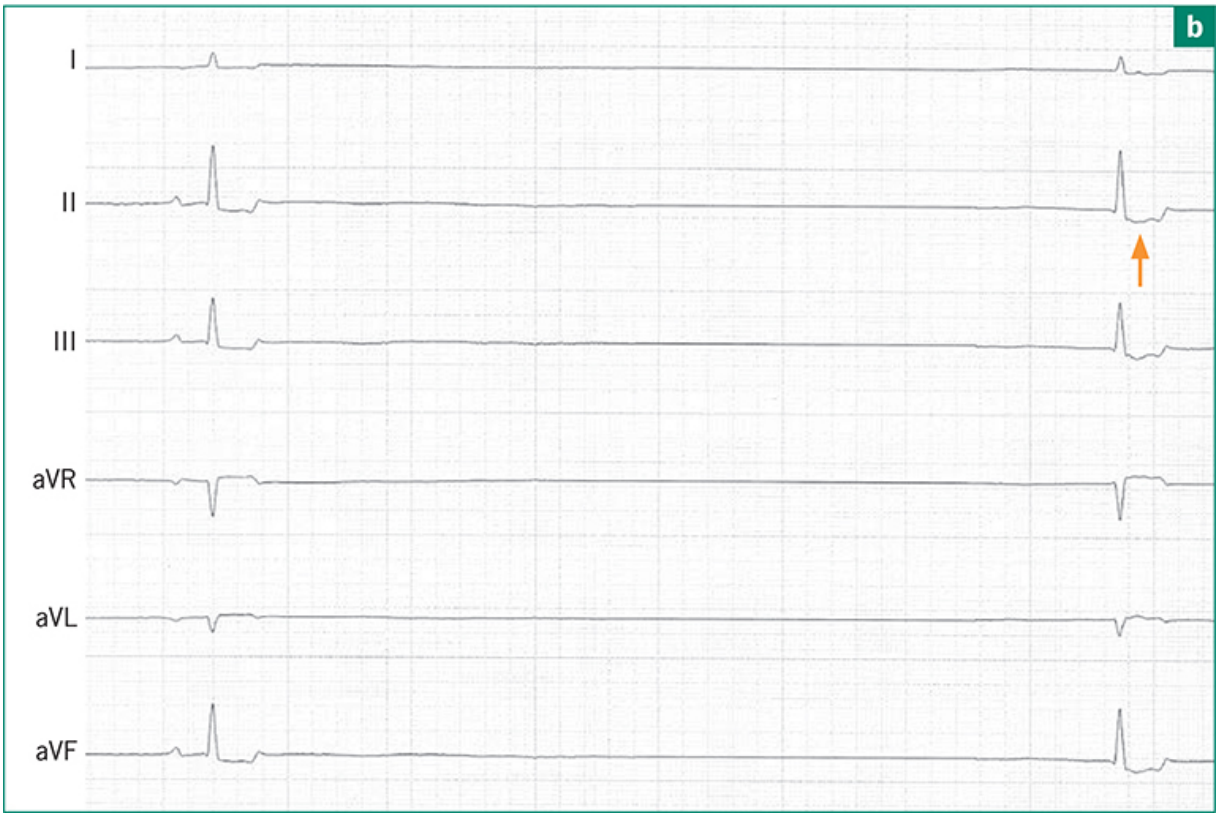

b
I
II
III
aVR
aVL
aVF

FIGURE 14.1. a) Sinus rhythm with sinus arrest and a junctional escape beat arising from the posterior right atrium (area of the coronary sinus) in a 14-year-old male Cocker Spaniel. During the sinus arrest (which lasts 180 ms), note the presence of an escape junctional beat with eccentric atrial retrograde activation characterized by a negative P' wave (arrow) in the inferior leads (II, III, aVF) with a duration of 80 ms, a right superior axis shift (–150°), and a long P'Q interval (140 ms). b) Sinus rhythm with sinus arrest and a junctional escape beat arising from the anterior right atrium (parahisian area) in a 13-year-old female West Highland White Terrier. At the end of the ventricular arrest (which lasts 370 ms), note the presence of a junctional escape beat from the parahisian area, with concentric retrograde atrial activation characterized by a negative P' wave (arrow) in the inferior leads (II, III, aVF) with a duration of 50 ms, a superior axis shift (–90°), and a short RP' interval (60 ms). Six limb leads (I, II, III, aVR, aVL, aVF); speed, 50 mm/s; calibration, 5 mm/1 mV.

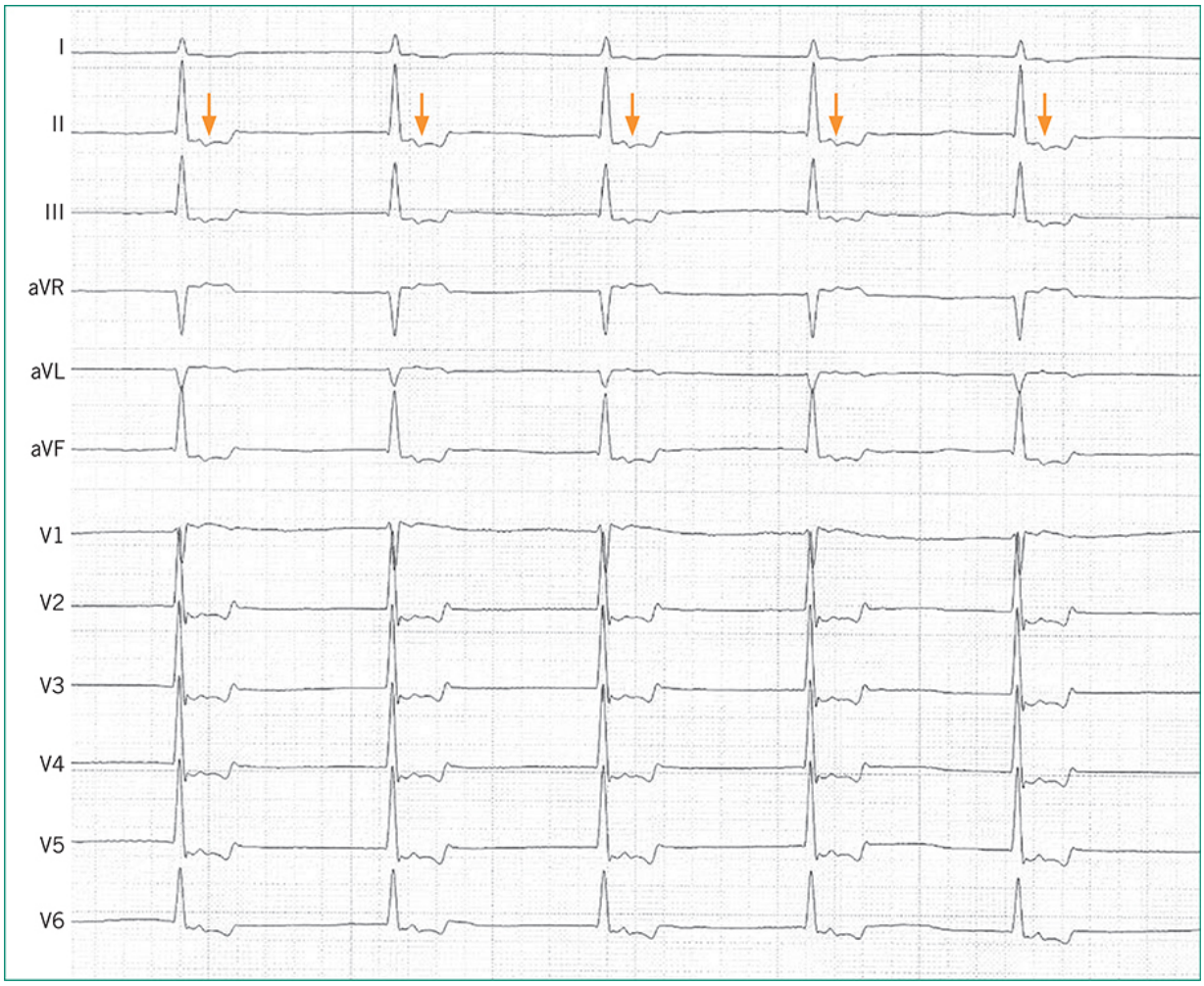


FIGURE 14.2. Sinus standstill with an accelerated junctional rhythm and concentric atrial retrograde activation in a 14-year-old female Cavalier King Charles Spaniel with sick sinus syndrome. Note the presence of narrow QRS complexes (40 ms) and negative P' waves (arrows) in the ST segment of the inferior leads (II, III, aVF), with a superior axis shift (–90°) and a short RP' interval (80 ms). Twelve leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6); speed, 50 mm/s; calibration, 5 mm/1 mV.

JUNCTIONAL TACHYCARDIAS

Focal junctional tachycardia is a narrow QRS complex tachycardia in which the median heart rate is 140 bpm. The median QRS complex duration is 52 ms, with a regular ventricular cycle length of 420 ms.[18] The RR intervals are usually regular but can sometimes display cycle length irregularity. Focal junctional tachycardia is frequently associated with isorhythmic atrioventricular dissociation. Isorhythmic atrioventricular dissociation is a rhythm in which the atria and ventricles are driven by independent pacemakers at equal or nearly equal discharge rates.[23] A particular aspect of isorhythmic atrioventricular dissociation is synchronization between the two pacemaker sites over a relatively long period.[23] Experimental studies have shown that when separate and distinct cellular elements with different discharge rates and no anatomical continuity are placed in contact, they start to discharge impulses simultaneously at a common rate, with the slower focus accelerating to approximate the rate of the faster focus. When this occurs, the phenomenon is called synchronization.[23] In case of focal junctional tachycardia, the atria and ventricles depolarize starting from their own separate pacemakers (sinus node and atrioventricular junction area, respectively) and beat synchronously.[18] In this case, P waves are present but dissociated from the narrow QRS complexes; this finding is called isorhythmic atrioventricular dissociation.

Isorhythmic atrioventricular dissociation can follow two main patterns (Figs. 14.3a–14.3c). Isorhythmic atrioventricular dissociation with type I synchronization is characterized by a rhythmic fluctuation of the interval between the P waves and the QRS complexes, most often with the P waves moving closer to and then farther away from the QRS complexes with a periodical variation of the PQ interval duration. P waves may sometimes be embedded in the QRS complexes or appear immediately after; however, because the difference between the two pacemaker discharge rates is very small, they are not usually seen after the descending branch of the R waves in the ST segment, or on top of the T waves (Fig. 14.3b).[18] Isorhythmic atrioventricular dissociation with type II synchronization is characterized by normal P waves and narrow QRS complexes showing a fixed position with respect to each other. The term *accrochage* was proposed to describe this electrocardiographic finding.[23] This term derives from the French word *accrocher*, which means “to hook something up”, to explain the fixed

relationship between the P waves and the QRS complexes (Fig. 14.3c).[18] In dogs, atrioventricular dissociation with type I synchronization is more common than type II synchronization.[18]

Different theories have been postulated to explain isorhythmic atrioventricular dissociation with synchronization. The main theories consider the mechanical effect, associated baroreflex mechanisms, and electrotonic influence of stroke volume on the sinus node discharge rate.[18,23] In isorhythmic atrioventricular dissociation with type I synchronization, when the P wave is located immediately before, immediately after, or embedded in the QRS complex, the systemic blood pressure falls, and right atrial pressure rises. The fall in arterial blood pressure is correlated with the loss of atrial contribution to the aortic stroke volume. This decrease in stroke volume stimulates the baroreflex mechanism, which induces an increase in sympathetic tone and, in turn, an increase in the sinus node discharge rate. As a result, the P wave comes before the QRS complex. Sinus node acceleration reestablishes a more normal atrioventricular activation sequence, thereby normalizing the stroke volume. The sinus node discharge rate therefore slows down and the P wave is embedded within or comes after the QRS complex. The cycle previously described then starts again. The discharge rate of the sinus node thus changes inversely to the left ventricular stroke volume and systolic arterial blood pressure via the baroreflex mechanisms originating from the sinoaortic baroreceptors located at the aortic arch.[18] Another theory is based on a mechanical concept. When the atria and ventricles contract simultaneously, the blood in the right atrium cannot empty into the right ventricle because the tricuspid valve is closed. The shortening of the atrial myocytes leads to distension of the fibrous, noncontracting portion of the atrial wall, which affects the junction of the cranial vena cava and atrial wall, where the sinus node is located. This results in stretching of the sinus node, with a consequent acceleration of the discharge rate.[18]

As previously explained, isorhythmic atrioventricular dissociation is present when the discharge rates of the sinus node and atrioventricular junction are similar. If the discharge rate of the sinus node is faster than that of the atrioventricular junction, sinus rhythm is present (Fig. 14.3a). Conversely, if the discharge rate of the atrioventricular junction is faster than that of the sinus node, retrograde atrial conduction of the wavefront

arising from the atrioventricular junction causes concentric retrograde activation of the atria with a 1:1 conduction. In this case, P waves are absent and concentric atrial activation is represented by P' waves that are negative in the inferior leads (II, III, and aVF), isodiphasic in lead I, and equally positive in aVR and aVL, with a mean electrical axis in the frontal plane between –80° and –100°. These P' waves are usually easily identifiable in the left precordial leads as positive atrial deflections located immediately after the descending branch of the QRS complexes. The P' waves are usually inscribed in the descending branch of the R waves or in the first portion of the ST segment, with a short RP' interval mimicking a S wave (pseudo-S wave) (Fig. 14.3d).[18]

Heart rate variability is usually decreased in junctional rhythms and focal junctional tachycardias.[2,3,24]

Nonparoxysmal junctional tachycardia presents a gradual onset and termination characterized by the warm-up and cool-down phenomena. Usually, the QRS complexes are narrow and preceded by a P' wave with concentric inferior-to-superior activation of the atria (mean electrical axis of the P' wave in the frontal plane, –80°/–100°), a P'Q interval that is shorter than normal, and a 1:1 atrioventricular conduction ratio (Fig. 14.4).

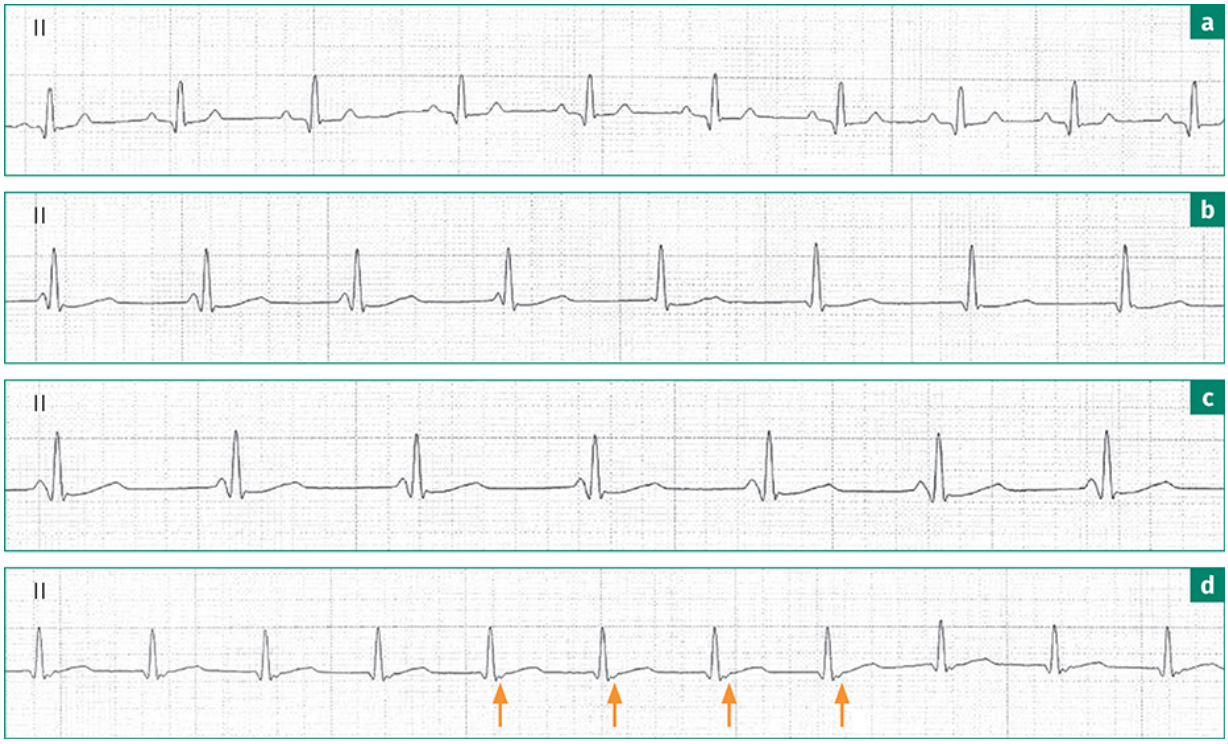


FIGURE 14.3. Transition from sinus rhythm (a) to focal junctional tachycardia with isorhythmic atrioventricular dissociation and type I synchronization (b), type II synchronization (c), and 1:1 ventriculoatrial concentric retroconduction (d) in a 4-year-old male Labrador Retriever. During sinus rhythm, the heart rate is 160 bpm, which is fast enough to overdrive the junctional rate. In b), the sinus rate slows down and focal junctional tachycardia occurs with a ventricular rate of 120 bpm and isorhythmic sinus P waves dissociated from the QRS complexes, with a rhythmic fluctuation of the interval between the P waves and QRS complexes and the P waves moving closer to and then farther away from the QRS complexes (type I synchronization). In c), the sinus P wave and junctional QRS complex rates become similar (*accrochage*); the P waves are seen before each QRS complex, with a slightly irregular PQ interval (type II synchronization). Finally, the junctional rate rises to 160 bpm and overdrives the sinus rate, leading to 1:1 concentric ventriculoatrial conduction. Negative P' waves (arrows) can be seen in lead II, with a duration of 40 ms and a superior axis (-90°). The RP' interval is short (60 ms). Lead II; speed, 50 mm/s; calibration, 5 mm/1 mV.



FIGURE 14.4. Nonparoxysmal junctional tachycardia in a 4-year-old Greyhound. Notice the narrow QRS complex (60 ms) rhythm with a rate of 140 bpm and negative P' waves before each QRS complex in the inferior leads (II, III, aVF), with a duration of 50 ms, concentric retrograde atrial activation, a superior axis shift (–90°), and a short P'Q interval (70 ms). Six limb leads (I, II, III, aVR, aVL, aVF); speed, 50 mm/s; calibration, 5 mm/1 mV.

CLINICAL PRESENTATION

Dogs and cats with junctional rhythms are usually affected by sinus node dysfunction, with a sinus node discharge rate slower than that of the atrioventricular junction area.[25]

Focal junctional tachycardia usually manifests at a median age of 7 years in Labrador Retrievers. This type of tachycardia may not be associated with clinical signs, or owners may report weakness. In approximately 50% of cases, focal junctional tachycardia is associated with decreased systolic function and correlated signs of left (pulmonary venous congestion/pulmonary edema) or right (abdominal or pleural effusion) congestive heart failure.[18]

OTHER METHODS OF EVALUATION

ECHOCARDIOGRAPHY

A complete echocardiographic examination should be performed in all patients with junctional tachycardia to assess for any concomitant acquired or congenital heart diseases and evaluate right and left ventricular systolic function.[18] Echocardiography is unremarkable in approximately 50% of cases. Dogs with incessant tachycardia and faster rates usually present with poor left and right systolic function with diffused hypokinesia (arrhythmia-induced cardiomyopathy) (see p. 395), increased end-diastolic volume of the ventricles, and biatrial enlargement. These echocardiographic findings lead to a higher likelihood of developing congestive heart failure.[18] The presence of focal junctional tachycardia and isorhythmic atrioventricular dissociation is also correlated with severe hemodynamic alterations. It has been demonstrated that important changes in cardiac dynamics are present due to the lack of normal sequential atrioventricular electrical and mechanical activity.[18] In normal conditions, the so-called atrial "booster pump" accounts for 15–20% of end-diastolic ventricular volume; it is partially or completely lost when atrioventricular synchrony is impaired, leading to a decrease in stroke volume. This mechanism is even more important in case of severe left ventricular systolic dysfunction. The most

important changes occur when the atrioventricular contraction sequence is reversed and the atria contracts against closed atrioventricular valves.[18]

ELECTROPHYSIOLOGICAL STUDY

Focal junctional tachycardia is a nonreentrant arrhythmia, so the lack of dependence on a critical coupling interval for tachycardia initiation, the irregularity of the tachycardia, and an inability to entrain the arrhythmia are the main differentiating findings from reentrant tachycardias.[2,3]

Focal junctional tachycardia can typically be initiated by rapid atrial or ventricular pacing or by isoprenaline infusion but not by programmed electrical stimulation, unless triggered activity is the underlying mechanism.[2,3]

The pivotal finding during the electrophysiological study is the presence of a His signal before each QRS complex (proof that the electrical impulse originates from the His bundle area), with a normal His–ventricular interval (range, 30–48 ms) compatible with antegrade conduction.[2,3,18]

When the discharge rates of the atrioventricular junction area and sinus node are similar, isorhythmic atrioventricular dissociation is recorded. In these patients, an atrial activation pattern arising from the high right atrium and dissociated from the ventricular activation arising from the His bundle is evident. In these cases, there are periods of variable atrial–His (AH) intervals (isorhythmic atrioventricular dissociation with type I synchronization) and periods of fixed AH interval (isorhythmic atrioventricular dissociation with type II synchronization) (Figs. 14.5a and 14.5b).[18] When the discharge rate of the atrioventricular junction is faster than that of the sinus node, retrograde atrial activation with 1:1 ventriculoatrial conduction is recorded. Concentric atrial activation occurs due to retrograde conduction of the impulses arising from the atrioventricular junction, with the atrial (A) signals following the ventricular (V) signals, a short VA interval duration, and the earliest site of atrial activation at the His bundle region (Fig. 14.5c).[18]

Other electrophysiological characteristics of focal junctional tachycardia include lack of resetting or termination of the tachycardia during His-refractory atrial extrastimulus pacing or when the HA interval is longer with ventricular pacing than during the arrhythmia.[2,3]

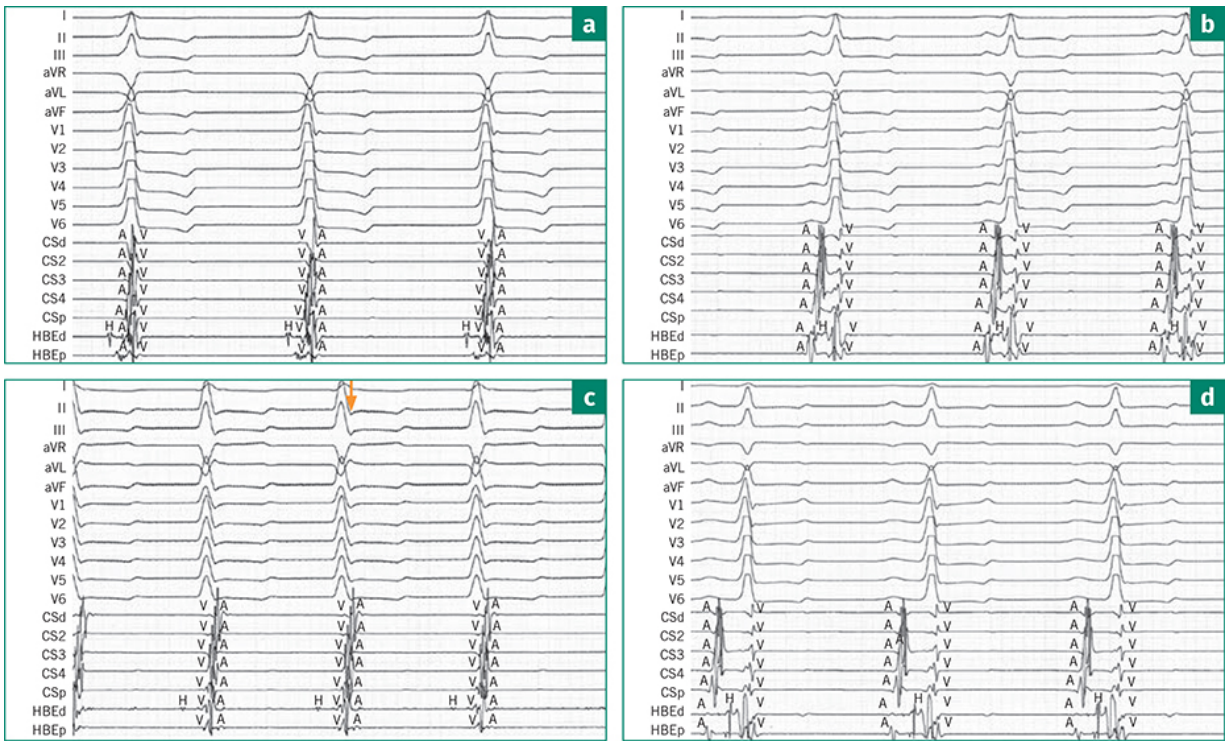


FIGURE 14.5. Focal junctional tachycardia before (a–c) and after (d) ablation of the posterior atrioventricular nodal pathway in a 9-year-old female Labrador Retriever with arrhythmia-induced cardiomyopathy. Endocardial mapping during isorhythmic atrioventricular dissociation and type I synchronization (a), type II synchronization (b), 1:1 ventriculoatrial atrial retroconduction (c), and sinus rhythm obtained after ablation (d). Notice the presence of sinus P waves moving across the narrow QRS complexes (70 ms) on the surface leads (I, II, III, aVR, aVL, aVF,V1, V2, V3, V4, V5, V6) during type I synchronization (a), while the P wave and QRS complex rates are isorhythmic during type II synchronization (b). P' waves (arrow) are visible after the QRS complexes during 1:1 ventriculoatrial atrial retroconduction (c), and P waves before the QRS complexes with a normal atrioventricular conduction time during sinus rhythm (d). The corresponding endocardial electrograms of the atrium (A), ventricle (V), and His region (H) and their relationship at different levels of the heart (coronary sinus ostium [CSp], great cardiac vein [CS2–CS4], posterior right atrium [CSd], His bundle [HBEd–HBEp]) are also shown. Speed, 150 mm/s; calibration, 22.5 mm/1 mV.

THERAPY

Treatment of junctional rhythms requires the assessment of sinus node function and, if necessary, pacemaker implantation (see p. 143).[25]

Focal junctional tachycardia can be treated both with pharmacological therapy and with radiofrequency catheter ablation.[26–31] In human beings, the recommended pharmacological treatments include amiodarone, ß-blockers, sotalol, flecainide, procainamide, and digoxin.[2,3] Ivabradine is a class 0 antiarrhythmic agent that can be used in the management of focal

junctional tachycardia as described in human medicine. Ivabradine has been used in monotherapy in infants with incessant focal junctional tachycardia and a structurally normal heart who were hemodynamically stable.[26,27] The drug has been demonstrated to be noninferior to amiodarone in converting postoperative focal junctional tachycardia to sinus rhythm, although rate control occurs earlier in patients receiving amiodarone.[28] Ivabradine has also been used to treat nonparoxysmal junctional tachycardia,[29] and it can be administered in association with procainamide for the management of pediatric postoperative focal junctional tachycardia.[30] Amiodarone, a class III agent, can be used as a prophylactic drug in children before open-heart surgery to reduce the incidence of postoperative focal junctional tachycardia.[31–33] Intravenous or oral administration of sotalol has also been described in the treatment of postoperative focal junctional tachycardia.[34]

Because focal junctional tachycardia in both human and veterinary medicine is often resistant to antiarrhythmic drug therapy, three-dimensional mapping and atrial overdrive pacing can be used for successful localization of the junctional ectopic focus in order to perform cryoablation or radiofrequency catheter ablation.[2,3,35,36] When there is ventriculoatrial conduction, ablation can be performed at the site of earliest retrograde atrial activation. When there is no ventriculoatrial conduction, ablation can be performed at the posterior septum close to the slow pathway location and, if it is not effective, moving anteriorly.[2,3] If cryoablation is available, it should be performed where cryomapping suppresses the arrhythmia. Although in human medicine, the success rate of radiofrequency catheter ablation and cryoablation has been reported to be approximately equal (82% and 84%, respectively), the risk of complete atrioventricular block seems to be significantly lower with cryoablation.[2,3,35,36]

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CHAPTER 15

Ventricular preexcitation and accessory pathway-mediated tachycardias

Roberto Santilli

DEFINITION

Accessory atrioventricular pathways are anomalous muscle bundles that directly connect the atrial to the ventricular myocardium, bypassing the His–Purkinje system.[1–5] Based on their position along the tricuspid and mitral valve annuli, they are classified as being right lateral, right posterior, right posteroseptal, midseptal, anteroseptal, left posterior, and left lateral.[6] In dogs, accessory pathways are mostly right-sided (91.7–96.4%) and single (90–92.1%), and rarely left-sided (3.6–8.3%) or multiple (7.9–10%).[3,5,7] Figure 15.1 shows the prevalence and anatomical distribution of accessory pathways in two large populations of dogs: right lateral (6–37.5%), right posterolateral (9–9.6%), right posterior (15.7–21.8%), right posteroseptal (42.2–46.9%), left posteroseptal (2.4–5.6%), left lateral (1.1–1.2 %), midseptal (7.8–10.8%), and anteroseptal (1.1–6%).[3,5,7]

During the early phases of cardiac development, the atrial and ventricular working myocardium is continuous throughout the atrioventricular junction. In the late fetal phase, as in the adult heart, a complete separation between the two regions appears, with the His tissue remaining the only connection between the atrial and ventricular myocardium.[8] Different hypotheses have been proposed to explain the occurrence of accessory pathways, since a

simple separation defect is very unlikely. During formation of the atrioventricular groove, the atrioventricular junctional myocardium becomes part of the definitive atrial myocardium, except for the area resulting from the lack of fusion of the tissue of the atrioventricular groove and the dorsal atrioventricular cushion. The right atrioventricular separation takes place earlier than the formation of the left-sided fibrous annulus. Accessory atrioventricular pathways may persist into adult life due to an incomplete fusion of the groove and cushion tissues.[8] Alteration of periostin formation and epicardium-derived cell migration may also play a role in fibrous ring formation and the occurrence of accessory atrioventricular pathways.[9,10] A mice model showed the occurrence of accessory pathways secondary to a defective Tbx-dependent development of the atrioventricular canal myocardium.[11]

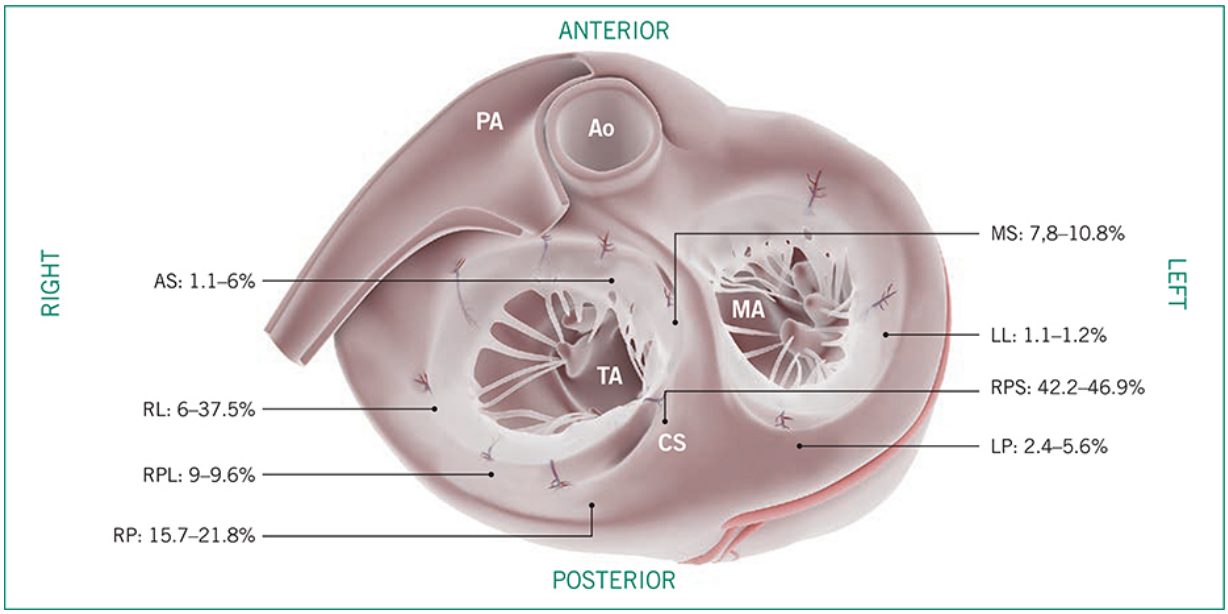


FIGURE 15.1. Anatomical distribution of 81 accessory pathways found in 76 dogs around the tricuspid valve annulus (TA) and mitral valve annulus (MA). Ao, aorta; PA, pulmonary artery; CS, coronary sinus ostium; RPS, right posteroseptal; RP, right posterior; RPL, right posterolateral; RL, right lateral; AS, anteroseptal; MS, midseptal; LP, left posterior; LL, left lateral. Source: Modified from Santilli R. et al.[5]

Accessory pathways can have unidirectional antegrade or retrograde conduction or bidirectional conduction with electrocardiographic signs of manifest preexcitation syndrome. In dogs, bidirectional conduction has been recorded in 31.3–43.8% of dogs with accessory pathways, a

percentage that decreases to 29.2% if only Labrador Retrievers are considered. Concealed or unidirectional retrograde conduction has been reported in almost 2/3 of the dogs studied (56.2–68.7%), while unidirectional antegrade conduction has been reported just in 1–1.2% of the cases. [3,5,7]

Retrograde conduction is crucial to mediate and maintain atrioventricular reciprocating tachycardias. In 92.1–100% of dogs, retrograde conduction along the accessory pathway is rapid, nondecremental and mediates orthodromic atrioventricular reciprocating tachycardia, while in 6.5% of the cases, conduction is slow and decremental, similarly to atrioventricular node conduction, and mediates permanent junctional reciprocating tachycardia (Coumel tachycardia).[3,5,7,12]

Of the different preexcited tachycardias associated with antegrade conduction along the accessory pathway reported in humans, such as antidromic atrioventricular reciprocating tachycardia, focal atrial tachycardia, and atrial fibrillation, only the latter has been described in dogs.[13]

Electrocardiographic features of preexcitation syndrome have also been described in cats, frequently in association with a cardiomyopathy, but definitive data regarding the localization and electrophysiological properties of the accessory pathways are lacking since no endocardial mapping findings are available.[14]

ELECTROPHYSIOLOGICAL MECHANISM

In dogs, atrioventricular accessory pathways are muscle bundles that most often have either antegrade and/or retrograde rapid, nondecremental conduction. As a result, during sinus rhythm, 1/3 of dogs with accessory pathways present with ventricular preexcitation, but rarely with preexcited tachycardia. In contrast, 92.1–100% of them have orthodromic atrioventricular reciprocating tachycardia. In few cases (6.5%), right posteroseptal accessory pathways have decremental, concealed retrograde conduction, which mediates permanent junctional reciprocating tachycardia.[3,5,7,12]

Orthodromic atrioventricular reciprocating tachycardia and permanent junctional reciprocating tachycardia are anatomical macroreentrant arrhythmias also called circus movement tachycardias. The anatomical circuit is the same for both arrhythmias and includes the atria, atrioventricular node, His–Purkinje system, ventricles, and accessory pathway. The atrial impulse travels along the atrioventricular node and the His–Purkinje system, activates the ventricles, and then returns to the atria along the accessory pathway. The only difference between these two tachycardias is the velocity of retrograde conduction of the accessory pathway: 1) in orthodromic atrioventricular reciprocating tachycardia, conduction is rapid and nondecremental, so atrial activation occurs during the ST segment with a fixed ventriculoatrial time; 2) in permanent junctional reciprocating tachycardia, conduction is slow and decremental, so that atrial depolarization occurs after ventricular repolarization (T wave), with a variable ventriculoatrial time.[3,5,7,12]

Antidromic atrioventricular reciprocating tachycardia follows the same circuit, but the impulse travels the other way around: from the atria to the ventricles along the accessory pathway, and then back to the atria along the atrioventricular node.[6] This type of tachycardia has not been documented in dogs, probably because most large breed dogs (47–68%) with accessory pathways do not have retrograde conduction along the atrioventricular node.[5,7]

In other forms of preexcited tachycardia such as atrial fibrillation, atrial flutter, or focal atrial tachycardia, the accessory pathway is a bystander and depending on its refractory period, the atrial impulse can reach the ventricle with different degrees of preexcitation, bypassing the normal His–Purkinje fibers.[6]

ELECTROCARDIOGRAPHIC FINDINGS

Surface electrocardiography has been widely used to diagnose preexcitation syndromes, orthodromic atrioventricular reciprocating tachycardia and permanent junctional reciprocating tachycardia.[3,7,12,15]

VENTRICULAR PREEXCITATION

The term ventricular preexcitation refers to the propagation of an atrial impulse along an accessory pathway with antegrade conduction properties, which allows early activation of a portion of the ventricular myocardium, earlier than it would be if the atrial impulse only reached the ventricles via the atrioventricular node and the specialized conduction system.[5–7] The term syndrome is used when the electrocardiographic or endocardial mapping evidence of ventricular preexcitation is associated with an accessory pathway–mediated tachycardia.[2]

Ventricular preexcitation is manifest or persistent in 76.9% of dogs and intermittent in 23.1%. Intermittent ventricular preexcitation is usually correlated with right posteroseptal and right posterior accessory pathways.[16]

The electrocardiographic features of ventricular preexcitation are a short PQ interval (<60 ms in dogs and <50 ms in cats), a wide QRS complex (≥80 ms in dogs and ≥50 ms in cats), and the presence of a delta wave and repolarization abnormalities (ST segment and T wave) (Figs. 15.2a–15.2c).[5,7,16,17]

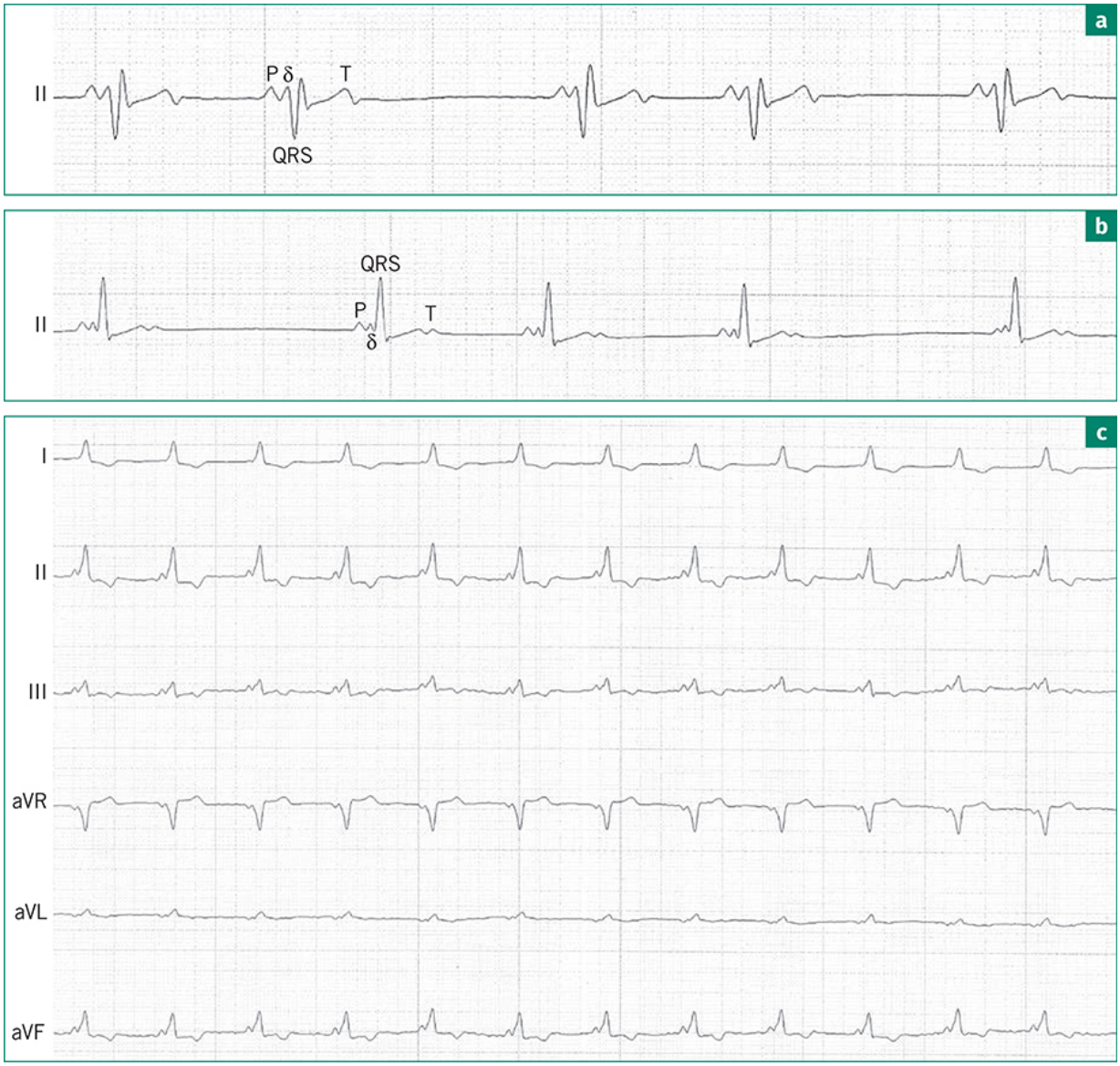


FIGURE 15.2. a) Ventricular preexcitation pattern in a 2-year-old female Golden Retriever with more than two deflections (lead II; speed, 50 mm/s; calibration, 5 mm/1 mV). b) Ventricular preexcitation pattern in a 6-month-old male Labrador with two deflections (lead II; speed, 50 mm/s; calibration, 5 mm/1 mV). c) Ventricular preexcitation pattern in a 5-month-old male domestic shorthair cat. Six limb leads (I, II, III, aVR, aVL, aVF); speed, 50 mm/s; calibration, 10 mm/1 mV.

The morphology of the δQRS complex in lead II shows more than two deflections in 69.2% of dogs (Fig. 15.2a), and two or less than two deflections in 30.8% of dogs (Fig. 15.2b).[16] The median δQRS complex axis in the frontal plane is usually +68° (interquartile range [IQR], 52.5) for right anterior accessory pathways, with a configuration of left bundle branch block (Fig. 15.3); –43.5° (IQR, 27.25) for right posterior accessory

pathways; and –24° (IQR, 24) for right posteroseptal accessory pathways, with a configuration of left anterior fascicular block (Fig. 15.4).[16]

In lead II, the polarity of the δ wave is positive in 100% of right anterior accessory pathways and negative in 63.6% of posteroseptal accessory pathways and 80% of right posterior accessory pathways. All right-sided accessory pathways have the same δQRS configuration in precordial leads; V1 presents a R/S ratio <1 and all leads from V2 to V6 present an R/S ratio >1 (Figs. 15.3 and 15.4).[16]

Variations in the degree of ventricular preexcitation can be found in case of preexcitation alternans[18] or in case of concertina effect.[19] Preexcitation alternans is characterized by a beat-to-beat alternation of normal and preexcited QRS complexes with no changes in heart rate and is due to regular antegrade block of an accessory pathway with a relatively long antegrade effective refractory period.[18] The concertina effect refers to the progressive shortening of the Pδ interval and corresponding widening of the QRS complex.[19] The presence of an accessory pathway with a long antegrade effective refractory period should also be suspected in this case (Fig. 15.5).

Differential diagnoses for ventricular preexcitation include enhanced atrioventricular conduction and focal junctional tachycardia with isorhythmic atrioventricular dissociation and type II synchronization.

Enhanced atrioventricular conduction is characterized by the presence of a short PQ interval (<60 ms in dogs) with a normal QRS complex (Fig. 15.6). Controversy exists regarding the structural determinant of subnormal atrioventricular nodal conduction shortening; suggested determinants include: 1) atrioventricular nodal bypass tract and 2) development disturbances altering atrioventricular nodal size and structure.[20]

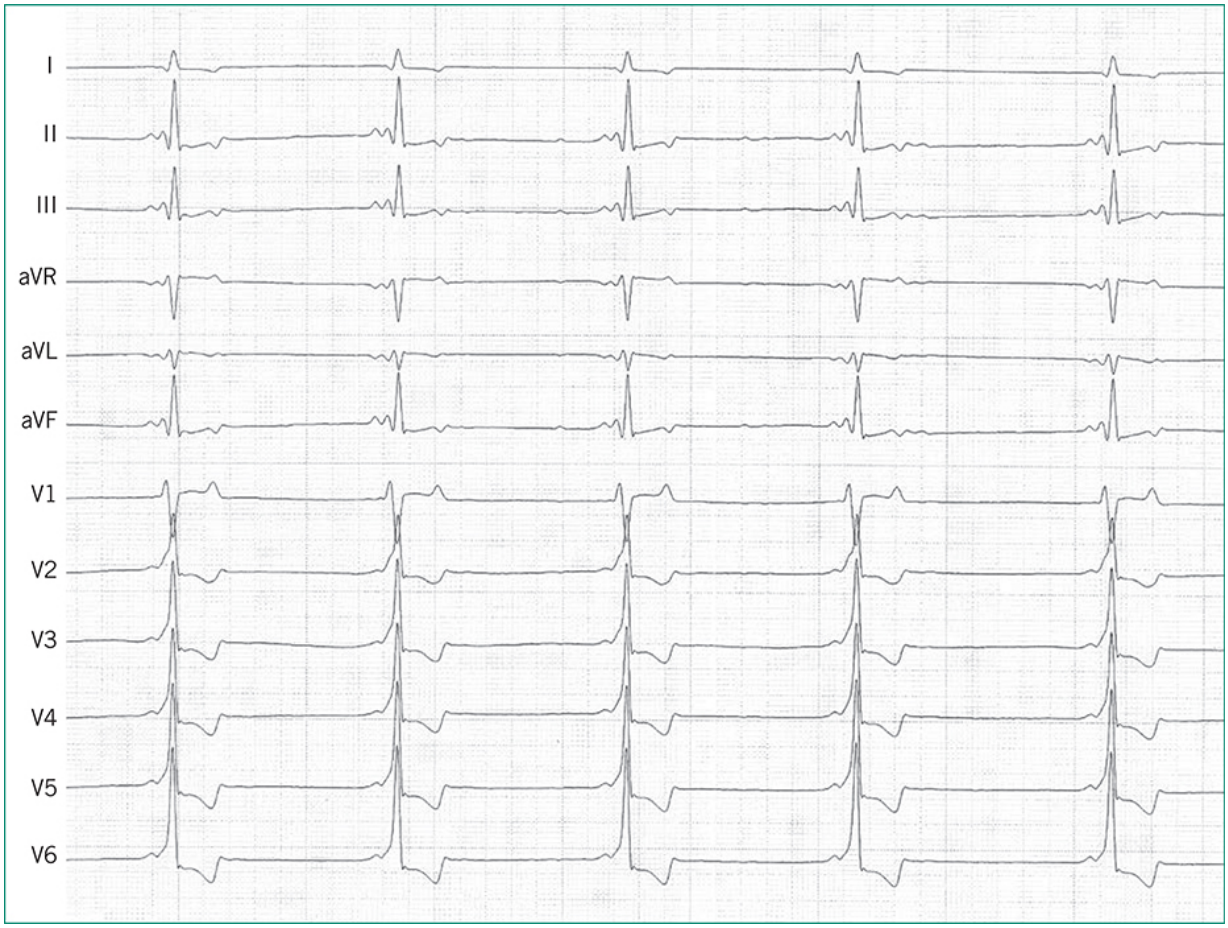


FIGURE 15.3. Ventricular preexcitation in a 1-year-old female Golden Retriever with a right anterior accessory pathway. Note the δQRS complex morphology in the frontal plane typical of a left bundle branch block (+ 60°), negative V1, and positive V2 to V6. Twelve leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6); speed, 50 mm/s; calibration, 5 mm/1 mV.

The presence of accessory conduction with atrionodal or atriofascicular fibers has been postulated in case of enhanced atrioventricular conduction in humans. These fibers are sometimes also present in patients with supraventricular tachycardias; the term of Lown–Ganong–Levine syndrome has been used in the past to describe this situation, but it is now outdated. Other theories that have been postulated to explain enhanced atrioventricular conduction are related to atrioventricular size and development. A smaller atrioventricular node has faster conduction, and, similarly, a difference in cell size or number, fast or slow channel responsiveness, and resistance of intercellular connections may be related to atrioventricular conduction time differences.[20]

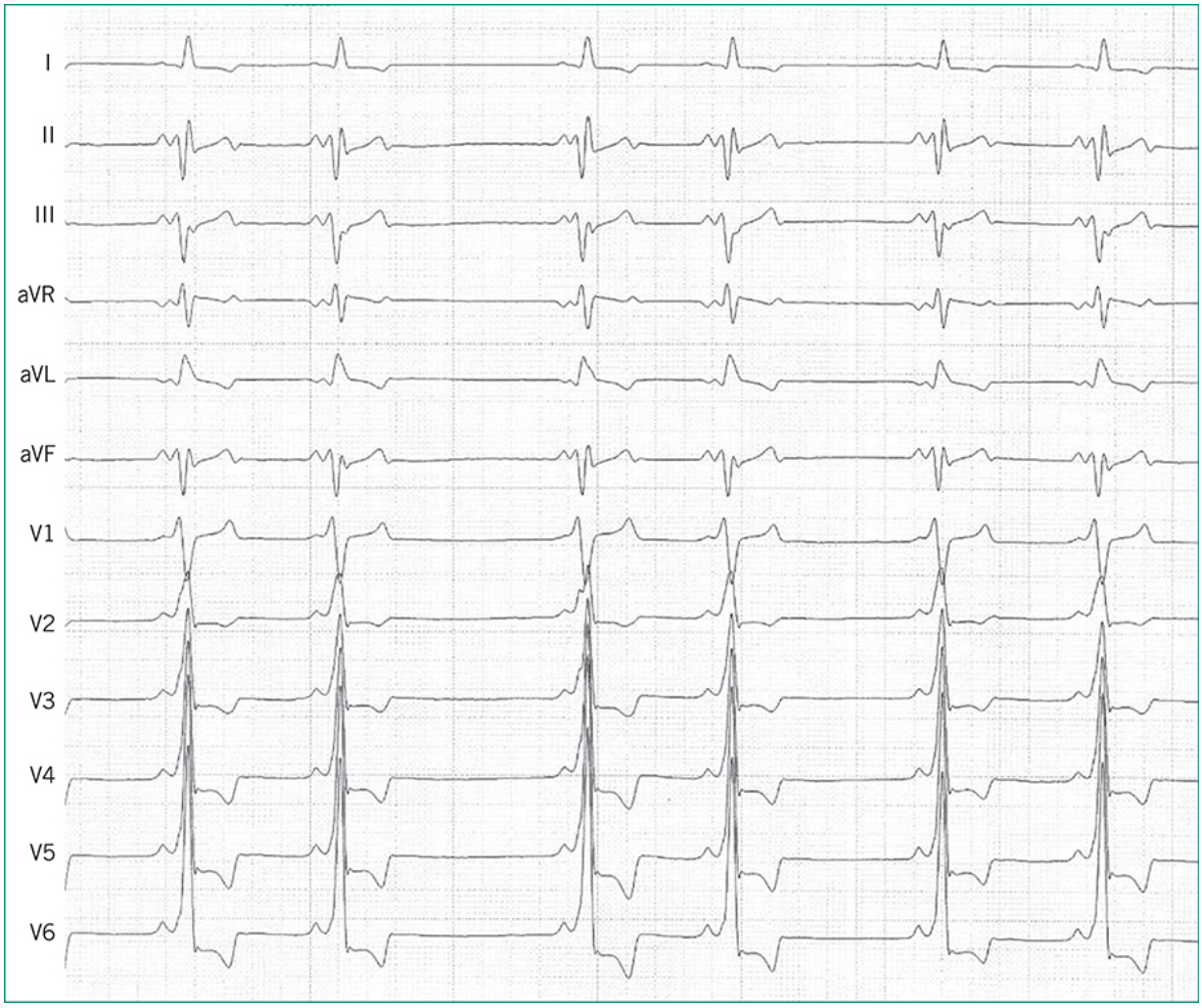


FIGURE 15.4. Ventricular preexcitation in a 2-year-old male Golden Retriever with a right posterior accessory pathway. Note the δQRS complex morphology in the frontal plane typical of a left anterior fascicular block (–30°), negative V1, and positive V2 to V6. Twelve leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6); speed, 50 mm/s; calibration, 5 mm/1 mV.

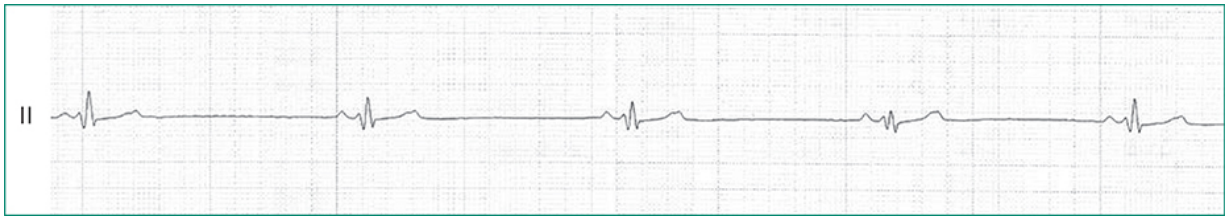


FIGURE 15.5. Concertina effect in a 2-year-old male Labrador Retriever with ventricular preexcitation. Note the progressive variation of the Pδ interval and QRS duration over time. Lead II; speed, 50 mm/s; calibration, 5 mm/1 mV.



FIGURE 15.6. Sinus rhythm with enhanced atrioventricular conduction in a 7-year-old male Chihuahua. Note the presence of a short PQ interval (50 ms), with a normal QRS complex duration and axis. Lead II; speed, 50 mm/s; calibration, 5 mm/1 mV.

Focal junctional tachycardia with isorhythmic atrioventricular dissociation and type II synchronization can mimic ventricular preexcitation since the PQ interval is very short in both conditions. However, in the former arrhythmia, the position of the P wave in relation to the QRS changes over a few milliseconds, and the QRS complex is narrow with a normal configuration, which confirms conduction along the His–Purkinje system.[21]

ORTHODROMIC ATRIOVENTRICULAR RECIPROCATING TACHYCARDIA

Orthodromic atrioventricular reciprocating tachycardia is the most common supraventricular tachycardia mediated by an accessory pathway in the dog (92.1–100%).[3,5,7,22] This tachycardia is characterized by narrow QRS complexes (50–70 ms) with an atrioventricular conduction ratio of 1/1 in 100% of cases and a ventricular rate ranging from 250 to 428 bpm at admission, before any medication is given, and 221–281 bpm during endocardial mapping under general anesthesia (Figs. 15.7a and 15.7b).[3,5,7,15,22] The RR interval during orthodromic atrioventricular reciprocating tachycardia is regular, with cycle length irregularity or alternans in 4–14% of cases (Fig. 15.7c). QRS complex alternans, a variation in the QRS amplitude of at least 0.1 mV on a beat-to-beat basis, is best visible in the left precordial leads (V2–V6) in 46–86% of cases and, when present, it should be considered an independent predictor of this type of tachycardia.[5,7,15,22]

In 93–100% of cases, retrograde eccentric ventriculoatrial activation is present with visible atrial depolarizations (P') in the inferior leads (II, III, aVF) with an inferior-to-superior axis (from –90° to –78°). The P' wave is

therefore negative in the ST segment of the inferior leads and positive in aVR (another independent predictor of the type of tachycardia) (Figs. 15.7a, 15.7b and 15.8).[3,5,7,15,22]

The RP' interval is shorter (from 77 ms prior to any medication to 68.2–85 ms during anesthesia for endocardial mapping) than the P'R interval (from 107 ms prior to any medication to 140–170 ms during anesthesia). The RP'/P'R ratio ranges from 0.54 to 0.78; orthodromic atrioventricular reciprocating tachycardia is therefore classified in the group of short RP' tachycardias.[3,5,7,15,22] The median QT interval in dogs with orthodromic atrioventricular reciprocating tachycardia ranges between 160 and 194 ms.

Orthodromic atrioventricular reciprocating tachycardia can be either paroxysmal and repetitive, sustained, or incessant. Very frequently (78.6% of cases) during periods of nonpreexcited sinus rhythm, blocked reciprocating beats can be seen with a retrograde P' wave in the ST segment and antegrade conduction blocked within the atrioventricular node (Fig. 15.9). This electrocardiographic feature helps in the diagnosis of a concealed accessory pathway with unidirectional retrograde conduction.[7]

In few cases, when the tachycardia paroxysm starts after a long pause of sinus rhythm, a phase 3 aberrancy (or *linking*) can be seen in the first beats (Fig. 15.10), and even more rarely, periods of fibrillary conduction can be observed after the first atrial retroconduction (Fig. 15.11). This event can be caused by a rapid retroconduction in the posterior right atrium, an area with slow and fragmented conduction.

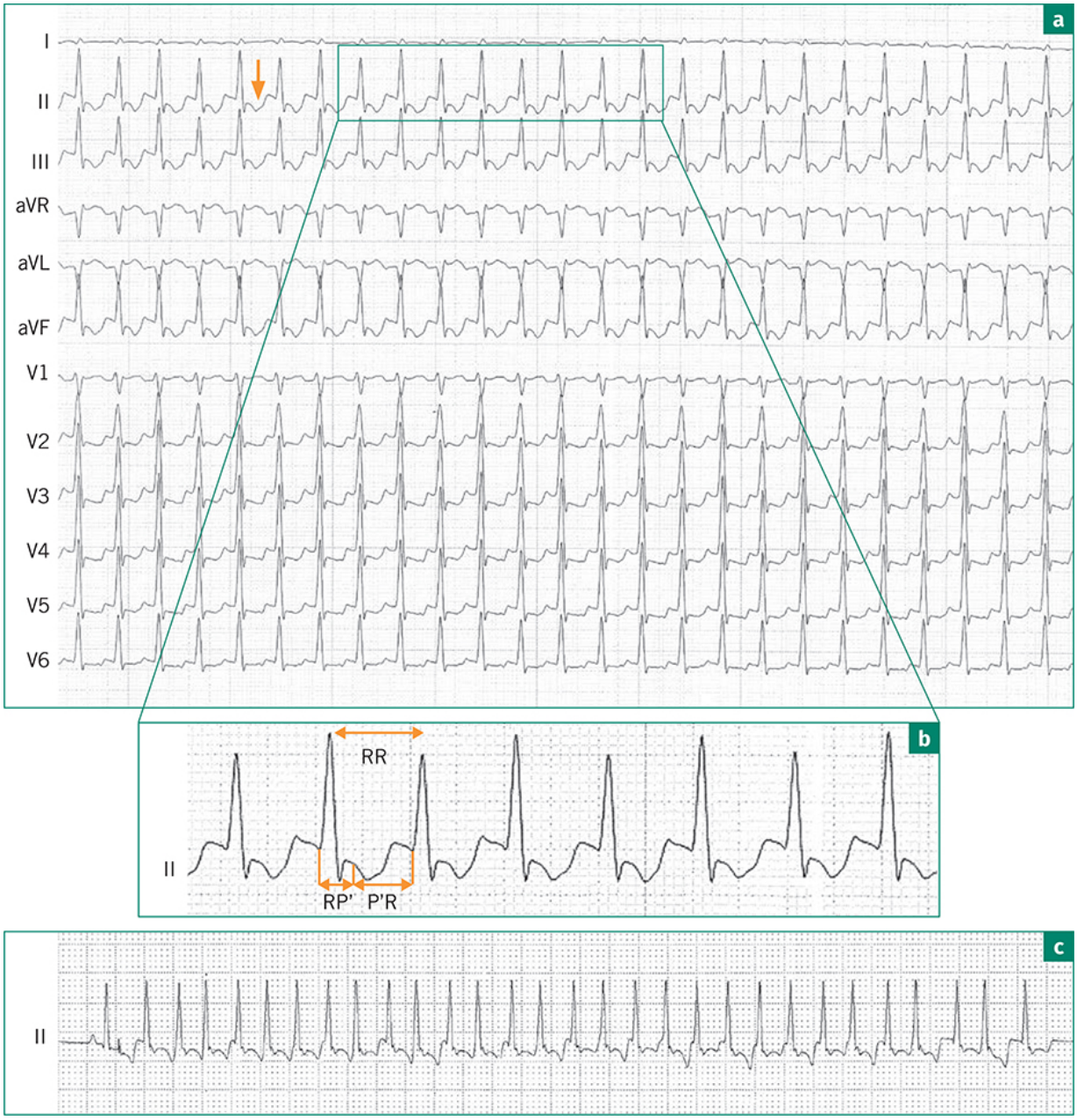


FIGURE 15.7. a) Orthodromic atrioventricular reciprocating tachycardia in an 18-month-old male Labrador. Note the presence of narrow QRS complexes (60 ms) with a ventricular rate of 300 bpm, QRS complex alternans visible in leads II and V2, and a P' wave in the ST segment (arrow). Twelve leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6); speed, 50 mm/s; calibration, 5 mm/1 mV. b) Zoom of lead II in the previous electrocardiogram to show the RP' and P'R intervals and RP'/P'R measurements. Orthodromic atrioventricular reciprocating tachycardia is a short RP' tachycardia (RP' <50% of the RR interval). In this case, the RP' interval measures 80 ms, the P'R interval 130 ms, and the RP'/P'R ratio is 0.61. Lead II; speed, 50 mm/s; calibration, 5 mm/1 mV. c) Orthodromic atrioventricular reciprocating tachycardia with cycle length alternans in a 1-year-old female Cavalier King Charles Spaniel. Note in the initial part of the tracing the variation on a beat-to-beat basis of the RR interval of 20 ms. Lead II; speed, 25 mm/s; calibration, 5 mm/1 mV.



FIGURE 15.8. Orthodromic atrioventricular reciprocating tachycardia in a 7-month-old male Exotic cat. Note the presence of narrow QRS complexes (35 ms) with a ventricular rate of 420 bpm and a P' wave in the ST segment (arrow). Six limb leads (I, II, III, aVR, aVL, aVF); speed, 50 mm/s; calibration, 10 mm/1 mV.

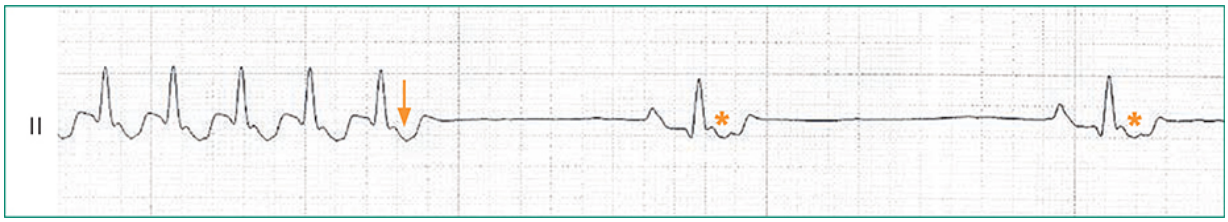


FIGURE 15.9. Orthodromic atrioventricular reciprocating tachycardia with blocked reciprocating beats in a 9-month-old male Swiss Shepherd. Note the presence of a narrow QRS complex (60 ms) tachycardia with a rate of 270 bpm in the first part of the tracing, with a P' wave in the ST segment; the tachycardia suddenly stops in the atrioventricular node (P' wave [arrow] in the ST segment not followed by a QRS complex). The following two sinus beats are blocked reciprocating beats; P' is inscribed in the ST segment (*).

PERMANENT JUNCTIONAL RECIPROCATING TACHYCARDIA

Permanent junctional reciprocating tachycardia or Coumel tachycardia has been described in 6.5% of dogs with concealed right posteroseptal accessory pathways.[5,12] This tachycardia is commonly incessant, with a median ventricular rate of 230 bpm, narrow QRS complexes (60–70 ms), and long RP' intervals (140 ms) with a RP'/P'R ratio of 1.16. The P' wave is visible in the inferior leads, with an inferior-to-superior axis (–45° to –38°). It is negative in the inferior leads (II, III and aVF) and positive in aVR. Due to the electrophysiological features of retrograde conduction along accessory pathways, permanent junctional reciprocating tachycardia can present cycle length irregularity, and it can therefore mimic a focal atrial tachycardia arising from the coronary sinus (Figs. 15.12a and 15.12b).[5,12]

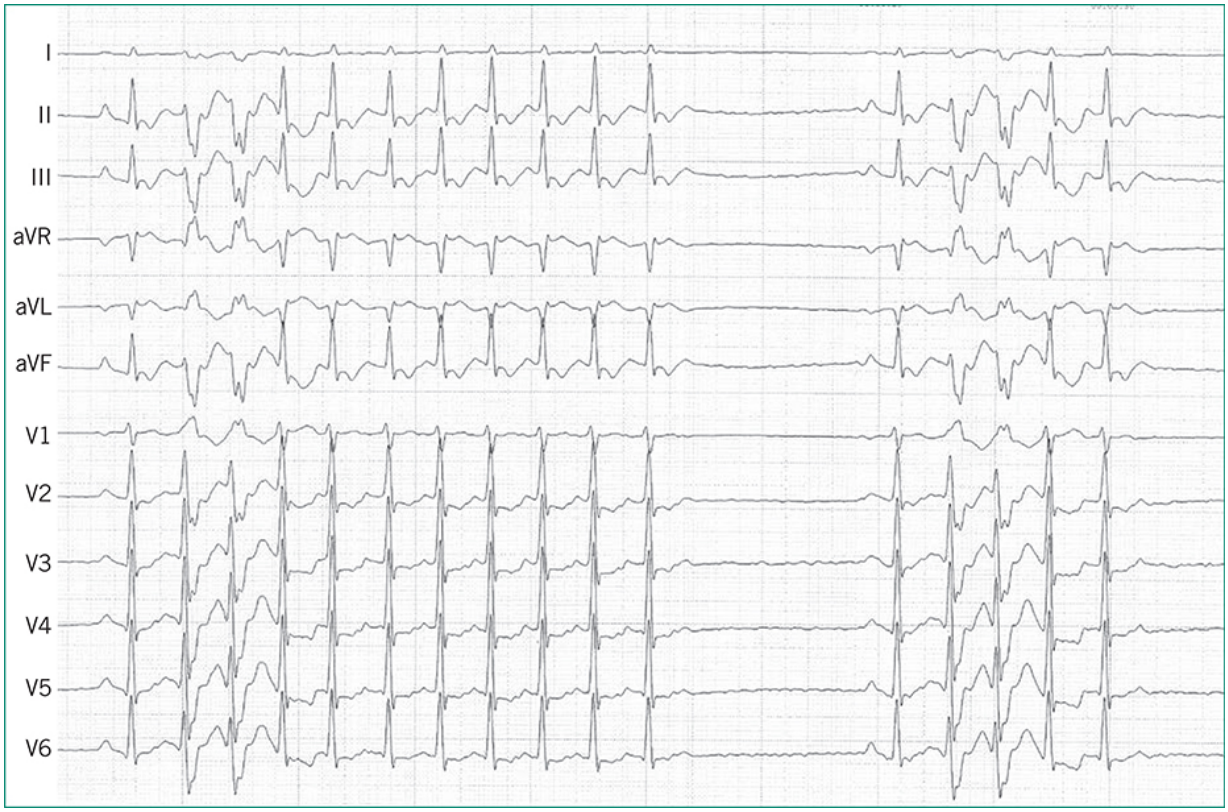


FIGURE 15.10. Orthodromic atrioventricular reciprocating tachycardia repetitive runs with first beat linking in a 9-month-old male Labrador. Note how, after each sinus beat, tachycardia begins with two wide QRS complexes with a right bundle branch block morphology in the 12 leads, which is suggestive of sustained tachycardia-dependent aberrancy (phase 3 linking). Twelve leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6); speed, 50 mm/s; calibration 5 mm/1 mV.



FIGURE 15.11. Fibrillatory conduction after atrial retroconduction along an accessory pathway in a 6-month-old male Golden Retriever. Note the eccentric retroconduction with a P' wave in the ST segment (first arrow) after the first sinus beat, followed by disorganized atrial activity preceding the following QRS complex. The second, fifth, and sixth QRS complexes are all blocked reciprocating beats (P' in the ST segment, arrows). Lead II; speed, 50 mm/s; calibration, 5 mm/1 mV.

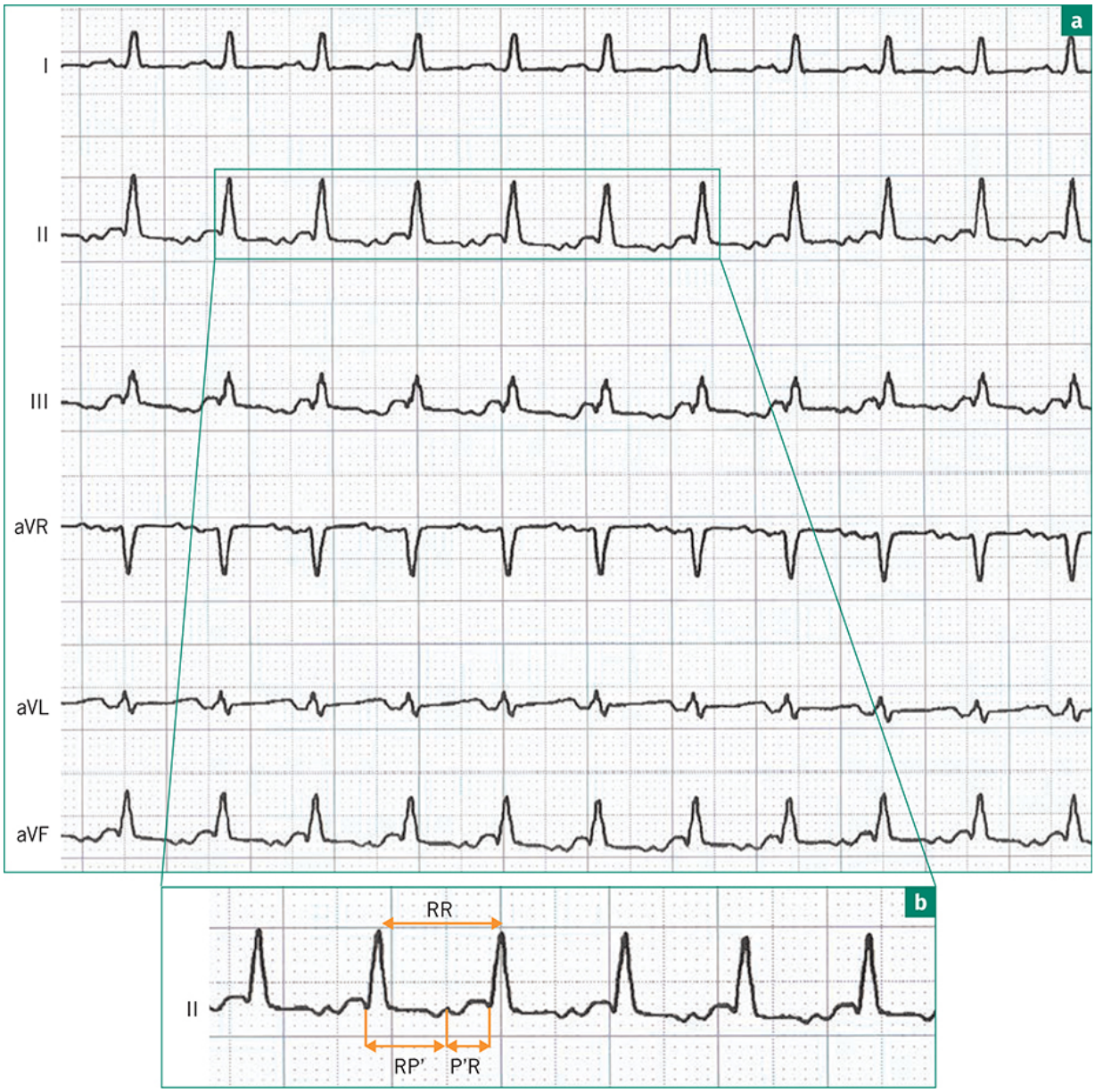


FIGURE 15.12. a) Permanent junctional reciprocating tachycardia or Coumel tachycardia in an 11-month-old female Labrador Retriever. Note the presence of a narrow QRS complex (40 ms) tachycardia with a ventricular rate of 270 bpm and the presence of a P' wave after the T wave (RP' of 180 ms). Six leads (I, II, III, aVR, aVL, aVF); speed, 50 mm/s; calibration 5 mm/1 mV. b) Zoom of lead II of the previous electrocardiogram to show the RP' and P'R intervals and RP'/P'R measurements. Permanent junctional reciprocating tachycardia is a long RP' tachycardia (RP' >50% of RR interval). In this case, the RP' interval measures 180 ms, the P'R interval 80 ms, and the RP'/P'R ratio 2.25. Lead II; speed, 50 mm/s; calibration, 5 mm/1 mV. ECG from Santilli R. et al. *Electrocardiography of the dog and cat*. 2nd ed. 2018, Edra S.p.A.

PREEXCITED TACHYCARDIAS

Antidromic conduction of atrial depolarization can be observed in patients with atrioventricular accessory pathways mediating preexcited tachycardias such as antidromic atrioventricular reciprocating tachycardia, preexcited atrial fibrillation, and preexcited focal or macroreentrant atrial tachycardias.[6]

So far, the only proven preexcited tachycardia reported in dogs is preexcited atrial fibrillation.[13] This is a life-threatening arrhythmia because of the fast heart rate and the absence of the filtering effect of the atrioventricular node. Preexcited atrial fibrillation is characterized by a fast ventricular rate (270 bpm), irregular RR intervals, wide QRS complexes (100 ms), and a δ wave preceding all QRS complexes (Fig. 15.13).[13]

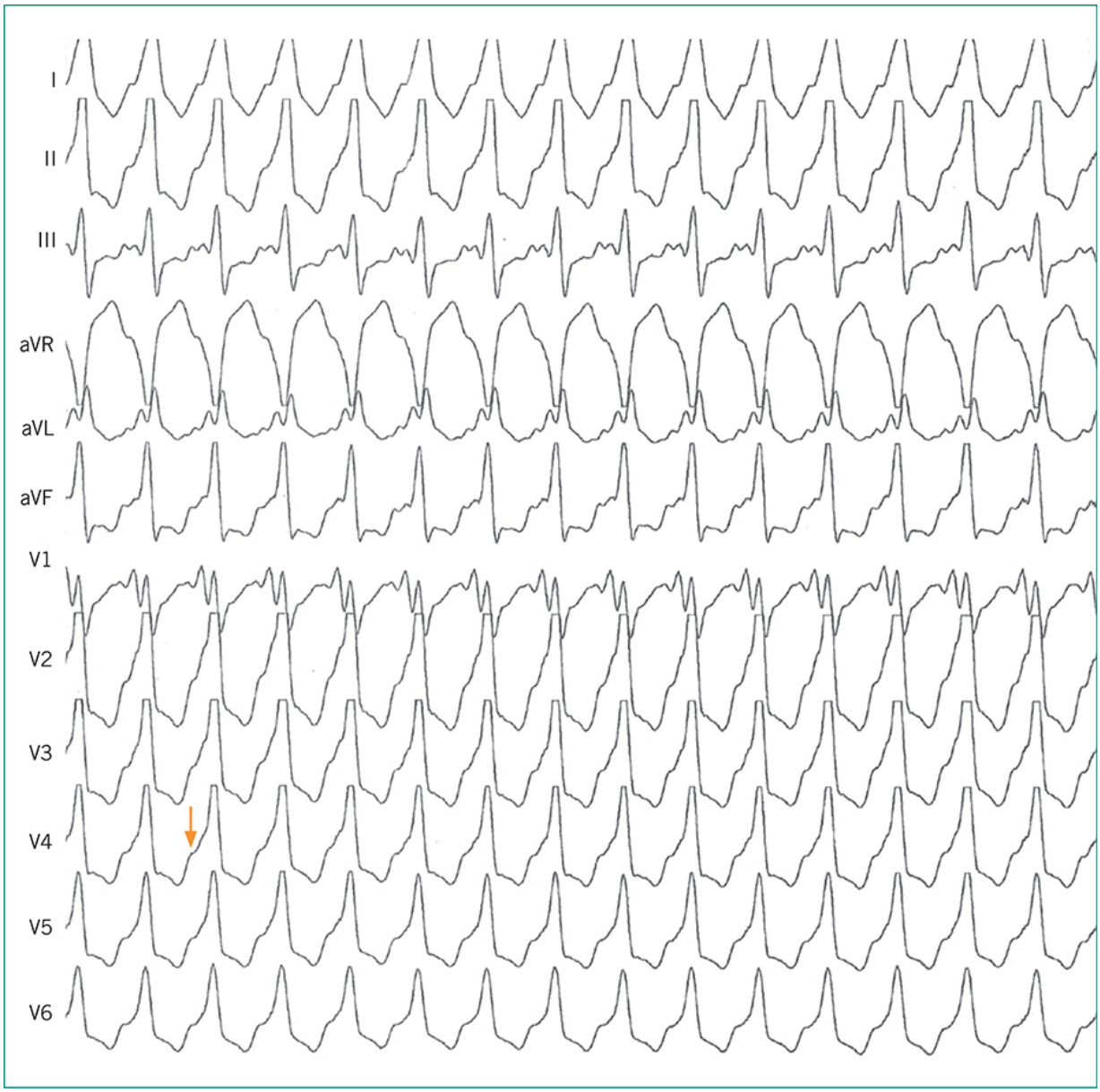


FIGURE 15.13. Preexcited atrial fibrillation in a 2-year-old male Golden Retriever. Note the presence of a wide QRS complex (80 ms) tachycardia with a ventricular rate of 280 bpm and a left bundle block morphology. At the beginning of the QRS complex, a δ wave is evident (arrow), particularly in the left precordial leads (V2–V6). Slight variations of the RR interval become evident and are suggestive of atrial fibrillation. Twelve leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6); speed, 50 mm/s; calibration, 5 mm/1 mV.

CLINICAL PRESENTATION

Accessory pathway–mediated tachycardias are very common in Labrador Retrievers (38.1–47.2%), Golden Retrievers (7.9–8%), English Bulldogs

(4.5–6.6%), and Boxers (4–5.6%). Males are overrepresented (67.4–72.3%), and the median age at presentation is 16–27 months. The time elapsed between the onset of the clinical signs and ablation is around 4 months.[3,5,7,12]

Dogs are usually referred to the electrophysiology laboratory after detection of the presence of supraventricular tachycardia (61%) or ventricular preexcitation (5%). The most common clinical signs correlated with reciprocating tachycardias are lethargy (69.7–85.1%), hyporexia (52.8%), ascites (37%), vomiting (37%), head bobbing or chest pulsations (30–32%), syncope (14.6%), weight loss and cachexia (3.3%), and cardiac arrest (2.2%).[3,5,7,12]

Congestive heart failure is present in 38.2% of the dogs (left in 15.7%, right in 12.4%, and biventricular in 10.1%). Congestive heart failure is not related to the tachycardia rate or to the age at presentation.[7]

Cats with ventricular preexcitation are usually presented for lethargy (58.8%), tachypnea (52.9%), and syncope (17.6%), while signs of congestive heart failure are uncommon (17.6%).[17]

OTHER METHODS OF EVALUATION

ECHOCARDIOGRAPHY

Segmental thinning and dyskinesia of the septal myocardium has been found in dogs with ventricular preexcitation. This focal hypotrophy has been attributed to the early segment activation and contraction under a low preload, with a diminished workload and displacement of the myocardium towards the right ventricle, mimicking an aneurysm.[23]

Echocardiography in dogs with reciprocating tachycardias often shows a dilated cardiomyopathy phenotype, known as tachycardia-induced cardiomyopathy, characterized by left ventricular systolic dysfunction (46.1%), left ventricular dilation (34.8%), left atrial dilation (33.7%), right ventricular dilation (6.74%) and right atrial dilation (22.4%). No relationship has been found between the presence of left ventricular systolic dysfunction and the length of the tachycardia cycle before the administration of medication, the time from initial diagnosis, or the age at

the time of ablation. Functional mitral or tricuspid valve regurgitation has been found in 49.4% and 22.4% of patients respectively.[7]

In around 13% of the cases, concomitant congenital disorders can be found in association with the presence of accessory pathways, and include tricuspid valve dysplasia (5.6–9%), mitral valve dysplasia (2.2%), persistent left cranial vena cava (4%), middle vein diverticulum (4%), patent ductus arteriosus (1.1%), and subaortic stenosis (1.1%).[3,5,7]

Cats with accessory pathways have been shown to have larger atria and a thicker left ventricular thickness compared to a control group.[17]

ELECTROPHYSIOLOGICAL STUDY

During an electrophysiology study, the electrophysiological properties and location of accessory pathways can be assessed and reciprocating tachycardias induced and mapped.

Antegrade conduction along the accessory pathway is usually less robust than retrograde conduction. The reported median antegrade effective refractory period is 158 ms (110–310 ms) and the shortest cycle length at which 1:1 antegrade conduction during right atrial pacing occurs ranges from 145 ms to 420 ms, with only 5.2% of cases at less than 200 ms. The cycle length at which 1:1 antegrade conduction occurs (200 ms versus 450 ms) is shorter with manifest preexcitation than with intermittent preexcitation.[3,5,7]

The effective retrograde refractory period of nondecremental bidirectional or concealed accessory pathways ranges from 120 ms to 180 ms, and the shortest cycle length at which 1:1 retrograde conduction during right ventricular pacing occurs ranges from 120 ms to 200 ms. The median effective retrograde refractory period of decremental concealed accessory pathways is usually <150 ms, and the shortest cycle length at which 1:1 retrograde conduction during right ventricular pacing occurs ranges from 120 ms to 140 ms.[3,5,7,12]

Accessory pathways can be localized using fluoroscopic and intracardiac electrocardiographic guidance. During sinus rhythm or atrial pacing, the accessory pathway is the earliest site of ventricular activation with the shortest atrioventricular conduction time and a distal ablation electrode unipolar recording with a sharp QS morphology (Fig. 15.14), while during reciprocating tachycardia or ventricular pacing, it is the earliest site of atrial

activation with the shortest ventriculoatrial conduction time (32–80 ms) and a distal ablation electrode unipolar recording with a sharp QS morphology (Fig. 15.15).[3,5,7,12] During ventricular preexcitation the atrial–His (AH) interval ranges from 40 to 125 ms, while the His–ventricular (HV) interval ranges from –26 to 49 ms.[7]

Reciprocating tachycardias can be induced with programmed atrial and ventricular pacing and rapid atrial pacing. Orthodromic atrioventricular reciprocating tachycardia is characterized by eccentric (rarely concentric in case of anteroseptal accessory pathways) retrograde atrial activation with a fixed ventriculoatrial conduction time.

Permanent junctional reciprocating tachycardia is characterized by eccentric retrograde atrial activation with a variable ventriculoatrial activation time, which is also visible during ventricular pacing to confirm the presence of decremental conduction (Fig. 15.16).[3,5,7,12] During orthodromic atrioventricular reciprocating tachycardia, the AH interval ranges from 48 ms to 206 ms, while the HV interval ranges from 24 ms to 49 ms.[7]

Both accessory pathway-mediated tachycardias can be differentiated from atrioventricular nodal reciprocating tachycardia by delivering a single ventricular extrastimulus during the refractory period of the bundle of His and demonstrating either interruption of the tachycardia or preexcitation of the atria, bundle of His, and ventricles with the same sequence of activation of the tachycardia. Orthodromic atrioventricular reciprocating tachycardia can be differentiated from focal atrial tachycardia when, after overdrive atrial pacing, the first postpacing ventriculoatrial interval is fixed.[3,5]

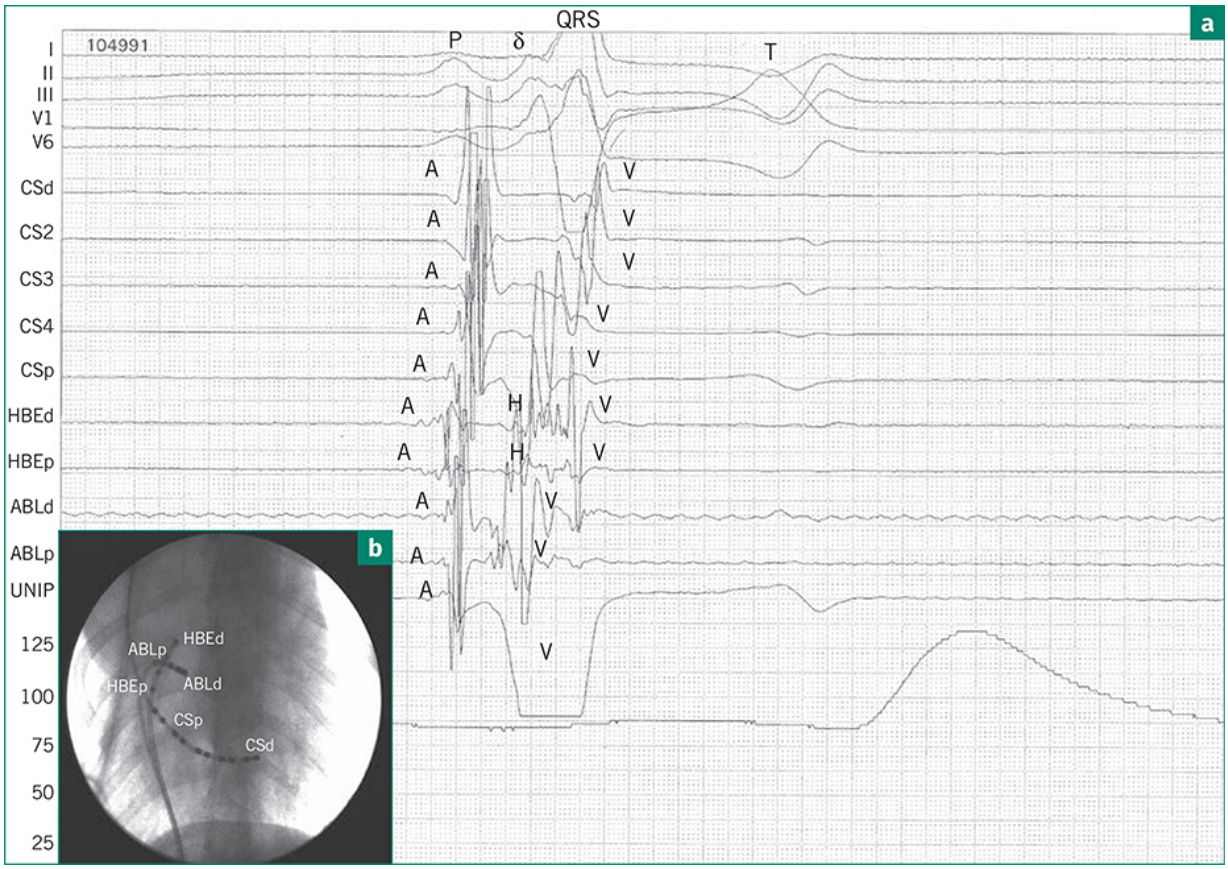


FIGURE 15.14. Ventricular preexcitation along a right midseptal accessory pathway in a 14-month-old male English Bulldog. a) Endocardial mapping of a preexcited sinus beat. Note the short P–δQRS interval (60 ms) with a wide QRS complex (110 ms) on the surface leads (I, II, III, V1, V6) and the relationship between the endocardial electrograms of the atrium (A), the ventricle (V) and the His region (H) at different levels of the heart: coronary sinus ostium (CSp), great cardiac vein (CS2–CS4), posterior left atrium (CSd), bundle of His (HBEp-HBEd), and the ablation catheter placed on top of the midseptal tricuspid valve annulus (ABLp-ABLd), where the accessory pathway is located. A and V become fused and the ventricular unipolar tracing (UNIP) has a QS morphology. A normal arterial pressure tracing is displayed below the intracardiac electrograms. Speed, 250 mm/s; calibration, 5 mm/1 mV. b) Dorsoventral fluoroscopic view of the same dog with the catheters in place: a decapolar catheter in the great cardiac vein (CSp-CSd), a quadripolar catheter at the bundle of His region (HBEd), and a steerable ablation catheter at the right midseptal tricuspid valve annulus (ABLd).

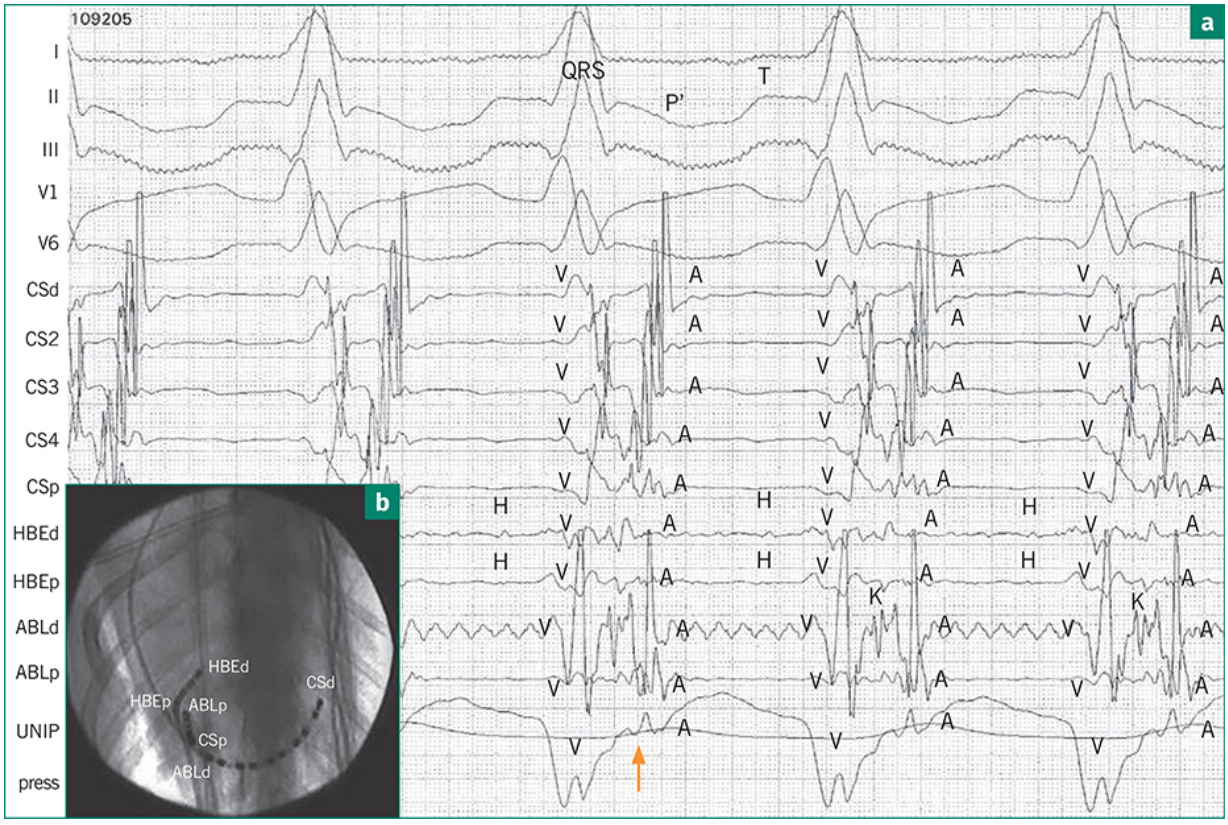


FIGURE 15.15. Orthodromic atrioventricular reciprocating tachycardia mediated by a right posterior accessory pathway in a 2-year-old male Labrador Retriever. a) Endocardial mapping during tachycardia. Note the presence of a narrow QRS complex (50 ms) tachycardia with a ventricular rate of 290 bpm, a rapid retrograde atrial activation inscribed in the ST segment (P') on the surface leads (I, II, III, V1, V6), and the relationship between the endocardial electrograms of the ventricle (V), the atrium (A) and the His region (H) at different levels of the heart: coronary sinus ostium (CSp), great cardiac vein (CS2–CS4), posterior left atrium (CSd), bundle of His (HBEp-HBEd), and the ablation catheter placed on top of the posterior tricuspid valve annulus (ABLp-ABLd), where the accessory pathway is located. V and A become fused and the atrial unipolar tracing (UNIP; arrow) has a QS morphology. A Kent signal has been recorded (K) at the ABLd dipole between V and A. A normal arterial pressure tracing is displayed below the intracardiac electrograms. Speed, 250 mm/s; calibration, 5 mm/1 mV. b) Dorsoventral fluoroscopic view of the same dog with the catheters in place: a decapolar catheter in the great cardiac vein (CSp-CSd), a quadripolar catheter at the His bundle region (HBEd), and a steerable ablation catheter at the posterior tricuspid valve annulus (ABLd).

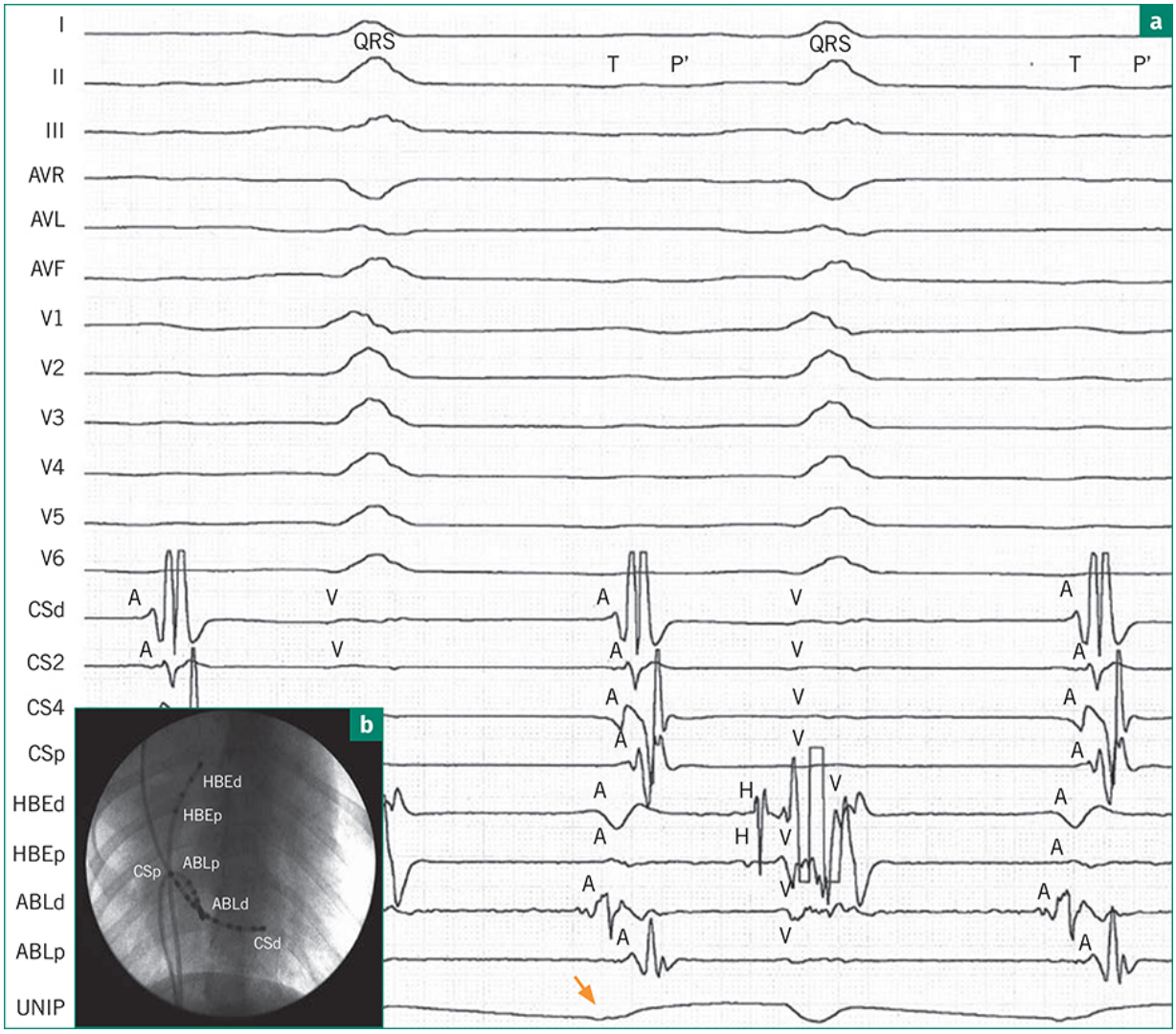


FIGURE 15.16. Permanent junctional reciprocating tachycardia or Coumel tachycardia mediated by a right posteroseptal accessory pathway in an 11-month-old female Labrador Retriever. a) Endocardial mapping during tachycardia. Note the presence of a narrow QRS complex (60 ms) tachycardia with a ventricular rate of 250 bpm and a slow retrograde atrial activation that appears after the T wave (P') on the surface leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6) and the relationship between the endocardial electrograms of the ventricle (V), the atrium (A), and the His region (H) at different levels of the heart: coronary sinus ostium (CSp), great cardiac vein (CS2–CS4), posterior left atrium (CSd), His bundle (HBEp-HBEd), and an ablation catheter placed on top of the posteroseptal tricuspid valve annulus (ABLp-ABLd), where the accessory pathway is located. V and A become shorter and the atrial unipolar tracing (UNIP; arrow) has a QS morphology. Speed, 250 mm/s; calibration, 10 mm/22.8 mV. b) Dorsoventral fluoroscopic view of the same dog with the catheters in place: a decapolar catheter in the great cardiac vein (CSp-CSd), a quadripolar catheter at the His bundle region (HBEd), and a steerable ablation catheter at the posteroseptal tricuspid valve annulus (ABLd).

THERAPY

Reciprocating tachycardias can be treated in the acute phase with intravenous lidocaine or diltiazem, chronically using different antiarrhythmic drugs, or definitively by radiofrequency catheter ablation.[3,5,7,24]

Intravenous treatment can be needed in case of an incessant tachycardia causing hemodynamic compromise, or before anesthesia to perform radiofrequency catheter ablation. Lidocaine is usually administered as an intravenous bolus of 2 mg/kg (IQR, 2–5.5 mg/kg) in 20–30 seconds. In case neither cardioversion nor adverse side effects are obtained within 1–2 minutes, further boluses can be used up to a maximum cumulative dose of 8 mg/kg.[24] Lidocaine is efficacious in 84.4% of dogs with orthodromic atrioventricular reciprocating tachycardia; in 43%, sinus rhythm can be restored with a single bolus followed by a constant rate infusion at 25–60 µg/kg/min (median, 50 µg/kg/min) and in 34%, sinus rhythm can be restored with intermittent boluses. Adverse side effects may be seen in up to 31% of the cases treated with lidocaine and include gastrointestinal signs (e.g., hypersalivation, lip smacking, and vomiting) and neurological signs (e.g., sedation, head tremor, opisthotonos, body tremors, and seizures). Dogs with right free wall accessory pathways have a higher rate of cardioversion to sinus rhythm than dogs with posteroseptal accessory pathways.[24]

Another drug that can be used intravenously to restore sinus rhythm in dogs with accessory pathway–mediated tachycardia is diltiazem.[7,24] In the author's experience, diltiazem often slows down conduction along the atrioventricular node, blocking the atrioventricular reentrant circuit, but it can also have a negative chronotropic effect. Therefore, it should be used with caution in patients with a severe dilated cardiomyopathy phenotype since inappropriate sinus bradycardia can develop after cardioversion, thereby promoting a drop in cardiac output.

In dogs, different antiarrhythmic drugs have been used to control long-term reciprocating tachycardia relapses, such as diltiazem (24–75%), sotalol (46–61%), procainamide (27%), mexiletine alone (1–13.5%) or in association with sotalol (3%) or diltiazem (4%), atenolol (6.7%), propafenone (15.6%), amiodarone (13.3 %), verapamil (13.3%), propranolol (13.3%), digoxin (4%), quinidine (3%), and flecainide (1%).[3,5,7]

In cats, the most common antiarrhythmics used to treat reciprocating tachycardia are sotalol (29.4%), diltiazem (29.4%), and atenolol (23.5%).[17] In the author's experience, amiodarone can also be considered as a valid option with good control of tachycardia recurrence.

Radiofrequency catheter ablation is the treatment of choice in dogs with atrioventricular reciprocating tachycardias,[3,5,7,12,25] but it cannot be used in cats due to their heart size.[17] Once the accessory pathway has been located, radiofrequency energy is delivered for 60 seconds with an average temperature of 64 °C, a power of 19 watts and an impedance of 107 ohms. Ablation is performed during tachycardia (74%), preexcited sinus rhythm (16%), or ventricular pacing (10%). To reduce the amount of damage to the atrioventricular region, in case of antero- and midseptal accessory pathways, low-energy ablation (<20 watts) for a reduced amount of time (<40 seconds) should be considered.[25]

Accessory pathway conduction disappears within 3.8–5 seconds in average after initiating radiofrequency energy delivery.[3,5,7,12,25] The ablation procedure duration ranges from 88 to 300 minutes, and the acute success rate is 95–100%, with a recurrence rate of 8%. The success rate with a second attempt reaches 98.8%.[3,5,7,12]

The rate of major complications (including death during anesthesia and iatrogenic atrioventricular block) varies from 4.5 and 7%, while the rate of minor complications (e.g., hematoma in the access regions) is around 3%.[3,5,7,12]

During Holter monitoring performed 1 month post-procedure, different arrhythmias occurred in up to 25% of the dogs that had undergone ablation. These arrhythmias were atrial premature beats, focal atrial tachycardia, ventricular ectopic beats, ventricular couplets, and ventricular tachycardia. However, arrhythmias were observed in only 3% of dogs during follow-up Holter monitoring performed 6 months to 2 years post procedure.[7]

Atrioventricular reverse remodeling of the arrhythmia-induced cardiomyopathy occurred in 100% of the dogs evaluated, ejection fraction increased (+12.5%) and internal systolic diameter of the left ventricle normalized to body weight decreased (–0.31).[7]

The mean survival time post ablation in dogs is 4±3.2 years, while the median survival time in cats with ventricular preexcitation is 1882 days (2–

1882 days).[17]

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CHAPTER 16

Atrial fibrillation

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DEFINITION

Atrial fibrillation is characterized by disorganized, rapid atrial depolarizations resulting in a loss of atrial contraction.[1,2] Atrial fibrillation is classified, according to its duration, as paroxysmal (self-limiting), persistent (not self-limiting, but able to be terminated through medical intervention), long-standing persistent (in humans when it lasts more than 1 year), and permanent (unable to be terminated). In dogs and cats, paroxysmal atrial fibrillation is rare, although it has been reported in dogs with presumed vagally mediated syncope.[3]

ELECTROPHYSIOLOGICAL MECHANISM

The initiation and maintenance of atrial fibrillation can be explained by reentry and/or rapid focal ectopic firing. Three proposed mechanisms, which are often thought of as independent but can work together, are:

1. Rapid, regular ectopic firing, also referred to as an atrial fibrillation driver
2. Single-circuit reentry
3. Multiple-circuit reentry, also referred to as multiple wavelets

Regular ectopic firing and single-circuit reentry are stable, regular impulses. They cause irregular rhythms of atrial fibrillation because the activation arising from the focus is too rapid to be conducted uniformly

throughout the atria, which leads to propagation of the depolarization wavefronts breaking up into irregular wavelets. This phenomenon is known as fibrillatory conduction.[4] Alternatively, multiple reentry circuits varying in time and space could create the irregular nature of fibrillatory activity.[5]

Potential mechanisms for focal ectopic firing include enhanced automaticity and triggered activity.[5] These focal ectopies are also called "drivers". Electrophysiological mapping of dogs in an experimental model of atrial fibrillation due to ventricular tachypacing-induced congestive heart failure showed support for this mechanism.[6] Single drivers of sustained atrial fibrillation have been described near the pulmonary veins, and simultaneous drivers from multiple sites have been documented in both the atria near the pulmonary veins and the high right atrium. When multiple drivers were found, they had different rates.

The multiple wavelet model is supported by studies in humans undergoing surgery[4] and in human explanted hearts.[7] In this mechanism, waves move in a seemingly random fashion as they seek tissue that is excitable. There are usually six or more wavelets. For atrial fibrillation to be self-sustaining, there must be sufficient space for multiple circuits to coexist. This is why atrial enlargement favors atrial fibrillation by increasing the surface area for the circuits. In addition, rapid recovery of the tissue following propagation of the wavefront (i.e., a short refractory period) will also support sustained atrial fibrillation.[4]

Atrial remodeling is an important feature for atrial fibrillation to occur. Electrical remodeling of the atrial tissue, due to atrial fibrillation itself or other atrial tachyarrhythmias, alter ion channel expression and/or function.[5] After a period of rapid atrial pacing in a canine model of atrial fibrillation, several genes for ion channels were down-regulated, including *Kv4.3* (a gene encoding for the transient outward potassium channel) and the genes encoding the alpha1c subunit of the L-type calcium channel and the alpha subunit of the cardiac sodium channel.[8] Tachycardias also lead to increased intracellular calcium loading in the sarcoplasmic reticulum, which can promote focal ectopies by triggered activity and turn into an atrial fibrillation driver.[9] In addition to electrical remodeling, structural remodeling (atrial fibrosis) can lead to interference with electric continuity and slowing of conduction, and fibroblasts can couple electrically to

cardiomyocytes, which can promote reentry and/or ectopic activity.[5] Electrical and anatomical remodeling increases over time and allows atrial fibrillation to become initially persistent, long-standing persistent, and finally permanent.[5]

Vagal stimulation is a factor that can promote atrial fibrillation. The acetylcholine-dependent potassium current (IK_{ACh}) in atrial myocytes decreases the action potential duration. Shorter action potentials will stabilize reentrant circuits by allowing more rapid recovery of the tissue following the wavefront, as described above.[4] In addition, the distribution of IK_{ACh} within the atrial myocardium is variable across the tissue. Thus, its activation leads to a wider range of repolarization times across the atria (greater dispersion of refractoriness), which also promotes sustained reentry.[10]

ELECTROCARDIOGRAPHIC FINDINGS

The two defining electrocardiographic features of atrial fibrillation are a lack of P waves and the presence of irregular RR intervals. P waves are replaced with fibrillation (f) waves, which represent the disorganized electrical signals occurring within the atria. The f waves have variable morphology and voltage and are continuous. They have a rate between 400 and 800 bpm.[2] In humans, these f waves are classified as fine (≤0.1 mV) or coarse (≥0.2 mV) (Fig. 16.1), and they are not always apparent on the surface leads.[5]

The rapid atrial signal is filtered at the atrioventricular node due to slowed conduction through the nodal tissue, which results in a ventricular response rate that is slower than the atrial rate. As the atrial depolarizing signals are continuous, whether or not they can be conducted through the atrioventricular node depends on the state of refractoriness of the node. The refractory period of the atrioventricular node changes over time due to its property of decremental conduction, and some signals are also able to depolarize part of the atrioventricular node before hitting refractory tissue later on (termed concealed conduction), leading to an unpredictability of when an atrial signal will conduct. This results in the irregular RR intervals seen on the electrocardiogram.[2]

The ventricular response rate can fall within a wide range of heart rates, which is heavily dependent on the autonomic influences on the atrioventricular node. Many dogs, particularly those with an underlying structural heart disease, will have a rapid ventricular response rate (Fig. 16.2a). However, for several reasons (high vagal tone due to underlying disease, disease of the atrioventricular node, treatment with rate-lowering medication), the ventricular response rate can fall within range of a normal heart rate (Fig. 16.2b) or even produce a bradycardia (Fig. 16.2c).[2]

The QRS complexes are typically normal in duration, although they can be prolonged in cases with aberrant conduction or anatomical conduction block (Fig. 16.3). Permanent prolongation of the QRS complexes may be seen, as in the case of a preexisting anatomical conduction block or in cases of structural heart disease due to slowed intraventricular conduction associated with fibrosis. QRS prolongation can also be intermittent due to RR interval irregularity, which produces beats that conduct through the Purkinje system at times when it is partially refractory. Aberrant conduction is also common when there is a long RR interval followed by a shorter one. The third beat (following the short RR interval) occurs while part of the conduction system is in a refractory state (either a left bundle branch block or a right bundle branch block). This is called *Ashman's phenomenon* (Fig. 16.4) (see p. 308). The *Brody effect* is a relatively common finding in atrial fibrillation that is characterized by an increase in the R-wave amplitude secondary to an increase in the ventricular preload with changes in chamber size (Fig. 16.5).[11]



FIGURE 16.1. a) Long-standing persistent atrial fibrillation in a 11-year-old male mixed-breed dog with stage C myxomatous mitral valve disease. Note the presence of a narrow QRS complex (40 ms) tachycardia (180 bpm) with irregular RR intervals and of disorganized atrial activations represented

by fine fibrillatory waves (f) with a low amplitude (0.1 mV), variable morphology and cycle length, and an average rate of 750 bpm. b) Post-pericardiocentesis paroxysmal atrial fibrillation in a 6-year-old male Boxer with idiopathic pericarditis. Note the presence of a narrow QRS complex (60 ms) tachycardia (190–210 bpm) with irregular RR intervals and of organized atrial activations represented by coarse fibrillatory waves (f) with a high amplitude (0.4 mV), stable morphology and cycle length, and an average rate of 500 bpm. Lead II; speed, 50 mm/s; calibration, 5 mm/1 mV.



FIGURE 16.2. a) Fast-response, long-standing persistent atrial fibrillation in a 13-year-old female mixed-breed dog with stage C myxomatous mitral valve disease. Note the presence of a narrow QRS complex (50 ms) tachycardia (220–240 bpm) with irregular RR intervals and of disorganized atrial activations represented by fine fibrillatory waves (f) with a low amplitude (0.1 mV), variable morphology and cycle length, and an average rate of 620 bpm. b) Fast-response, long-standing persistent atrial fibrillation in a 14-year-old male Newfoundland without structural heart disease. Note the presence of a narrow QRS complex (50 ms) rhythm (100–120 bpm) with irregular RR intervals and of disorganized atrial activations represented by fine fibrillatory waves (f) with a low amplitude (0.1 mV), variable morphology and cycle length, and an average rate of 700 bpm. c) Persistent atrial fibrillation with third-degree atrioventricular block in a 11-year-old male mixed-breed dog with conduction system fibrosis. Note the presence of a wide QRS complex (80 ms) bradycardia (50 bpm) with regular RR intervals and of disorganized atrial activations represented by coarse fibrillatory waves (f) with a high amplitude (0.3 mV), variable morphology and cycle length, and an average rate of 600 bpm. Lead II; speed, 50 mm/s; calibration, 5 mm/1 mV.



FIGURE 16.3. Fast-response, long-standing persistent atrial fibrillation conducted with a predivisional left bundle branch block in a 9-year-old female Akita Inu with a dilated cardiomyopathy phenotype. Note the wide QRS complexes (90 ms), which have a typical left bundle branch block morphology in the frontal plane (normal mean electrical axis, +60°) and are negative in V1 and positive from V2 to V6. The QRS complex rate is 220–240 bpm, with irregular RR intervals. Note also the disorganized atrial activations represented by fine fibrillatory waves (f) with a low amplitude (0.1 mV), variable morphology and cycle length, and an average rate of 600 bpm. The fibrillatory waves appear fine in lead II (facing the interatrial septum), lead aVL (facing the left atrium), and lead V1 (facing the right atrium), which confirms the disorganized activation of both atrial chambers. Twelve leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6); speed, 50 mm/s; calibration 5 mm/1 mV.



FIGURE 16.4. Long-standing persistent atrial fibrillation and Ashman's phenomenon in an 8-year-old female German Shepherd with primary mitral valve disease. Note the presence of a narrow QRS complex (50 ms) tachycardia (220–250 bpm) with irregular RR intervals and of disorganized atrial activations represented by fine fibrillatory waves (f) with a low amplitude (0.1 mV), variable morphology and cycle length, and an average rate of 550 bpm. After the fourth beat, a long-short RR interval pattern appears, followed by a taller and larger QRS complex (arrow) representing tachycardia-dependent aberrancy with a left bundle branch block morphology (Ashman's phenomenon). Lead II; speed, 50 mm/s; calibration, 5 mm/1 mV.



FIGURE 16.5. Persistent atrial fibrillation in a 11-year-old male domestic shorthair cat with restrictive cardiomyopathy. Note the presence of a narrow QRS complex (30 ms) tachycardia (280–300 bpm) with irregular RR intervals and of disorganized atrial activations represented by fine fibrillatory waves (f) with a low amplitude (0.05 mV), stable morphology and cycle length, and an average rate of 750 bpm. The QRS amplitude changes according to previous RR interval duration (Brody effect): shorter RR intervals are followed by lower QRS complexes, while longer intervals are followed by taller QRS complexes. The decreased diastolic time causes a reduction in ventricular filling and chamber size, which appears as changes in the QRS complex amplitude on the surface electrocardiogram. Six limb leads (I, II, III, aVR, aVL, aVF); speed, 50 mm/s; calibration, 5 mm/1 mV.

CLINICAL PRESENTATION

Atrial fibrillation is the most common pathological arrhythmia in dogs; it accounts for approximately 33% of all arrhythmias detected by electrocardiogram in a cardiology referral population,[12] and with a prevalence estimated at around 23 per 10,000 canine admissions in the United States.[13] It can occur without underlying structural disease, in which case it is termed lone or primary atrial fibrillation. However, atrial fibrillation is more commonly associated with cardiac diseases resulting in atrial enlargement.[14]

Body size is an important risk factor for the development of canine atrial fibrillation. Giant breed dogs (Irish Wolfhound, Great Dane, Newfoundland, Mastiff, Saint Bernard, and Great Pyrenees) are at highest risk for atrial fibrillation, followed by large breed dogs. Small breed dogs are considered to be at low risk.[13] In addition to its large size, pedigree analysis has shown there is likely a genetic component to the development of atrial fibrillation in the Irish Wolfhound.[15] Some studies have shown male sex to be a risk factor for development of atrial fibrillation,[13–15] although a recent systematic review for risk factors of atrial fibrillation did not find sex to be a reliable indicator of atrial fibrillation in dogs.[16,17] Atrial fibrillation is commonly associated with structural heart diseases that cause atrial dilation, and left atrial enlargement was found to be an important risk factor.[16,17]

Most dogs with lone atrial fibrillation do not have clinical signs, and those that do exhibit milder signs than dogs with structural heart disease. In dogs with structural heart disease, the most common clinical signs include generalized weakness, syncope, and exercise intolerance. Because many dogs with atrial fibrillation have an underlying disease with atrial dilation, they can also present with signs of congestive heart failure, such as dyspnea, abdominal distension, and coughing.[14] An association was found between atrial fibrillation and right-sided heart failure in dogs with dilated cardiomyopathy and myxomatous mitral valve disease, despite these diseases primarily causing left atrial dilation.[17,18] This may be a sign that atrial fibrillation is more common when these diseases impact both sides of the heart (as occurs in dilated cardiomyopathy that affects both ventricles or in degenerative mitral valve disease with significant pulmonary hypertension). It is also possible that atrial fibrillation directly affects the

hemodynamics of the right heart independently of the underlying structural disease, leading to right-sided heart failure. In general, the presence of atrial fibrillation is a negative prognostic indicator in dogs with degenerative mitral valve disease[19] and dilated cardiomyopathy.[20] Furthermore, dogs with atrial fibrillation have a higher incidence of sudden cardiac death compared to those without this arrhythmia.[21]

Atrial fibrillation is rarer in cats (Fig. 16.5) than in dogs, likely because the surface area of their atria is smaller and unable to sustain multiple reentry circuits without severe atrial enlargement.[22] Therefore, cats with atrial fibrillation are expected to have an underlying cardiomyopathy (hypertrophic, dilated, and restrictive cardiomyopathy all reported) with severe atrial enlargement.[22,23] Many cats show signs of decompensated congestive heart failure at the time of diagnosis. The prognosis for cats with atrial fibrillation also appears to be quite poor, with one study reporting that cats with atrial fibrillation had worse outcomes than those with other supraventricular tachycardias.[23]

OTHER METHODS OF EVALUATION

ECHOCARDIOGRAPHY

An echocardiogram can be used to identify characteristic flow patterns in patients with atrial fibrillation. Pulse wave Doppler will show an absence of A waves on mitral inflow and A reversal waves on pulmonary vein flow assessment; these findings are both caused by abnormal atrial contraction.[24] Similarly, pulse-wave tissue Doppler imaging at the mitral valve annulus will show disappearance of the A' wave.

Pulse-wave tissue Doppler imaging at the mitral valve annulus can also be utilized as a predictor of new-onset atrial fibrillation for dogs currently in sinus rhythm. The time from onset of the P wave on the electrocardiogram to the peak of the A' wave (PA-TDI), which represents the total atrial conduction time, has been shown to be significantly longer in dogs that later went on to develop atrial fibrillation than in dogs that did not. A cutoff of 81.2 ms is suggested as a tool to predict development of atrial fibrillation within 6 months.[25] Another echocardiographic variable that could be used as a predictor of atrial fibrillation is peak left atrial strain,

which is reported to be an independent predictor of development of atrial fibrillation within 1 year in dogs with degenerative mitral valve disease when decreased (≤28%).[26] Peak left atrial strain is measured from a left apical four-chamber view using speckle tracking echocardiography.

In addition to providing predictive information or confirming a diagnosis of atrial fibrillation, echocardiography is also useful to characterize the type of atrial fibrillation in a patient once the arrhythmia has been diagnosed. Differentiating lone atrial fibrillation from atrial fibrillation secondary to structural heart disease is important for choosing a treatment and establishing a prognosis. Furthermore, the prognosis may vary depending on the underlying heart disease (congenital disease, dilated cardiomyopathy, degenerative mitral valve disease).

ELECTROPHYSIOLOGICAL STUDY

Atrial fibrillation produces a continuous and chaotic intra-atrial electrogram (Fig. 16.6). Atrial fibrillation can be stimulated by pacing via atrial burst pacing or programmed extra stimuli. It cannot be terminated by pacing.[27] Recording of intra-atrial electrograms can be useful to differentiate atrial fibrillation with third-degree atrioventricular block from atrial standstill, both of which can have similar surface electrocardiographic features (ventricular escape rhythm with no P waves) (see p. 294).

In humans, spontaneous atrial fibrillation can be caused by ectopic beats originating in the pulmonary veins. A study of focal atrial tachycardia in dogs found that persistent or paroxysmal atrial fibrillation could be triggered by focal atrial ectopic activity arising from the pulmonary veins, among other possible sites (see p. 182). Electrophysiological mapping of the right and left atria can be used to find a trigger for atrial fibrillation in such cases, with radiofrequency catheter ablation performed to abolish the ectopic focus.[28,29]



FIGURE 16.6. Endocardial mapping of persistent atrial fibrillation in an 8-year-old female Dogue de Bordeaux without structural heart disease. Note the presence of a narrow QRS complex (60 ms) tachycardia (180–200 bpm) with coarse atrial fibrillation waves on the surface leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6) and the rapid atrial (A) and ventricular (V) electrograms at different levels of the great cardiac vein: coronary sinus ostium (CSp), great cardiac vein (CS3), posterior left atrium (CSd). Speed, 100 mm/s; calibration, 10 mm/1 mV.

THERAPY

The management of atrial fibrillation can be divided into two approaches: rate control and rhythm control. Rate control aims to slow conduction through the atrioventricular node to lower the ventricular response rate. Rhythm control aims to terminate the fibrillation within the atria to convert to sinus rhythm.

Which approach should be preferred depends primarily on the presence of structural heart disease and the duration of atrial fibrillation.[30] A rate control approach is preferred when atrial fibrillation is long-standing and structural heart disease is present. Rhythm control may be attempted in cases of lone atrial fibrillation with a recent onset.[31] In cases in which rhythm control fails, rate control is the typical fallback option.

The rate control strategy leverages the inherent conduction slowing properties of the atrioventricular node to regulate heart rate. Its goal is to target an "ideal" number of beats per minute that make it through the atrioventricular node to the ventricle in order to optimize cardiac function and improve both clinical signs and survival. Not all dogs will need treatment to lower the ventricular response rate. In particular, dogs with lone atrial fibrillation are more likely to have an autonomic balance that favors parasympathetic tone, which slows atrioventricular nodal conduction.[13,29] On the other hand, dogs with structural heart disease and congestive heart failure have increased sympathetic tone and are more likely to have rapid ventricular response rates.

The methods to best evaluate the ventricular response rate and the determination of an acceptable rate are topics of much research. It is generally understood that faster rates are associated with a worse prognosis, but studies have used different rates (based on a short duration in-clinic electrocardiogram or 24-hour Holter monitoring) to define "fast atrial fibrillation".[14,19,32,33] Medium- to large-sized dogs with degenerative mitral valve disease and atrial fibrillation with a heart rate above 160 bpm using an in-clinic electrocardiogram have a worse prognosis than those with a heart rate below 160 bpm.[19] In a retrospective study using Holter recordings, every 10 bpm increase in the mean 24-hour heart rate increased the risk of all-cause mortality by 35%, and ultimately a heart rate cutoff of less than 125 bpm was used to classify dogs into the group of adequate rate control.[32] A follow-up prospective study with Holter monitor data confirmed that dogs with a mean heart rate equal to or below 125 bpm survived longer than those with a higher rate.[32] Based on these studies, it is generally accepted that medical intervention to lower heart rate should be used in dogs with atrial fibrillation that have either an in-clinic heart rate above 160 bpm or a mean heart rate on Holter monitoring above 125 bpm. Though the heart rate on a shorter in-clinic electrocardiogram does correlate with the mean heart rate on Holter monitoring,[34,35] a 24-hour Holter study remains the recommended technique for assessing the ventricular response rate, because it provides information on heart rate distribution as well as the mean heart rate and detects concomitant ventricular arrhythmias.[30]

RATE CONTROL DRUGS

Diltiazem, a nondihydropyridine calcium channel blocker, slows action potential propagation in the atrioventricular node and is widely used for the treatment of atrial fibrillation.[30] An intravenous formulation is available that can be administered in bolus dosing or as a constant rate infusion in cases in which urgent rate control is deemed necessary, particularly during acute decompensated congestive heart failure when the failure is unable to be adequately controlled due to the tachycardia of atrial fibrillation. An experimental model of induced atrial fibrillation in anesthetized dogs showed cumulative intravenous doses of 0.438–0.938 mg/kg achieved heart rates closest to those obtained during sinus rhythm.[36] For long-term management of atrial fibrillation, oral diltiazem is often used. Although it can be used as a sole therapy, combination treatment with diltiazem and digoxin is more effective at achieving adequate rate control than either drug alone.[37] Digoxin slows conduction in the atrioventricular node through an increase in vagal tone. Digoxin has a narrow therapeutic index, which can lead to toxicity if not carefully monitored. Spikes in blood digoxin levels have been noted even after prolonged use, with no complications and in the absence of clinical and biochemical changes.[38]

ß-Blockers can also be used to slow the ventricular response rate through an increase the ability of the atrioventricular node to block impulses.[30] In a case report of a cat with atrial fibrillation, atenolol was used to achieve rate control,[39] but it was not reported as a medication received in any of 50 cats from a retrospective cohort.[22] Sotalol, which has both potassium-blocking and ß-blocking effects, may be added on to other rate control medications in patients that require treatment of ventricular arrhythmias in addition to atrial fibrillation. It is typically not used solely for rate control.[30]

RHYTHM CONTROL DRUGS

Conversion of atrial fibrillation to sinus rhythm through pharmacological methods is not frequently attempted, though there are some reports of effectiveness of various drugs with cases in both clinical and experimental settings. In dogs, intravenous lidocaine was able to terminate atrial fibrillation triggered by vagal tone when administered within one hour of initiation.[40,41] Ranolazine successfully terminated atrial fibrillation when

administered intravenously by bolus and constant rate infusion in an experimental model of canine atrial fibrillation.[42]

Amiodarone administered intravenously was also reported to terminate atrial fibrillation in 2 dogs in which atrial fibrillation was diagnosed following surgical procedures,[43] which may indicate a vagal trigger. Both patients had structurally normal hearts. In addition, in a retrospective study of 17 dogs, conversion to sinus rhythm was achieved in 35% of dogs with atrial fibrillation that received oral amiodarone as the sole treatment. In dogs that did not convert to sinus rhythm, amiodarone was frequently effective at decreasing the heart rate and thus may also be used as an option for rate control.[44]

RHYTHM CONTROL VIA ELECTRICAL CARDIOVERSION

Termination of atrial fibrillation with conversion to sinus rhythm can be achieved in dogs with synchronized electrical cardioversion. Most reports describe the use of transthoracic paddles or patches,[31,45] but this technique can also be performed via a transvenous approach.[46] Patient selection for electrical cardioversion is based on selecting dogs in which this method is most likely to be successful in both converting to sinus rhythm and maintaining sinus rhythm. The two main factors in this selection are:

1. Presence of underlying structural heart disease
2. Duration of documented atrial fibrillation before cardioversion

In one analysis, dogs with no underlying structural heart disease remained in sinus rhythm substantially longer (median of 343 days) than those with underlying disease (median of 53 days).

In addition, the duration of documented atrial fibrillation prior to cardioversion was significantly and inversely related to the duration of sinus rhythm regardless of the presence or absence of underlying structural disease. That is, patients that had been in atrial fibrillation longer were more likely to have shorter periods of maintaining sinus rhythm.[31] This is likely because chronic atrial fibrillation causes electrical remodeling of the atria in a manner that promotes the occurrence of atrial fibrillation.[8]

Transthoracic electrical cardioversion consists in delivering a direct current shock to the heart at a specific time in the cardiac cycle. It is timed to not coincide with the vulnerable period of repolarization to avoid induction of ventricular fibrillation. This is typically performed using a biphasic energy waveform, which adjusts for transthoracic impedance and enables delivery of a constant current through the heart using lower energy levels. Cardioversion is performed under general anesthesia. The first shock is performed with a low energy level (35–50 joules), and if unsuccessful, additional shocks are delivered using upward titration to a maximum of 200 joules. In a retrospective analysis of 39 dogs, restoration of sinus rhythm was achieved in 92.3% of dogs using a median of 75 joules (1.8 joules/kg of body weight) with a median of 2 shocks (Fig. 16.7).[45]

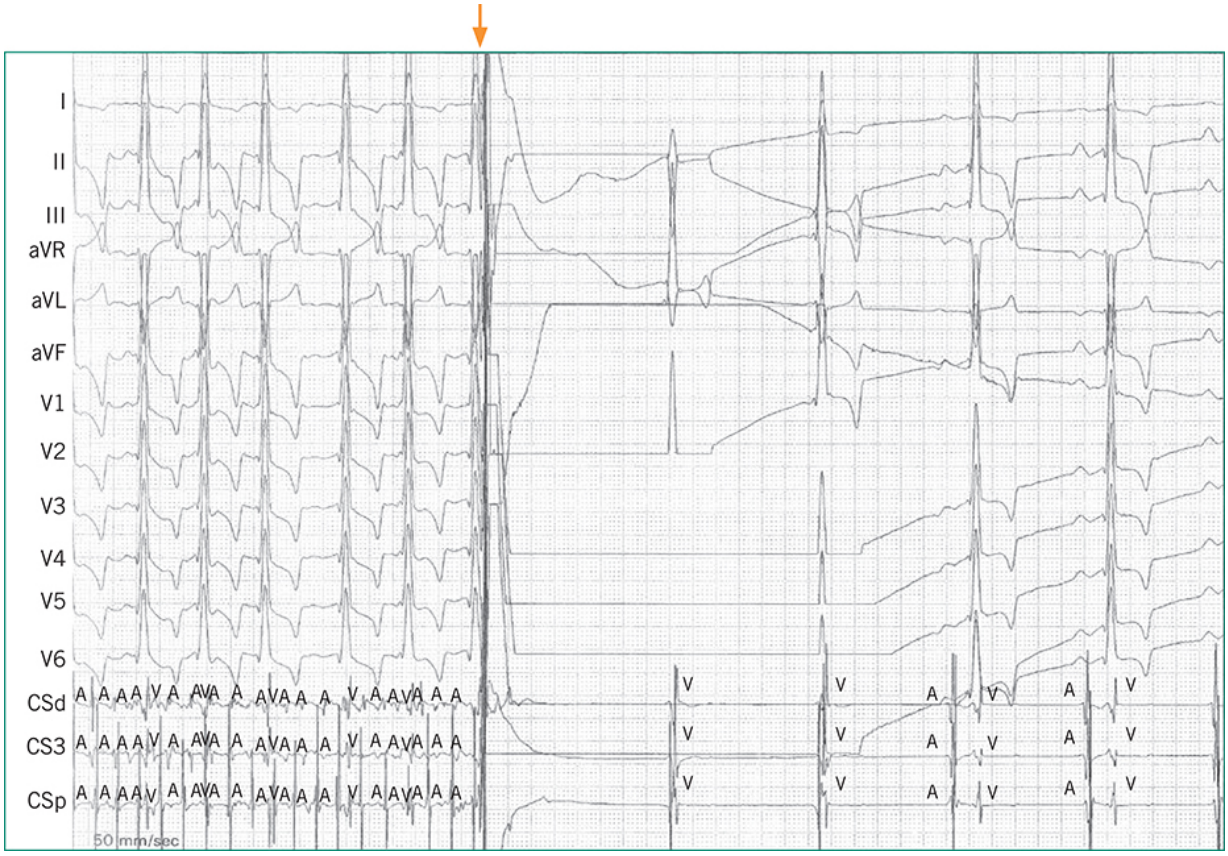


FIGURE 16.7. Endocardial mapping of persistent atrial fibrillation in a 9-year-old female Labrador Retriever without structural heart disease during electrical cardioversion. Note the presence of a narrow QRS complex (50 ms) tachycardia (170–190 bpm) with fine atrial fibrillation waves on the surface leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6) and the rapid atrial (A) and ventricular (V) electrograms at different levels of the great cardiac vein: coronary sinus ostium (CSp), great cardiac vein (CS3), posterior left atrium (CSd). After the electrical shock (90 J, arrow),

two ventricular escape beats occur, followed by restoration of sinus rhythm. Speed, 50 mm/s; calibration, 10 mm/1 mV.

Transvenous electrical cardioversion was reported to be successful in a case report of 2 dogs.[46] An electrode catheter was placed in the proximal left pulmonary artery (used as the cathode) and another one at the junction of the proximal cranial vena cava and right atrium (used as the anode). Biphasic cardioversion was successful using 30–50 joules. Both patients had underlying structural heart disease and were documented to have remained in sinus rhythm for at least 3 months following the procedure.

Amiodarone and sotalol have been reportedly used prior to and following electrical cardioversion to maintain sinus rhythm for longer periods of time.[45,46] The effectiveness of either of these medications for this purpose is unclear.

RHYTHM CONTROL VIA RADIOFREQUENCY CATHETER ABLATION

As described previously in this chapter, focal atrial tachycardia originating from the pulmonary veins or other foci can trigger atrial fibrillation in dogs. These arrhythmias can be treated by electrical cardioversion, followed by electrophysiological mapping to find the ectopic focus and finally, radiofrequency catheter ablation to abolish the focus (see p. 161).[28]

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CHAPTER 17

Macroreentrant atrial tachycardias

Roberto Santilli, Cortney Pelzek

DEFINITION

Macroreentrant atrial tachycardia, also commonly referred to as atrial flutter, is a supraventricular tachyarrhythmia in which a large circuit is found within the left or right atrium, surrounding an obstacle consisting of a normal or abnormal cardiac structure.[1] Atrial flutter was initially classified by Wells et al. as type I atrial flutter, a circuit involving an anatomical substrate, or type II atrial flutter, a circuit involving a functional substrate.[2,3] As further electrophysiological data have been obtained, the classification of macroreentrant atrial tachycardia has transitioned to consider not only the electrophysiological mechanism (anatomical reentry or functional reentry) but also the location within the atria and associated structures.[3]

In dogs, several anatomical structures contribute to the initiation and maintenance of a macroreentrant atrial tachycardia, the majority of which lie within the right atrium.[4–6] The right atrium can be divided into two components: the smooth-walled *sinus venosus*, which contains the orifices for systemic drainage from the cranial and caudal venae cavae and the coronary sinus, and the *body of the right atrium*, which is composed of the right auricle and right atrial free wall.[7] Key structures involved in macroreentrant tachycardia circuits can be found within both components of the right atrium, and to a lesser degree within the left atrium (Fig. 17.1).

The crista terminalis is a muscle bundle located between the sinus venosus of the right atrium and the right atrial body.[7] The myocardial fiber

bundles within the crista terminalis exhibit low resistance and faster conduction in the longitudinal plane, which commonly results in nonuniform anisotropic conduction (see p. 297).[8] The crista terminalis serves as a critical isthmus for right atrial free wall atypical atrial flutter and as an anatomical boundary for most right atrial flutters.[4,5]

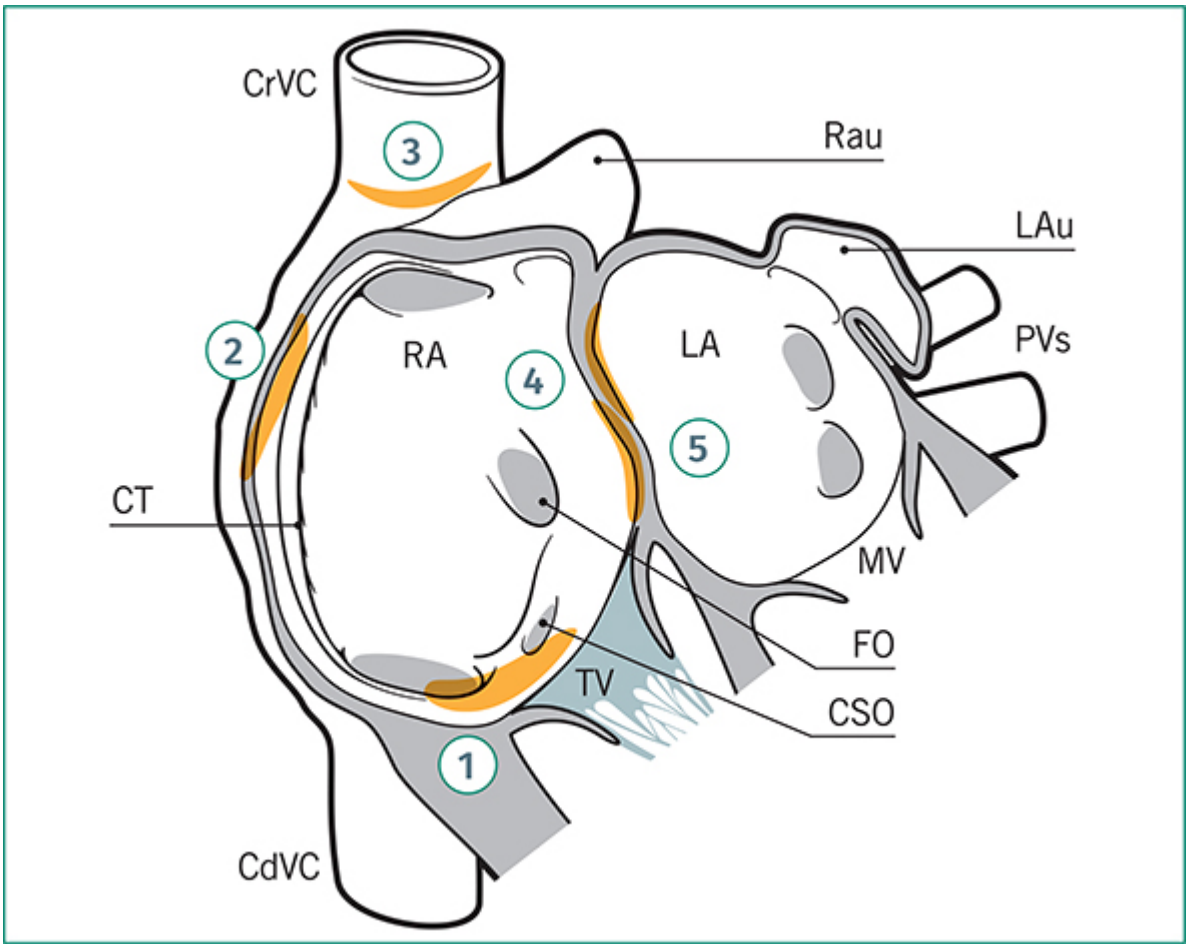


FIGURE 17.1. Anatomical view of the atria and tributary veins after removal of the atrial walls, with the different locations of the critical protected isthmuses (highlighted in orange) of canine macroreentrant atrial tachycardias or atrial flutters. 1, Cavotricuspid isthmus; 2, right atrial free wall isthmus; 3, cranial vena cava isthmus; 4, right atrial septum isthmus; 5, left atrial septum isthmus; CrVC, cranial vena cava; CdVC, caudal vena cava; CT, crista terminalis; RA, right atrium, Rau, right auricle; FO, fossa ovalis; CSO, coronary sinus ostium; TV, tricuspid valve; LA, left atrium; Lau, left auricle; MV, mitral valve; PVs, pulmonary veins.

The cavotricuspid isthmus is a critical component of typical and reverse typical atrial flutter, which together comprise most cases of atrial flutter in dogs.[4] The cavotricuspid isthmus is bordered by the septal leaflet of the

tricuspid valve anteriorly and the Eustachian valve and ridge posteriorly.[9] Grossly, the cavotricuspid isthmus is divided in humans into paraseptal, central, and inferolateral isthmuses.[9] The paraseptal isthmus, located between the left end of the Eustachian ridge and the tricuspid annulus, serves as the medial edge of the cavotricuspid isthmus and contains the thickest muscular layer within the cavotricuspid isthmus. Due to both the proximity of the paraseptal isthmus to the atrioventricular node and the high energy required to ablate thickened muscle tissue, this region should be avoided during cardiac ablation due to the increased risk of induction of atrioventricular block. The central isthmus is characterized as a line located parallel to the paraseptal isthmus starting from the midpoint of the Eustachian ridge and extending to the septal leaflet of the tricuspid valve. The inferolateral isthmus serves as the lateral edge of the cavotricuspid isthmus and is found parallel to both the paraseptal and central isthmuses, between the right end of the Eustachian ridge and the septal leaflet of the tricuspid valve. While both the central and inferolateral isthmuses have been identified as appropriate locations for cardiac ablation in humans, the presence of sub-Eustachian recesses and proximity of the right coronary artery to the central isthmus may increase the risk of complications and supports the necessity for assessment of the surrounding anatomy prior to cardiac ablation.[9]

The cranial vena cava enters the right atrium superiorly and is found within the sinus venosus component of the right atrium. The cranial vena cava has frequently been found as an arrhythmogenic isthmus in atypical flutter in dogs.[6] Atrial myocardial sleeves have been found within the superior and inferior venae cavae in humans with or without atrial fibrillation, in addition to slow inhomogeneous conduction within the superior vena cava resulting in atrial tachycardia.[1,10] In dogs, the combined presence of atrial myocardial sleeves within the cranial vena cava and differing action potentials and ionic currents in the cranial vena cava and atrial cardiomyocytes is suspected as the underlying arrhythmogenic mechanism for atypical cranial vena cava isthmus–dependent flutter in dogs.[6,10–12] Unlike the caudal vena cava, which may have a Eustachian valve that anatomically hinders right atrial catheterization, the cranial vena cava has no anatomical obstructions and allows for easier catheterization in most patients.[9]

The *interatrial septum* is composed of fibromuscular tissue and separates the right and left atria. The interatrial septum is bordered by the caudal vena cava inferiorly, the tricuspid annulus anteriorly, the cranial vena cava superiorly, the atrial wall posteriorly, the noncoronary sinus of Valsalva anterosuperiorly, and the coronary sinus ostium anteroinferiorly.[9] The activation pattern of the interatrial septum and left atrium contributes to the appearance of flutter waves on surface electrocardiograms, which may contribute to the low specificity for localization of the critical isthmus.[8] The interatrial septum serves both as a component of all atrial flutter circuits and as an arrhythmogenic isthmus on both the right and left atrial surfaces.[4,5,13]

ELECTROPHYSIOLOGICAL MECHANISM

Anatomical macroreentrant tachycardia refers to reentrant circuits that rely on a region of slowed conduction within the atrium; this region of slowed conduction acts as a necessary component for initiation and propagation of the circuit.[1,14] For initiation of macroreentry, several components must be present and include a circuit, the pathway of activation involving several structures within the atrium, a region of slowed conduction (known as the *protected critical isthmus*), unidirectional conduction block that directs activation along the circuit, and a triggering event such a premature atrial depolarization.[1,3,14]

The propensity for various structures within the atria to alter conduction velocity or direction, termed *anisotropy*, plays a vital role in the origination of a reentrant circuit in anatomical atrial flutter.[14] While healthy atrial myocytes have a greater conduction velocity along the longitudinal axis than along the transverse axis, several anatomical structures including the cavotricuspid isthmus and the crista terminalis exhibit nonuniform anisotropic conduction, which results in significant slowing of transverse conduction and predisposes these structures to a higher risk of functional unidirectional block.[14]

A normal action potential arising from the sinus node propagates as a wavefront in a superior-to-inferior direction along the right atrium and rapidly towards the atrioventricular node along the longitudinal axis. When the action potential reaches the critical isthmus of a reentrant circuit,

conduction is slowed in the transverse axis, thus prolonging the refractoriness of this region while the surrounding atrial tissue becomes excitable again. If an additional stimulus such as a premature beat occurs during a period of refractoriness within the critical isthmus, this can serve as a triggering event for initiation of a reentrant circuit. When the stimulus reaches the critical isthmus, functional block due to prolonged refractoriness prevents the action potential from propagating along this region; the action potential is instead directed along the circuit away from the region of unidirectional block. As the wavefront of activation travels along the circuit, it will be directed again towards the critical isthmus, which has become excitable again. The critical isthmus is reexcited by the action potential and subsequently directs the wavefront forward along the circuit. Once the wavefront of activation is within the macroreentrant circuit, the critical isthmus will serve to slow conduction while the previously activated tissue of the reentrant circuit becomes excitable again, serving to continually propagate the signal forward. The continuous presence of excitable tissue ahead of the wavefront of activation along the circuit is termed the *excitable gap*, and it is necessary to continue to propagate the impulse along the circuit to maintain atrial flutter.[14]

As outlined above, macroreentrant atrial tachycardias in dogs have been classified into three large groups, each of which are based on the different anatomical substrates that serve as the arrhythmogenic isthmus or the functional substrate. Further subclassifications have been established and are usually used clinically to denote the underlying mechanism, localization of the observed isthmuses, rotation pattern, and sequence of activation of these tachycardias.[1,4–6,8,15]

These subclassifications include:

- Anatomical reentrant atrial flutter
  - Cavotricuspid isthmus–dependent atrial flutter
    - Typical atrial flutter
    - Reverse typical atrial flutter
  - Atypical or non-cavotricuspid-isthmus-dependent atrial flutter
    - Right septal atrial flutter
    - Right atrial free wall flutter (without prior atriotomy)
    - Cranial vena cava atrial flutter
    - Left septal atrial flutter

- Functional reentrant atrial flutter

The anatomical or functional substrate and associated electrophysiological mechanism for each type of macroreentrant atrial tachycardia are further explained below.

ANATOMICAL REENTRY ATRIAL FLUTTERS

Cavotricuspid isthmus–dependent atrial flutter

The cavotricuspid isthmus is a narrow region of tissue found between the tricuspid valve anteriorly and the Eustachian ridge and caudal vena cava orifice posteriorly; it serves as an essential region of slowed conduction within the reentrant circuit of both *typical and reverse typical atrial flutter*.[1,4,15–17] While both typical and reverse typical atrial flutter use the same circuit for reentry, which includes the interatrial septum, the roof of the right atrium, the right atrial free wall (in front of the crista terminalis), and the floor of the right atrium along the cavotricuspid isthmus, the direction of activation differs, with a counterclockwise or clockwise propagation respectively along these structures within the right atrium.[14,15] In both typical and reverse typical atrial flutter, the cavotricuspid isthmus serves as the region of anisotropic conduction resulting in the electrical unidirectional block that directs activation counterclockwise or clockwise along the reentry circuit respectively (Fig. 17.2).[14]

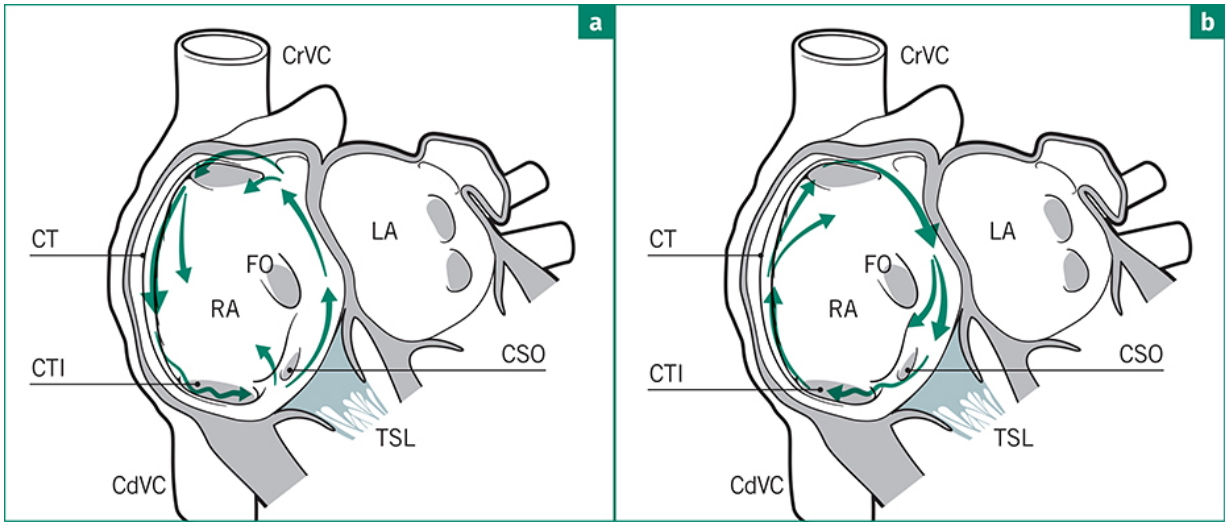


FIGURE 17.2. Anatomical view of the rotation patterns of typical (a) and typical reverse (b) atrial flutter. Both types of macroreentrant atrial tachycardia depend on the cavotricuspid critical isthmus;

however, while the activation wavefront in typical atrial flutter rotates counterclockwise around the tricuspid valve annulus, it rotates clockwise in typical reverse atrial flutter. CTI, cavotricuspid isthmus; CdVC, caudal vena cava; CT, crista terminalis; CrVC, cranial vena cava; FO, fossa ovalis; CSO, coronary sinus ostium; TSL, tricuspid septal leaflet; RA, right atrium; LA, left atrium.

Atypical or non-cavotricuspid-isthmus-dependent atrial flutters

Right septal, right atrial free wall, and cranial vena cava flutter

While in humans, right atrial free wall flutter is commonly observed with previous cardiac surgery (right atriotomy), and right septal atrial flutter can be observed following atrial septal repair, atypical right atrial flutter in dogs is often observed without previous cardiac surgery.[5,6,8,15] As in humans in the absence of a previous surgical intervention, an electrically silent region within the right atrial free wall or interatrial septum secondary to fibrosis, chronic atrial stretch, anisotropic conduction near the crista terminalis, wavefront movement around the cranial vena cava, or spontaneous (idiopathic) etiologies may contribute to the underlying mechanism of non-cavotricuspid-isthmus-dependent right atrial flutter in dogs.[15,18]

Left septal flutter

While the left interatrial septum was recently identified as a non–cavotricuspid isthmus resulting in atrial flutter in the dog, the activation pattern and electrophysiological mechanism of left septal flutter was not further elucidated due to routine placement of mapping catheters within the right atrium.[13] In humans, left atrial macroreentrant tachycardias are mostly associated with atrial degeneration and fibrosis secondary to primary cardiac disease resulting in electrically silent isthmuses with a circuit that commonly involves the mitral valve annulus or pulmonary veins.[8,18]

Functional reentrant atrial flutter

Previously termed type II flutter, functional macroreentrant tachycardia is used to describe wave-like atrial activity of unknown origin that originally appears similar to atypical flutter but is unable to be entrained and is usually unstable, with rapid degeneration into atrial fibrillation or return to typical atrial flutter.[1,15] Electrophysiological mapping may reveal several regions

of continuous activation within either atrium, or fractionated electrograms and lack of a dominant circuit.[1,8] While the exact mechanism is unknown, induction via rapid pacing during an electrophysiological study or periods of high parasympathetic tone associated with high acetylcholine may result in observation of this type of atrial flutter.[12,15,19] Because it there is no fixed arrhythmogenic isthmus, functional reentrant atrial flutter more closely resembles atrial fibrillation, and targeted treatment with cardiac ablation is therefore unlikely to be successful.[8]

ELECTROCARDIOGRAPHIC FINDINGS

Right atrial flutter is characterized by regular, monomorphic atrial depolarizations termed flutter waves (F waves) with a median cycle length of 199 ms (range, 142–256 ms). Flutter waves correspond to rapid atrial depolarizations, and atrial flutter is characterized as the supraventricular tachycardia with the shortest atrial cycle length observed in dogs, although it is not statistically different from orthodromic atrioventricular reciprocating tachycardia. The conduction ratio of atrial flutter is variable; a study in dogs revealed 41% of cases exhibited a 1:1 conduction ratio, 41% a 2:1 conduction ratio, and 18% a variable conduction ratio. As a result of this variable atrioventricular conduction ratio and regular atrial cycle length, most atrial flutter cases (65%) exhibit ventricular cycle length regularity with an average RR interval of 270 ms (range, 240–300 ms), while the remainder of atrial flutter cases may reveal cycle length irregularity.[20]

The duration of flutter waves differs significantly from that of P waves during sinus tachycardia, with an average F wave duration of 50 ms (range, 40–60 ms). The electrical axis depends on the site of origin of the flutter (mean electrical axis, + 76°; range, + 72 to + 81°). The position of the F wave is variable in 59% of flutter cases and is due to the different atrioventricular conduction ratios, with 18% of cases exhibiting a long RF interval, 18% of cases exhibiting a short RF interval, and 5% of cases exhibiting an F wave occurring on a T wave. The median RF interval was 120 ms (range, 72–144 ms) and the median FR interval was 126 ms (range, 83–169 ms), resulting in a RF/FR median ratio of 0.81 (range, 0.63–1.13). All cases of right atrial flutter other than typical cavotricuspid isthmus–dependent atrial flutter have noncontinuous atrial activation on the surface

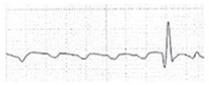
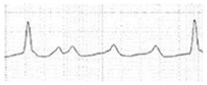
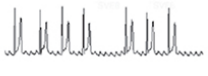
electrocardiogram, characterized by an isoelectric line interposed between consecutive F waves.[20]

The QRS complex duration in atrial flutter is narrow except in cases of aberrant conduction (56 ms; range, 50–60 ms), with a normal QT interval (200 ms; range, 170–220 ms). All right atrial flutters have an incessant behavior unless pharmacological treatment is started.[20]

Left atrial flutter is characterized by an incessant narrow QRS tachycardia (QRS duration, 70 ms), monomorphic F waves with a regular atrial cycle length of 180 ms, and a visible isoelectric line interposed between consecutive F waves. The atrioventricular conduction ratio can be variable, ranging from 1:1 to 8:1, with a ventricular cycle length ranging from 360 ms to 620 ms. Negative F waves appear in the inferior leads (II, III, and aVF) and an isoelectric lead I.[13]

The specific electrocardiogram findings characteristic of the location of the arrhythmogenic isthmus are outlined in Table 17.1.

TABLE 17.1. Electrocardiographic (ECG) appearance of anatomical and functional atrial flutter in the dog.

Arrhythmogenic substrate and ECG appearance	Typical atrial flutter	Reverse-typical atrial flutter	Atypical right	Atypical left	Functional
F wave appearance	Monomorphic Saw-tooth Negative cusp in inferior leads	Monomorphic Positive in inferior leads	Monomorphic Positive in inferior leads	Monomorphic Negative in inferior leads	Polymorphic Positive in inferior leads
FF interval	Regular 360–450 bpm 130–170 ms	Regular 360–450 bpm 130–170 ms	Regular 230–280 bpm 215–260 ms	Regular 300 bpm 200 ms	Variable ≥500 bpm ≤120 ms
Isoelectric line	No	Yes	Yes	Yes	No
ECG lead II					
QRS complex duration	≤70 ms Unless concurrent interventricular conduction block	≤70 ms Unless concurrent interventricular conduction block	≤70 ms Unless concurrent interventricular conduction block	≤70 ms Unless concurrent interventricular conduction block	≤70 ms Unless concurrent interventricular conduction block
Atrioventricular conduction ratio	2:1 or variable	2:1 or variable	1:1 or 2:1	2:1 or variable	2:1 or variable
RR interval	Regular	Regular	Regular	Regular	Regular or irregular Converts rapidly into sinus rhythm or atrial fibrillation

CAVOTRICUSPID ISTHMUS–DEPENDENT ATRIAL FLUTTER

Typical atrial flutter

Counterclockwise cavotricuspid isthmus–dependent atrial flutter is the most common flutter in humans, accounting for about two-thirds of atrial flutter cases;[16] in the authors' experience, it is also the most common atrial flutter identified in dogs.

The electrocardiogram appearance of typical atrial flutter is characterized by organized atrial depolarizations across all leads observed as regular, identical flutter waves (F waves) with a saw-tooth appearance and no isoelectric line between them.[4] F waves exhibit both positive and negative components, but with a predominant negative cusp in the inferior leads (II, III, and aVF) due to the inferior-to-superior activation of the interatrial septum (Fig. 17.3).[8] The ventricular rate depends on the atrioventricular conduction ratio, resulting in a narrow QRS complex tachycardia with a fixed atrioventricular block or a variable atrioventricular block ranging from 2:1 to 6:1.[4]

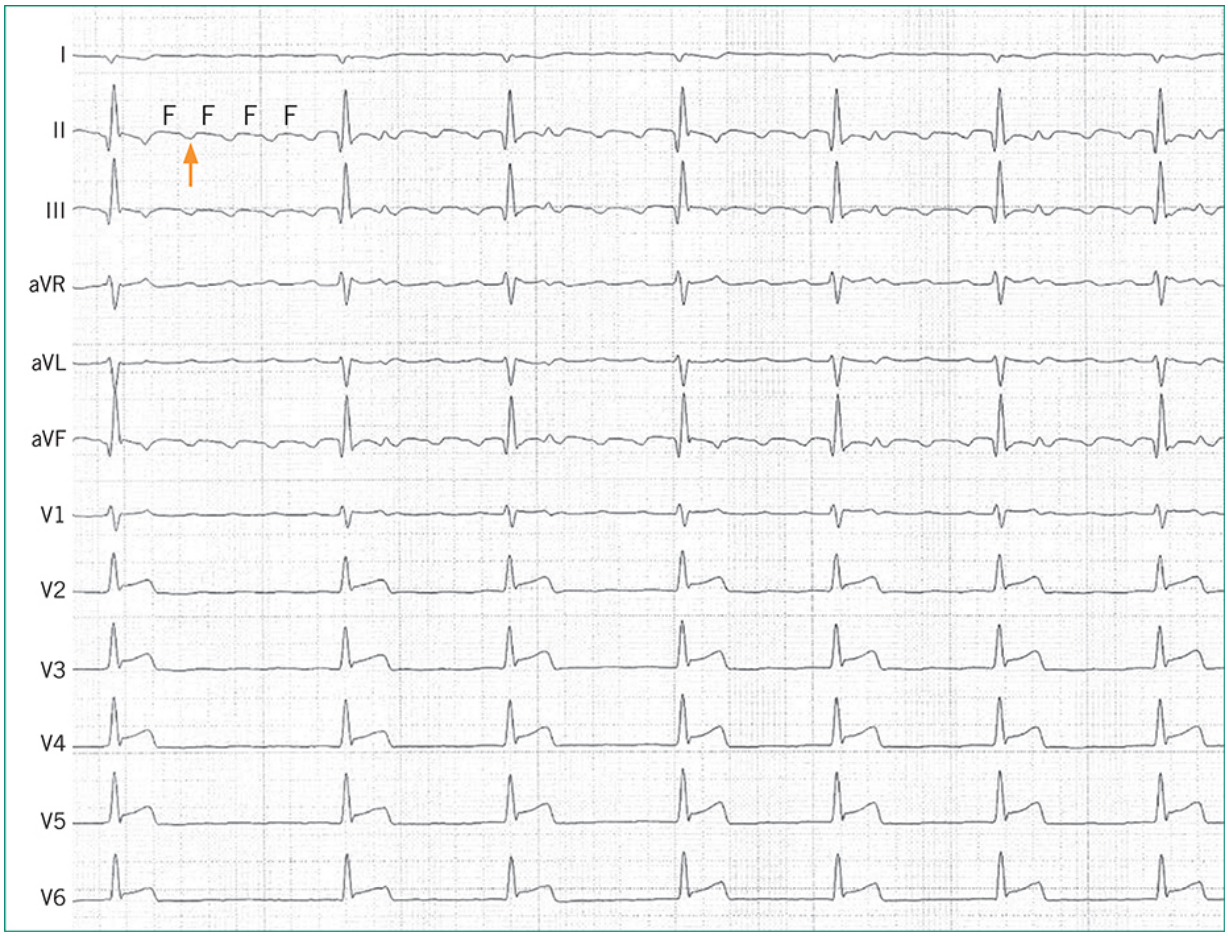


FIGURE 17.3. Cavotricuspid isthmus–dependent typical atrial flutter in a 12-year-old male Labrador with tricuspid valve dysplasia. Note the presence of continuous, regular monomorphic atrial flutter waves (F) with a saw-tooth appearance (positive component and negative cusp in lead II) with a rate of 390 bpm and a regressive atrioventricular conduction ratio from 6:1 to 4:1. The negative cusp (arrow) represents the inferior-to-superior activation of the interatrial septum. Twelve leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6); speed, 50 mm/s; calibration, 5 mm/1 mV.

Reverse typical atrial flutter

Clockwise cavotricuspid isthmus–dependent atrial flutter uses the same circuit as typical atrial flutter; however, the wavefront travels through the circuit in the opposite direction, which results in positive flutter waves in the inferior leads (II, III, and aVF) due to the superior-to-inferior activation of the interatrial septum.[15] An isoelectric line is usually present between two consecutive F waves (Fig. 17.4).[4] Although the atrial activation is continuous, an isoelectric line appears very likely due to the slow diastolic activation time of the isthmus, which is not visible on the surface electrocardiogram.[4]

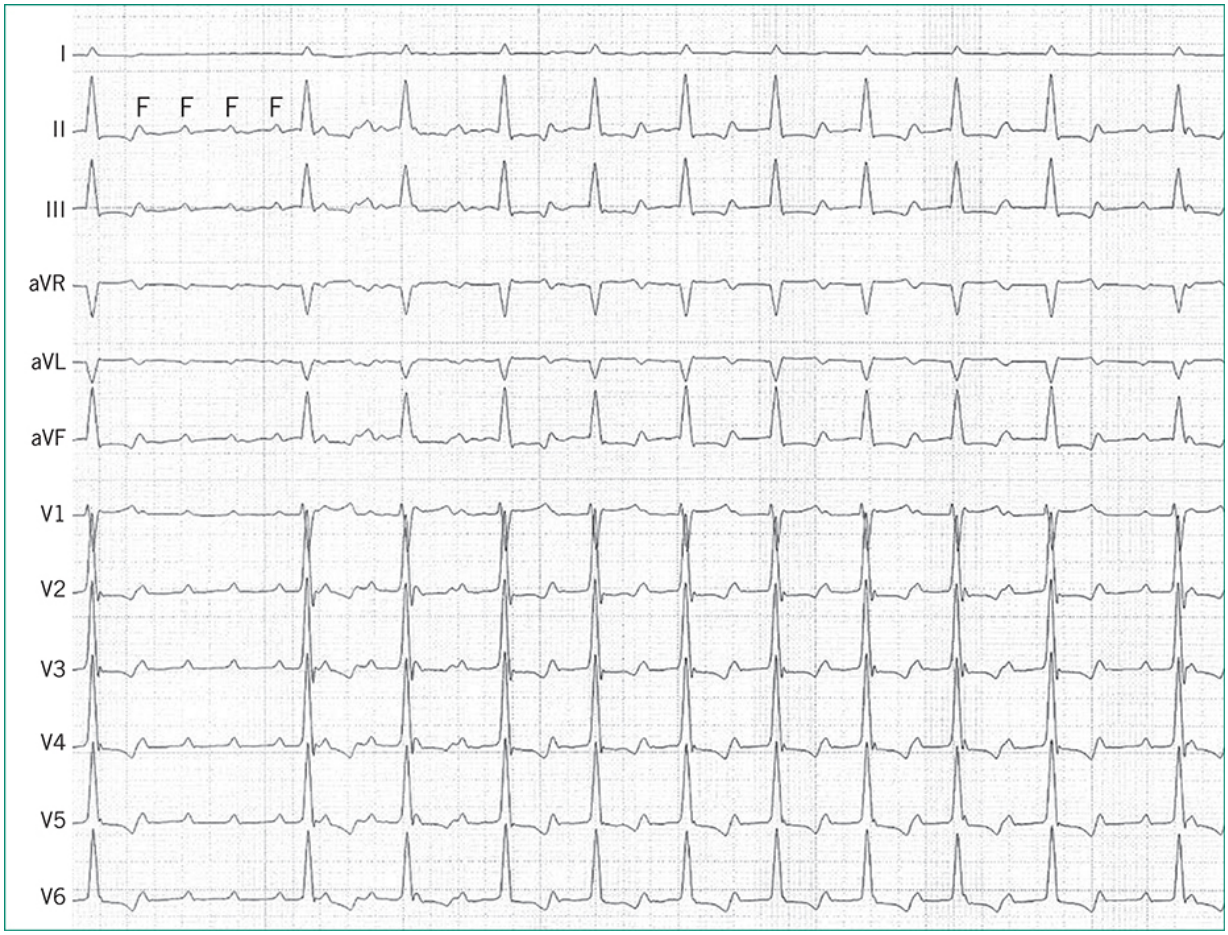


FIGURE 17.4. Cavotricuspid isthmus–dependent typical reverse atrial flutter in an 8-year-old female English Bulldog with arrhythmogenic cardiomyopathy. Note the presence of regular monomorphic atrial flutter waves (F) positive in lead II with isoelectric lines between them, with a rate of 380 bpm, and a regressive atrioventricular conduction ratio from 5:1 to 3:1. The positive wave represents the superior-to-inferior activation of the interatrial septum. Twelve leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6); speed, 50 mm/s; calibration, 5 mm/1 mV.

Atypical or non-cavotricuspid-isthmus-dependent atrial flutters

Right septal, right atrial free wall, and cranial vena cava flutter

Atypical right atrial flutters arising from the right interatrial septum, right atrial free wall, or cranial vena cava in the dog usually share electrocardiographic characteristics, with regular, monomorphic, F waves that are positive in the inferior leads (II, III, and aVF) and have a superior-to-inferior and right-to-left axis commonly observed within the previous ST segment. The F waves can frequently be observed moving back and forth across the previous R wave. An isoelectric line is commonly visible

between two consecutive F waves.[5,6] As with cavotricuspid isthmus–dependent atrial flutter, the QRS complex duration is narrow, unless a concurrent conduction block is present with an either fixed or variable atrioventricular conduction ratio (1:1, 2:1, or variable from 1:1 to 3:1) (Fig. 17.5).[5,6]

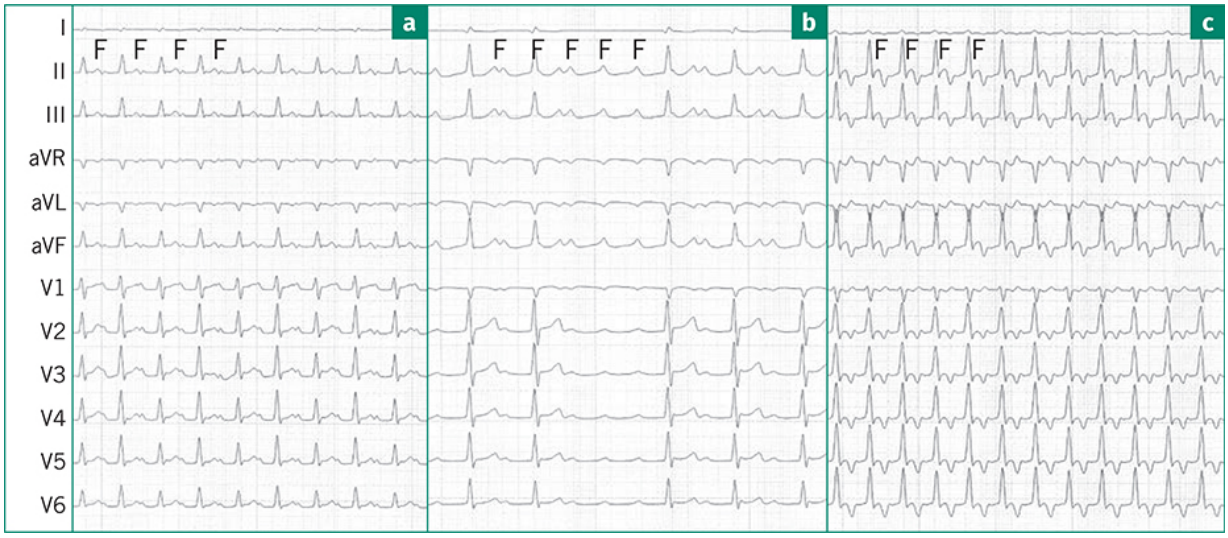


FIGURE 17.5. Right atypical atrial flutters. a) Right septal atrial flutter in a 7-year-old male Bernese Mountain Dog. Note the presence of regular monomorphic atrial flutter waves (F) with isoelectric lines between them and a rate of 240 bpm. They are positive in lead II, have a 1:1 atrioventricular conduction ratio, and can be seen in a fixed position of the previous ST segment. b) Right atrial free wall without atriotomy flutter in a 6-year-old male Dogue de Bordeaux. Note the presence of regular monomorphic atrial flutter waves (F) with isoelectric lines between them and a rate of 270 bpm. They are positive in lead II, have a progressive atrioventricular conduction ratio from 3:1 to 5:1, and their position in the previous ST segment is variable depending on the atrioventricular conduction delay. c) Cranial vena cava flutter in a 9-year-old female Bernese Mountain Dog. Note the presence of regular monomorphic atrial flutter waves (F) positive in lead II with isoelectric lines between them, with a rate of 270 bpm, and a 1:1 atrioventricular conduction ratio, located in a fixed position of previous ST segment. Twelve leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6); speed, 50 mm/s; calibration, 5 mm/1 mV.

Left septal flutter

In humans, left atrial flutter may produce an electrocardiographic pattern similar to that of typical or atypical atrial flutter, with a predominantly positive F wave morphology in the V1 precordial lead and the presence of a third-degree or advanced interatrial block associated with atrial remodeling.[1,15] The single case of left septal flutter identified in a dog was characterized by regular, monomorphic, negative flutter waves in the

inferior leads (II, III, and aVF) located in a fixed position within the previous ST segment. An isoelectric line was present between two consecutive flutter waves, and the atrioventricular conduction ratio was variable, ranging from 1:1 to 8:1 (Fig. 17.6).[13]

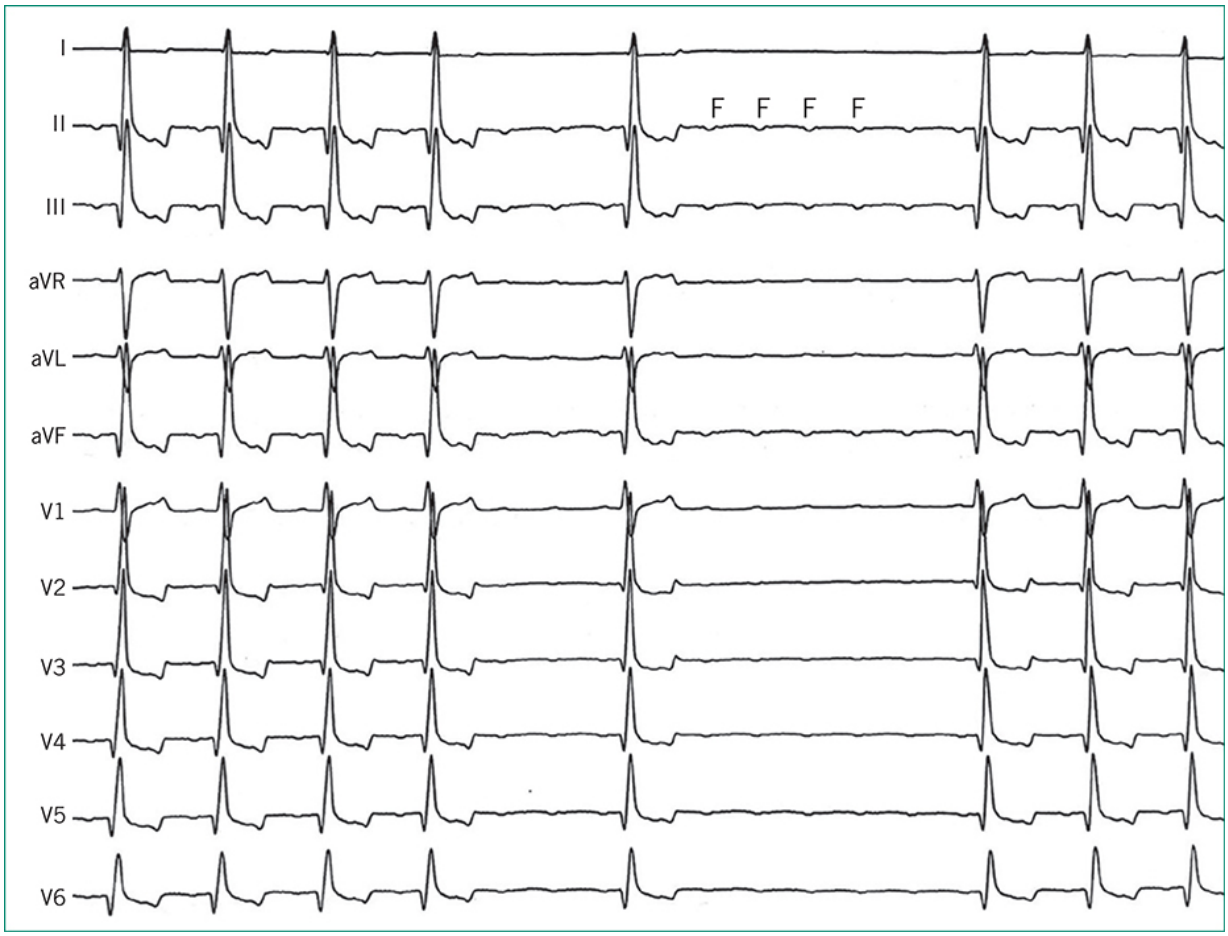


FIGURE 17.6. Left septal atypical atrial flutter in 6-year-old male Chesapeake Bay Retriever. Note the presence of regular monomorphic atrial flutter waves (F) with isoelectric lines between them, a rate of 330 bpm, and a progressive atrioventricular conduction ratio from 5:1 to 8:1. They are negative in lead II due to the inferior-to-superior activation of the right atrial free wall with simultaneous activation of the posterior left atrium and superior-to-inferior and left-to-right activation of the interatrial septum. Twelve leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6); speed, 50 mm/s; calibration, 10 mm/1 mV.

Functional atrial flutter

In the absence of a stable circuit, functional atrial flutter is characterized by atrial waves of variable morphology, which are typically positive in the inferior leads (II, III, and aVF) and have an irregular and extremely short atrial cycle length (usually ≤120 ms). This is an unstable rhythm commonly

found during Holter recordings in dogs with reflex syncope; it rapidly converts to atrial fibrillation, typical atrial flutter, or sinus rhythm (Fig. 17.7).[1,8,19]

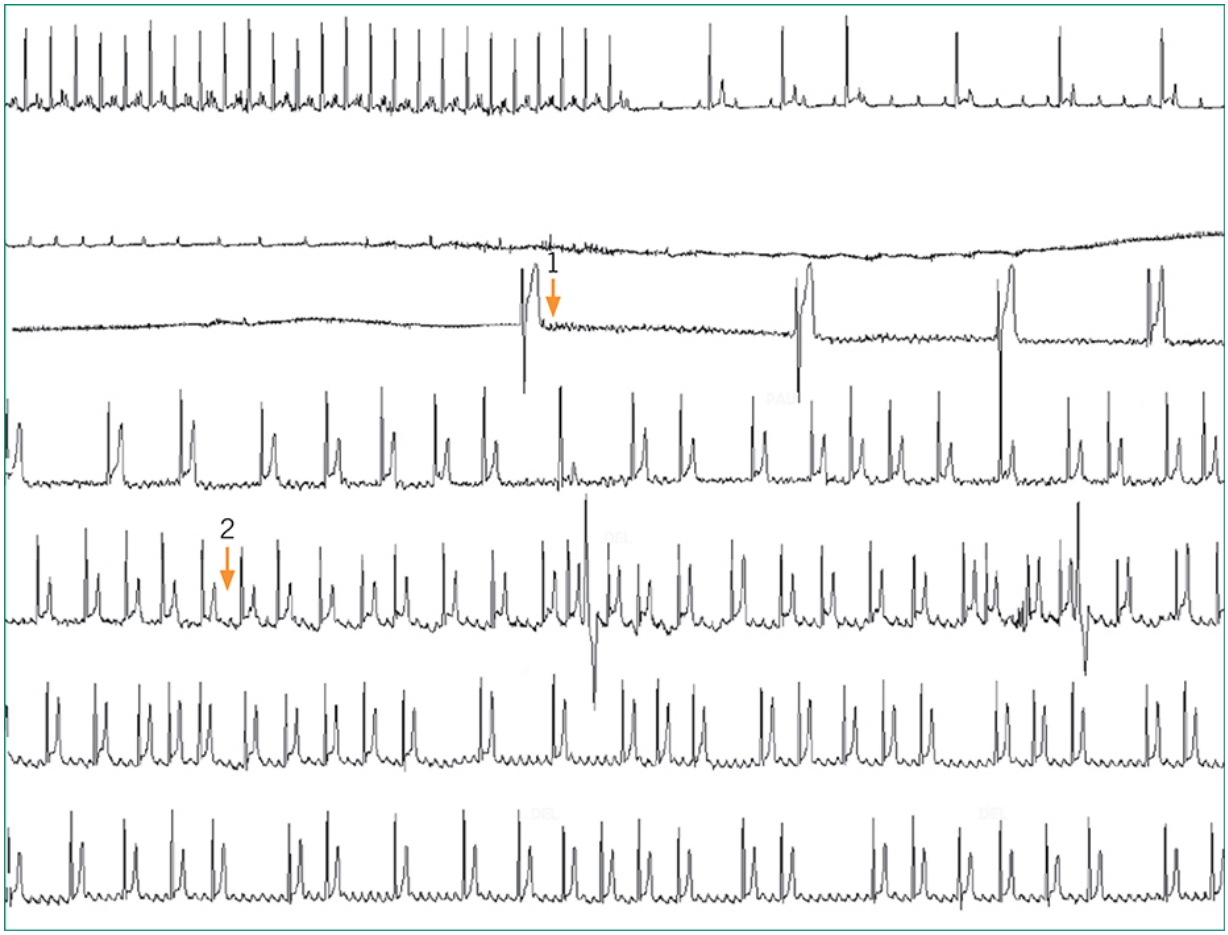


FIGURE 17.7. Ambulatory electrocardiographic recording of a 7-year-old male mixed-breed dog with an initial paroxysmal atrioventricular block with sinus bradycardia (1B), followed by type 1A sinus arrest due to an inappropriate vagal reflex.[26] The tracing starts with a sinus tachycardia (185 bpm) followed by a progressive atrioventricular block and sinus bradycardia (from 140 to 35 bpm) until sinus arrest occurs, interrupted by a ventricular escape rhythm concomitant with vagally induced paroxysmal atrial fibrillation (first arrow). After 24 seconds (second arrow), cardioversion to functional atrial flutter occurs. Atrial activity at this point appears more regular and organized with an atrial rate of 530 bpm. Lead Y; each line corresponds to 15 seconds. Speed, 18.6 mm/s; calibration, 5 mm/mV.

Fibrillo-flutter

The term fibrillo-flutter has been used to define the presence of organized atrial fibrillation that intermittently converts into macroreentrant atrial tachycardia and back into atrial fibrillation. In dogs, atrial activations

during atrial flutter periods are usually very rapid (irregular cycle length that is usually ≤120 ms), with variable morphology and characteristics similar to those of functional atrial flutter, followed in some cases by a conversion into macroreentrant atrial tachycardia with regular F waves (average cycle length >120 ms) or into coarse atrial fibrillation (Fig. 17.8).

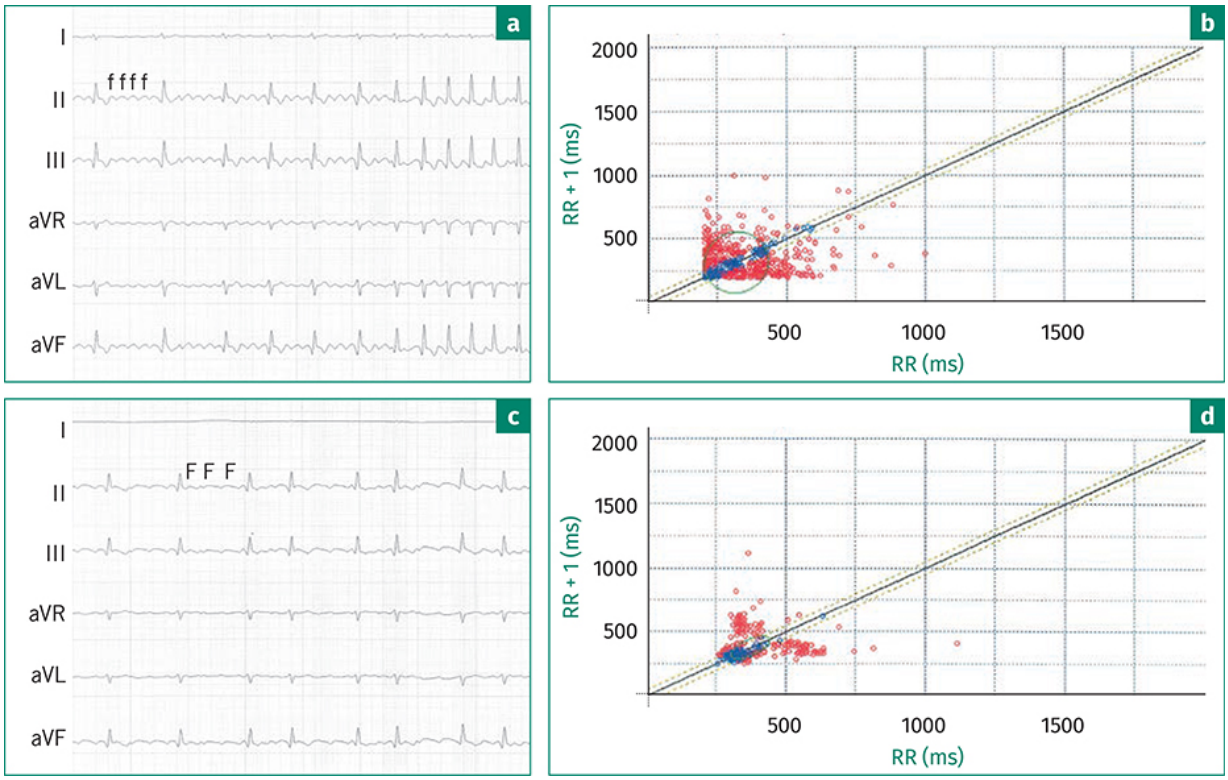


FIGURE 17.8. a) Fibrillo-flutter in a 5-year-old male Boxer with a dilated cardiomyopathy phenotype. Note the presence of regular monomorphic atrial fibrillatory waves (f) that are positive in lead II and have a saw-tooth appearance, a rate of 600 bpm, and variable ventricular response characteristic of functional reentry. b) Five-minute Poincaré plot showing a random and irregular RR interval distribution clustering in the bottom left corner of the tachycardia rates, typical of atrial fibrillation. c) Twenty-four hours after admission, the atrial fibrillation organized into atrial flutter with regular monomorphic atrial flutter waves (F) that are positive in lead II and have a saw-tooth appearance, a rate of 430 bpm, and a variable atrioventricular conduction ratio from 5:1 to 3:1, characteristic of anatomical reentry. d) Five-minute Poincaré plot showing an exit block pattern of distribution of the RR intervals typical of atrial flutter, with a variable atrioventricular conduction ratio. Note the more regular grouping of the RR intervals in the bottom right corner with separate areas of clustering due to the variable atrioventricular conduction ratio. Six limb leads (I, II, III, aVR, aVL, aVF); speed, 50 mm/s; calibration, 5 mm/1 mV.

Atrial flutter in the cat

In the authors' experience, atrial flutter is an extremely rare arrhythmia in cats. Their atrial anatomy, electrophysiology, and size can probably explain

the reason why a sustained macroreentrant atrial tachycardia is unlikely to occur in cats. Since no data are available in the veterinary literature on electrophysiological mapping findings in cats with atrial flutter, this arrhythmia can only be suspected using the electrocardiographic criteria defined for dogs. In the authors' experience, atrial flutter in cats can be paroxysmal; the atrial rate ranges from 400 to 500 bpm with isoelectric lines between consecutive F waves and very commonly 2:1 atrioventricular conduction ratio (Fig. 17.9).

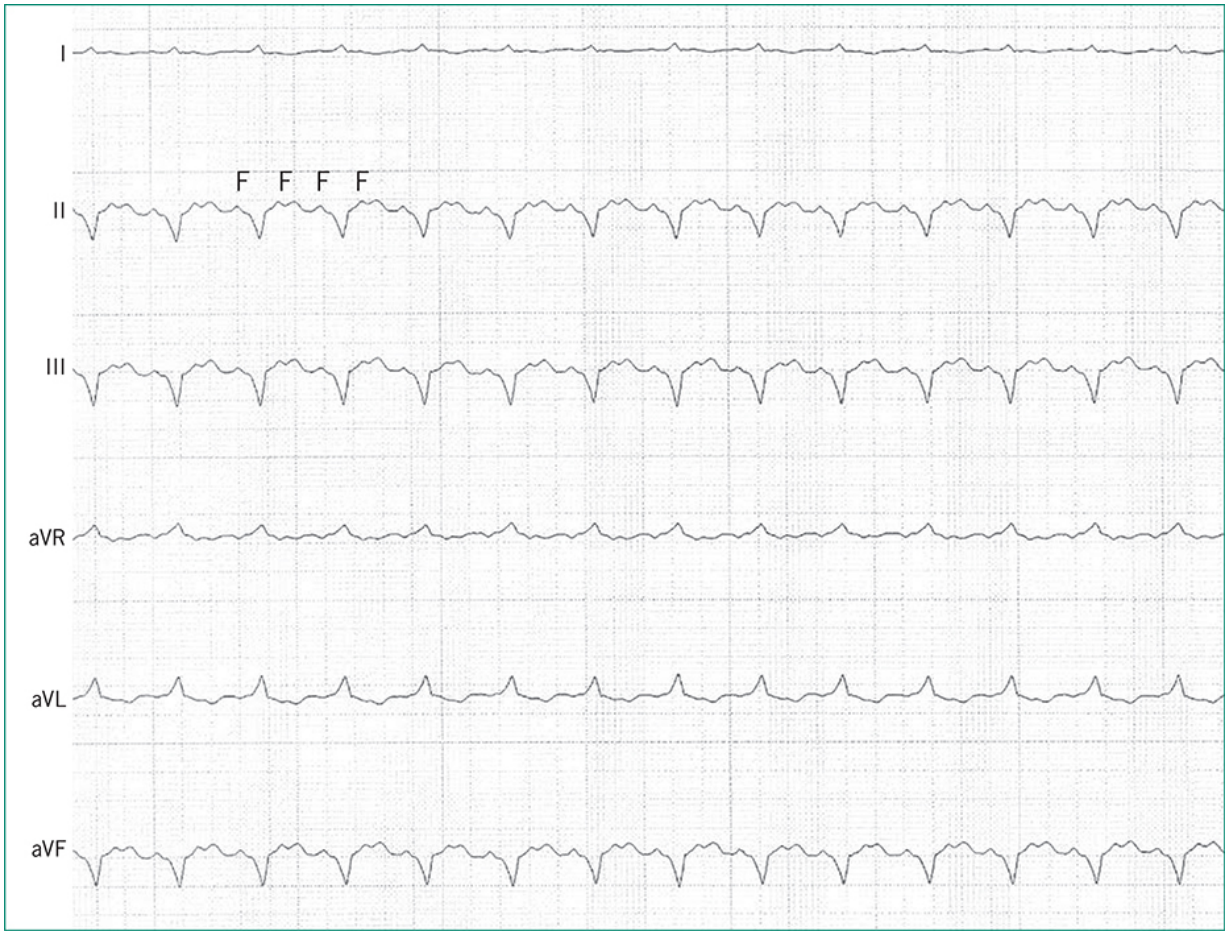


FIGURE 17.9. Atrial flutter in a 13-year-old male domestic shorthair cat with a restrictive cardiomyopathy phenotype. Note the presence of regular monomorphic atrial flutter waves (F) that are positive in lead II, with isoelectric lines between them, a rate of 430 bpm, and a fixed 2:1 atrioventricular conduction ratio. QRS complexes appear wide (45 ms) with a left axis shift (–30°) due to the presence of a bifascicular block (right bundle branch block plus left anterior fascicular block). Six limb leads (I, II, III, aVR, aVL, aVF); speed, 50 mm/s; calibration, 5 mm/1 mV.

CLINICAL PRESENTATION

Although it is found in both male and female dogs, atrial flutter is diagnosed more frequently in females (65%). The most represented breed with atrial flutter is the Bernese Mountain Dog (35%), with other commonly observed breeds including both English Bulldogs (12%) and English Setters (12%), with a median age at diagnosis of 8 years (interquartile range, 3.7 years) and a median body weight of 38 +/– 15.8 kg.[20] Episodic weakness of variable duration usually precedes presentation to the hospital, with some dogs additionally displaying dysorexia or signs of right-sided congestive heart failure such as jugular pulsations or ascites.[4–6] At the time of presentation, a depressed mentation, weight loss, a rapid heart rate, or pulse deficits may be appreciated.[4–6]

OTHER METHODS OF EVALUATION

ECHOCARDIOGRAPHY

As with all tachyarrhythmias, a complete echocardiogram should be performed to assess for morphological changes associated with long-standing tachycardia. These changes can range from mild systolic dysfunction without chamber dilation to a dilated cardiomyopathy phenotype with varying degrees of cardiac dilation and systolic dysfunction, also known as arrhythmia-induced cardiomyopathy (see p. 397).[4–6] Echocardiography can also be used to screen for concurrent cardiac diseases, such as degenerative valve disease, cardiac masses, or, in the authors' experience, arrhythmogenic cardiomyopathy in English Bulldogs, which may predispose to the development of cardiac remodeling and atrial flutter.[4–6] While identification of arrhythmia-induced cardiac remodeling or concomitant heart disease is possible, an echocardiographically normal heart may also be observed and should not be used as a basis for diagnosis or exclusion of atrial flutter.[4]

ELECTROPHYSIOLOGICAL STUDY

Electrophysiological mapping of macroreentrant atrial tachycardias should be performed as previously described in chapters 6 and 11, with three catheters placed to record electrical activity and assist in determining the activation pattern within the atria.

A decapolar catheter is advanced along the jugular vein into the great cardiac vein to record the electrical activity of the left (CSd) and right (CSp) atria with the distal and proximal electrodes, respectively. A second decapolar catheter advanced along the femoral vein is placed around the tricuspid valve annulus to record the electrical activity of the low posterior right atrial wall (LRA), the middle lateral right atrial wall (MRA), and the anterolateral high right atrium (HRA) at the crista terminalis with the distal electrode pair, middle electrode pair, and proximal electrode pair, respectively. A steerable ablation catheter is then positioned at multiple locations in the left atrium, right atrium, and tributary veins to map endomyocardial electrograms to determine the location of the critical isthmus and perform programmed stimulation.[4–6,20]

If atrial flutter is not observed during the basal study, programmed atrial pacing with a train of eight paced beats at a cycle length shorter than the atrial flutter rate should be performed followed by an extra stimulus with a progressively shorter coupling interval until initiation of the arrhythmia.[16] To confirm the presence of a macroreentrant tachycardia, continuous atrial activation, concealed entrainment within the isthmus, and a short postpacing interval (within 20–30 ms of the tachycardia cycle length) must be observed on electrophysiological mapping.[4–6,17]

The arrhythmogenic mechanism of atrial flutter can be determined by the pattern of continuous activation observed during periods of sustained flutter.

Counterclockwise or typical atrial flutter is identified by the observation of superior-to-inferior activation of the right atrial free wall and inferior-to-superior activation of the interatrial septum. The atrial wavefront propagates from the HRA coinciding with the beginning of the suspected F wave and then activates along the MRA, LRA, and the coronary sinus (CS) ostium before completing the circuit by returning to the HRA (Fig. 17.10a).[4,17]

Clockwise or reverse-typical atrial flutter is characterized by inferior-to-superior activation of the right atrial free wall and superior-to-inferior activation of the interatrial septum. As in typical atrial flutter, the atrial wavefront propagates from the His area coinciding with the beginning of the suspected F wave but then activates along the CS ostium, LRA, MRA, and HRA before completing the circuit by returning to the His area (Fig. 17.10b).[4,17]

Atypical atrial flutter activation patterns vary depending on the location of the circuit and critical isthmus, with continuous atrial activation observed as follows:

a. Cranial vena cava isthmus: Continuous activation of the right atrium in a clockwise pattern resulting in superior-to-inferior activation of the interatrial septum.[6]
b. Right interatrial septum isthmus: Continuous activation of the right atrium in a clockwise pattern with superior-to-inferior activation of the interatrial septum.[5]
c. Right posterior free wall isthmus: Continuous activation of the right atrium in a clockwise pattern with inferior-to-superior activation of the right atrial free wall and superior-to-inferior activation of the interatrial septum.[5]
d. Left interatrial septal isthmus: Continuous activation of the right atrium in a clockwise activation pattern, with inferior-to-superior activation of the right atrial free wall with simultaneous activation of the posterior left atrium, superior-to-inferior activation of the interatrial septum, and then activation back to the posterior right atrium and low right atrium to start the cycle again.[13]

The location of the critical isthmus should be suspected in the presence of *mid-diastolic fragmented intracardiac electrograms*, which support a region of slowed conduction. However, the location of the critical isthmus must be verified based on the presence of concealed entrainment and on the postpacing interval (within 20–30 ms of the tachycardia cycle length).

When pacing within the flutter circuit, atrial activation will follow both an orthodromic wavefront (same direction as that of baseline atrial activation) and an antidromic wavefront (opposite direction from that of baseline atrial activation). An orthodromic wavefront will reset the circuit, whereas an antidromic wavefront will result in fusion due to mixed activation combining the patterns of both the antidromic and orthodromic wavefronts. The fusion of these two wavefronts will result in flutter waves with an intermediate morphology on the surface electrocardiogram and in intracardiac electrograms ruling out the location of pacing as the arrhythmogenic isthmus. If pacing is performed within the flutter circuit at the arrhythmogenic isthmus, the activation wavefront will only be directed orthodromically around the circuit due to the presence of a unidirectional

block within the isthmus. This will result in concealed entrainment and in the surface electrocardiogram and intracardiac electrograms being identical to the baseline flutter activation pattern.[16]

Following entrainment within the flutter circuit, the cycle length should return to its baseline value immediately following termination (within 20–30 ms of the tachycardia cycle length) if pacing is performed at the arrhythmogenic isthmus. If pacing is done outside the flutter circuit, the activation wavefront must travel to the flutter circuit and then into the circuit, which will prolong the postpacing interval (Fig. 17.11).[16]

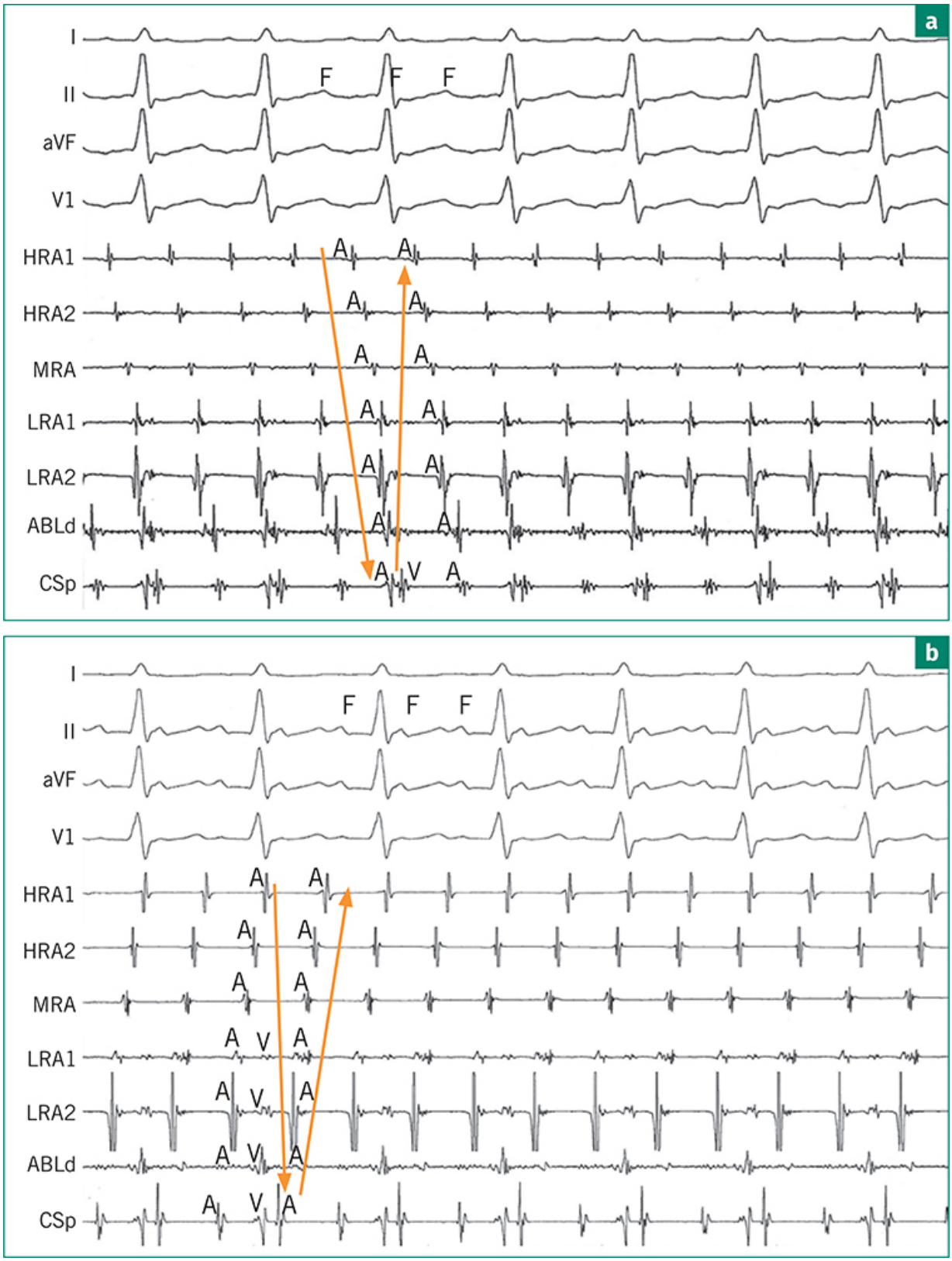


FIGURE 17.10. a) Endocardial mapping during typical atrial flutter in a 9-year-old male English Setter. Four-lead surface electrocardiogram (I, II, aVF, V1) and seven intracardiac electrocardiograms

recorded at the high right atrial wall (HRA 1-2), medium right atrial wall (MRA), low right atrial wall (LRA 1-2), cavotricuspid isthmus (ABLd, recorded with the ablation catheter), and proximal coronary sinus (CSp). Notice the sequence of atrial activation, with the orange arrows that rotate counterclockwise around the tricuspid valve annulus from the HRA, to the MRA, LRA, ABLd, CSp, and back to the HRA. The cavotricuspid isthmus, i.e., the area of slow conduction of this anatomical circuit, is located between the LRA2 and the CSp. b) Endocardial mapping during typical reverse atrial flutter in the same dog. Four-lead electrocardiogram (I, II, aVF, V1) and seven intracardiac electrocardiograms recorded at the high right atrial wall (HRA 1-2), medium right atrial wall (MRA), low right atrial wall (LRA1-2), cavotricuspid isthmus (ABLd, recorded with the ablation catheter), and proximal coronary sinus (CSp). Note the sequence of atrial activation, with the orange arrows that rotate clockwise around the tricuspid valve annulus from the LRA to the MRA, HRA, ABLd, CSp, and back to the LRA. The cavotricuspid isthmus, i.e., the area of slow conduction of this anatomical circuit, is located between the LRA2 and the CSP. This area is characterized by the presence of low amplitude, diastolic fragmented potentials (ABLd electrograms). Speed, 100 mm/s; 5 mV/cm. F, flutter waves; A, atrial electrograms; V, ventricular. Source: Santilli R. et al.[4]

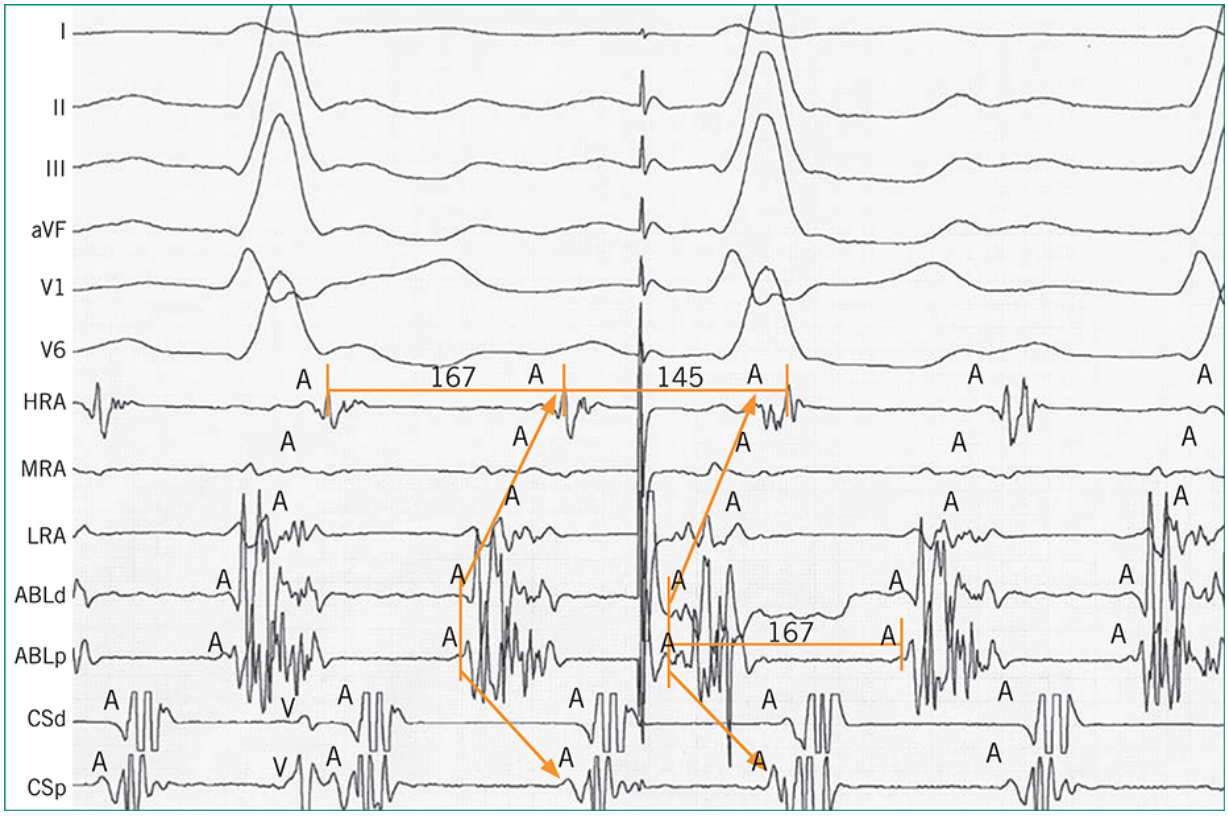


FIGURE 17.11. Endocardial mapping during concealed entrainment of an atypical right atrial free wall flutter in a 10-year-old female English Setter. Six lead-surface electrocardiogram (I, II, III, AVF, V1, V6) and seven intracardiac electrocardiograms recorded at the high right atrial wall (HRA), medium right atrial wall (MRA), low right atrial wall (LRA), right atrial free wall isthmus (ABLd, ABLp; recorded by the ablation catheter), and distal and proximal coronary sinus (CSd, CSp). Note the inferior-to-superior activation of the right atrial free wall moving from the isthmic area (ABLd), where mid-diastolic, delayed and fractionated electrograms were recorded (ABLd electrograms), to the LRA, MRA, HRA, and CSd. The atrial cycle length during atrial flutter was 167 ms with a 2:1 atrioventricular conduction ratio. An atrial extrastimulus was introduced from the ABLd and

accelerated the tachycardia cycle length (145 ms), with the same sequence of activation on intracardiac recording and no changes in atrial morphology on the surface electrocardiogram. After pacing, the tachycardia cycle length returned to its original value with a postpacing interval below 30 ms. Paper speed, 300 mm/s; amplitude, 22.8 mV/cm. A, atrial electrograms; V, ventricular. Source: Santilli R. et al.[5]

THERAPY

As for previously discussed supraventricular tachycardias, the published literature on acute and chronic treatment of atrial flutter in dogs is scarce. In the authors' experience, acute intravenous (IV) therapy is often not indicated unless clinical signs of hemodynamic instability are observed. In dogs with hemodynamic instability, acute treatment may be considered, with administration of the following drugs:

- Diltiazem: 0.05–0.15 mg/kg slowly IV, which can be repeated every 5 minutes up to a total dose of 0.1–0.3 mg/kg.[21]
- Procainamide: 6–8 mg/kg as an IV bolus over 3 minutes then as a continuous rate infusion (CRI) at 25–50 µg/kg/min if needed.[21]
- Esmolol: 200–500 µg/kg as an IV bolus (loading dose), followed by 25–200 µg/kg CRI; 50 µg/kg/min constant rate infusion usually sufficient following loading dose.[22]
- Amiodarone: 2 mg/kg bolus over 10 minutes followed by a CRI of 0.8 mg/kg/h IV for 6 hours, then decrease to 0.4 mg/kg/h if needed. Or, in cases of vagally mediated functional flutters, lidocaine (2 mg/kg IV bolus, up to 8 mg/kg followed by 25–80 µg/kg/min CRI).[23]

In cats with hemodynamic compromise, diltiazem (0.125–0.35 mg/kg IV) or procainamide (1–2 mg/kg slowly IV) followed by 10–20 µg/kg/minute can be used.

Chronic treatment of atrial flutter in veterinary patients or in symptomatic human patients is mostly targeted at ventricular rate control. While rate control of atrial flutter is best achieved with calcium channel blockers such as diltiazem or β-blockers that reduce atrioventricular node conduction, drugs that result in prolongation of the atrial refractory period should be selected if chemical cardioversion to a sinus rhythm is attempted.[8,15,24] Although chemical cardioversion is not frequently observed in dogs, in the authors' experience, treatment with class III

antiarrhythmics such as sotalol (0.5–2 mg/kg per os [PO] every 12–24 hours) or amiodarone (10–25 mg PO every 12 hours for 7 days, followed by 5–7.5 mg PO every 12 hours for 14 days, followed by 7.5 mg PO every 24 hours), or class Ia antiarrhythmics such as procainamide (10–20 mg/kg PO every 6–8 hours) can be attempted as in humans and may result in conversion to sinus rhythm.[25] In cats, chronic treatment with sotalol (1–3 mg/kg PO every 12 hours), amiodarone (12.5 mg/kg PO every 24 hours), or procainamide (3–8 mg/kg PO every 6–8 hours) can also be attempted.

Radiofrequency catheter ablation should be considered in patients with atrial flutter that is nonresponsive to pharmacological management and results in persistent clinical signs or cardiac remodeling, in patients that become noncompliant with daily medication administration, or in patients in which elimination of the circuit is possible.[8] Once the location of the arrhythmogenic isthmus has been identified based on mid-to-late diastolic fractionated potentials and concealed entrainment, radiofrequency should be delivered at the site for 45 seconds at a maximum temperature of 65 °C with a power of 75–100 W depending on the location (75W atypical flutter; 100 W cavotricuspid isthmus–dependent).[4–6] Ablation should ideally be performed during of atrial flutter, with the endpoint of the procedure determined by acute termination of the atrial flutter, the presence of bidirectional isthmic block (in cases of cavotricuspid isthmus–dependent atrial flutter), and the inability to reinduce the arrhythmia with programmed atrial stimulation.[4–6]

In the authors' electrophysiology laboratory, radiofrequency catheter ablation is routinely performed, with an overall success rate of 100% for cavotricuspid isthmus–dependent atrial flutter and a recurrence rate of 15%. Recurrence may include return of the previously observed atrial flutter or deterioration into persistent atrial fibrillation.[4] Success rates for atypical atrial flutter have not been reported due to a lower frequency of incidence. Overall complication rates for cardiac ablations targeted at atrial rhythms including accessory pathways, focal atrial tachycardia, and atrial flutter are low (6.2%).[17]

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CHAPTER 18

Ventricular arrhythmias

Romain Pariaut

DEFINITION

Ventricular arrhythmias include ventricular ectopic beats, ventricular parasystole, idioventricular rhythm, accelerated idioventricular rhythm, ventricular tachycardia, and ventricular fibrillation.

Premature electrical impulses arising within the ventricles, from either the specialized conduction system or the working ventricular myocytes, are termed *ventricular ectopic beats*. Ventricular ectopic beats are also frequently referred to as premature ventricular beats or premature ventricular complexes. The components of the conduction system responsible for ventricular ectopic beats include the Purkinje network and the conduction system distal to the atrioventricular node, although some choose to exclude the His bundle.[1–3] Ventricular ectopic beats are dissociated from atrial activity but frequently conduct retrogradely to the atria via the atrioventricular junction or, less commonly, an accessory pathway.[4,5]

Ventricular parasystole refers to ventricular beats that occur independently of the underlying rhythm, regardless of whether that rhythm is sinus or not. Unlike typical ventricular ectopic beats, which often have a consistent timing or coupling interval with the previous QRS complex, ventricular parasystole's unique characteristic is an entrance block that prevents the influence of the baseline rhythm on the ventricular focus. This means that the timing of parasystolic beats does not align predictably with the baseline rhythm. In the classic form of ventricular parasystole, although

the interval between parasystolic beats is consistently a multiple of a fundamental interval due to the fixed firing rate of the parasystolic focus, the ability of the parasystolic focus to control or "capture" the ventricles depends on its timing in relation to the underlying rhythm and the refractory state of the surrounding ventricular myocardium. Fusion beats frequently occur during ventricular parasystole. These fusion beats result from the partial and simultaneous control of the ventricles by both a supraventricular (usually sinus) beat and a ventricular parasystolic beat.[6] Modulated parasystole is a form of parasystole in which the protected focus is not completely insulated from the electrical influence of the surrounding myocardial tissue. This influence leads to variations in the discharge rate of the ectopic focus.[7]

Accelerated idioventricular rhythm does not have a clear definition, and therefore when to use the term can be confusing. It is sometimes called "slow ventricular tachycardia" and corresponds to a ventricular rhythm of four or more ventricular complexes that exceeds the rate of a ventricular escape rhythm but is below the cutoff rate for ventricular tachycardia. *Ventricular escape rhythms (idioventricular rhythms)* originate from subsidiary ventricular pacemaker cells in the Purkinje fibers when the dominant pacemakers at the supraventricular level (sinus node and atrioventricular junction) fail to depolarize. Ventricular escape rhythms have a rate of 20–60 bpm in dogs and 80–140 bpm in cats.[2] Certain metabolic conditions can however alter the discharge rate of the subsidiary ventricular pacemaker cells, resulting in a ventricular rhythm that approaches or slightly exceeds the rate of the underlying sinus rhythm at that moment. In those patients, the sinus rhythm, which overdrive-suppresses the ventricular focus, is dominant whenever its rate surpasses the discharge rate of the ventricular cells, but the accelerated idioventricular rhythm takes control of the cardiac rhythm whenever the sinus rate slows down. Based on its behavior, an accelerated idioventricular rhythm can be described as persistent and dominant, persistent and competitive, or intermittent and competitive.[8] Another electrocardiographic characteristic of an accelerated idioventricular rhythm is the frequent presence of fusion and capture beats.[9]

Ventricular tachycardia is defined as four or more consecutive ventricular ectopic beats occurring at a rate exceeding 180 bpm in dogs and

220 bpm in cats.[2] Ventricular tachycardia can be further characterized based on the morphology of the ventricular complexes and its behavior. Ventricular tachycardia is described as monomorphic when all the ventricular complexes share the same morphology, pleomorphic when there is more than one QRS morphology during the same episode of ventricular tachycardia but each morphology is stable for at least several beats, and polymorphic when it displays a beat-to-beat variation in QRS morphology or axis (bidirectional) (Fig. 18.1).[2,9,10] Based on their behavior, episodes of ventricular tachycardia can be described as nonsustained, sustained, repetitive or incessant. Ventricular tachycardia is nonsustained when it lasts less than 30 seconds and sustained if it persists for more than 30 seconds or necessitates medical or electrical cardioversion. Repetitive ventricular tachycardia refers to repeated occurrences of nonsustained ventricular tachycardia. Incessant ventricular tachycardia corresponds to a sustained ventricular tachycardia episode that lasts many hours, sometimes more than 12 hours, despite multiple attempts at cardioversion.[2,10] Whenever three or more episodes of sustained ventricular tachycardia separated by at least 5 minutes occur over a 24-hour period, the term electrical storm is applicable.[10] Each episode usually requires medical or electrical cardioversion. Most electrical storms are caused by monomorphic ventricular tachycardia, and an underlying structural heart disease is typically present. In dogs, arrhythmogenic cardiomyopathy is the common cause of electrical storms. Ventricular flutter describes very rapid monomorphic ventricular tachycardia that blurs the distinction between the QRS complexes and the T waves. On an electrocardiogram, the tracing takes a sinusoidal appearance, appearing remarkably similar when viewed upside down (Fig. 18.2).[2,6] In their 2009 consensus on catheter ablation of ventricular arrhythmias, the authors suggested steering clear of the term “ventricular flutter” and instead proposed using “monomorphic ventricular tachycardia with indeterminate QRS morphology”.[10]

Ventricular fibrillation represents a critical cardiac arrhythmia characterized by rapid, apparently disorganized electrical impulses within the ventricles. This erratic electrical activity induces uncoordinated contractions of the myocardium, resulting in cessation of effective cardiac output. Without timely intervention through defibrillation, it invariably leads to death.[2]



FIGURE 18.1. a) Monomorphic ventricular tachycardia. b) Pleomorphic ventricular tachycardia. c) Polymorphic ventricular tachycardia. d) Bidirectional ventricular tachycardia. See text for explanation. Lead II; speed: 50 mm/s (a–c), 25 mm/s (d); calibration: 5 mm/1 mV.

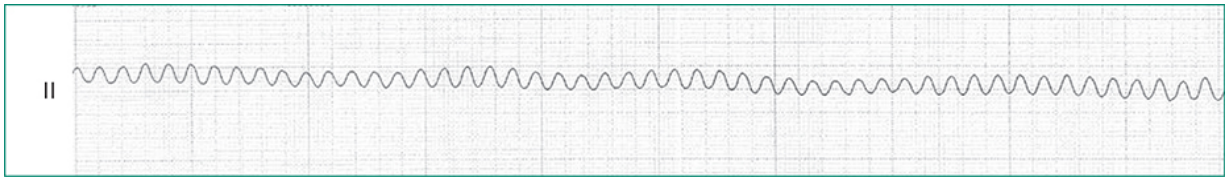


FIGURE 18.2. Ventricular flutter in a 10-month-old, mixed breed, male dog. Notice the rapid and regular oscillation of the isoelectric line with a sinusoidal appearance and a ventricular rate of 600 bpm. Lead II; speed, 50 mm/s; calibration, 5 mm/1 mV.

ELECTROPHYSIOLOGICAL MECHANISM

Ventricular arrhythmias need three essential components to occur: an arrhythmogenic substrate, environmental modifiers, and a trigger. When these elements coexist, arrhythmias can arise and persist through various recognized mechanisms including enhanced automaticity, triggered activity, and reentry, either separately or in conjunction (see p. 2).[11] Arrhythmogenic substrates commonly stem from a structural heart disease, although they can also emerge in apparently normal hearts. In dogs and cats,

cardiomyopathies are the predominant cause of clinically significant ventricular arrhythmias. Heart disease is closely linked with interstitial fibrosis, which disrupts the typical architecture of the ventricular myocardium and fosters reentry. Alongside these structural alterations, electrical remodeling takes place at the cellular level, resulting in a prolonged and more varied action potential duration, primarily due to a decrease in potassium channel activity. Other changes encompass heightened intracellular calcium concentration and impaired cell-to-cell action potential propagation due to gap junction dysfunction. These alterations heighten the likelihood of reentry and delayed afterdepolarizations.[12] Occasionally, minimal structural alterations are observed alongside substantial electrical remodeling, as seen in certain instances of long QT syndrome and the inherited ventricular arrhythmia prevalent in German Shepherds (see p. 341).[13,14] These conditions are associated with polymorphic ventricular tachycardia. Although not yet well described in veterinary medicine, normal cardiac structures can be the source of idiopathic ventricular arrhythmias in young patients. Typically, these arrhythmias manifest as monomorphic ventricular ectopic beats and tachycardia. Common locations for idiopathic ventricular arrhythmias include the right ventricular outflow tract, the ostium of the left ventricle at the base of the aorta, the annulus of the atrioventricular valves, the papillary muscles of both the left and right ventricles, and the fascicles of the intraventricular conduction system. Idiopathic ventricular arrhythmias usually stem from triggered activity or abnormal automaticity, while fascicular ventricular tachycardia is caused by reentry.[15] Modifiers include worsening heart failure, ischemia, inflammation, sympathetic stimulation, catecholamine release, electrolyte imbalances (such as hypokalemia and hypomagnesemia), and metabolic disturbances. In addition, drugs, including antiarrhythmics, can induce arrhythmias, for example via an effect on tissue repolarization.[16] Finally, triggers can be an increase or decrease in heart rate, afterdepolarizations, and in the case of ventricular tachycardia, single or repetitive ventricular ectopic beats that enter an anatomical reentrant circuit or impact the refractory state of the ventricular tissue, encouraging functional reentry.[11]

Most of the time, identifying the precise mechanisms responsible for ventricular arrhythmias remains challenging. It is probable that various

arrhythmias originate from one mechanism but are sustained by another. Sometimes, the characteristics of the arrhythmia and an understanding of the underlying heart condition can hint at a potential mechanism. For instance, in a Boxer with arrhythmogenic cardiomyopathy, monomorphic ventricular tachycardia likely arises from a reentrant mechanism, while in a young German Shepherd dog, polymorphic ventricular ectopic beats are probably triggered by early afterdepolarizations. In contrast, accelerated idioventricular rhythm is usually attributed to enhanced automaticity in the Purkinje fibers. This heightened automaticity often occurs in the setting of cardiac or systemic ischemia–reperfusion injury.[6,9] Cardiologists employ drug challenges and invasive electrophysiology testing protocols to unravel the mechanisms behind ventricular arrhythmias. However, diagnostic procedures in veterinary medicine still lack validation.[10]

ELECTROCARDIOGRAPHIC FINDINGS

VENTRICULAR ECTOPIC BEATS

Ventricular ectopic beats display a wide QRS complex (≥70 ms in dogs; ≥40 ms in cats) followed by a broad T wave in the opposite direction of the main QRS deflection, and are not associated with a P wave.[17] Ventricular ectopic beats originating within the interventricular septum, which usually involve fascicles of the conduction system, can have a more narrow appearance.[18] Various morphological features of ventricular ectopic beats can offer clues regarding the presence of an abnormal substrate. The duration of the QRS complex, the intrinsicoid deflection time (also known as R-peak time), and the presence or absence of QRS notching depend on the site of origin of the ectopies and the degree of structural cardiac remodeling (Fig. 18.3).[19,20] In apparently normal hearts, ventricular ectopic beats may have a larger amplitude, and notched QRS complexes are less common.[6] The axis of ventricular ectopic beats varies across the limb leads and precordial leads depending on their site of origin and the path of the electrical impulse through the ventricles. In veterinary medicine, comprehensive studies have not yet been conducted to predict the exact source of ventricular arrhythmias based on electrocardiographic criteria. There is one exception: ventricular arrhythmias originating from the right

ventricular outflow tract, which were investigated in English Bulldogs suffering from arrhythmogenic cardiomyopathy. Santilli et al.[21] conducted research using intracardiac electrophysiological mapping, revealing that ventricular ectopic beats arising from the right posterior area of the right ventricular outflow tract had a left bundle branch block morphology in all 12 leads. Meanwhile, ectopic beats originating from the left anterior part of the outflow tract displayed a negative polarity in lead I, with the remaining leads displaying a left bundle branch block pattern (Fig. 18.4).[21] Various morphologies of ectopic beats seen on a single electrocardiogram can suggest either multiple sources (multifocal ectopic beats) or a single origin with variable conduction through the ventricles (multiform ectopic beats). The variability in morphology often depends on prematurity: rapid ectopic beats occurring shortly after a previous QRS complex may exhibit aberrant features as the electrical impulse travels through tissue that has not fully recovered from the prior depolarization. On the other hand, ectopic beats occurring late after the preceding beat, known as late-diastolic ventricular ectopic beats, are more indicative of multiple origins if they display different QRS configurations. The presence of structural heart disease is often associated with multiformity, where regions of slow impulse propagation and delayed refractory periods are present. Therefore, it is advisable not to presume multifocality but rather use the term “multiform” when describing ventricular ectopic beats with different morphologies (Fig. 18.5).[22]

Most ventricular ectopic beats have a relatively fixed coupling interval with the previous beat. The precise factors determining the timing between ectopic beats and the preceding QRS complex remain partially unknown.[23] Reentry and triggered activity are suspected when ventricular ectopic beats have a consistent timing, whereas automaticity and parasystole are more likely linked to variable timing intervals.[24]

Ventricular ectopic beats are typically followed by an extrasystolic pause, as it places the ventricles in a refractory state that blocks, but sometimes only delays, the conduction of supraventricular impulses (typically a sinus P wave) to the ventricles (Figs. 18.6a and 18.6b). If the underlying sinus rhythm is slower, there is a chance that the ventricular ectopy does not interfere with the sinus pacemaker and the underlying rhythm. In such cases, the ventricular ectopy is referred to as interpolated (Fig. 18.6c). Post-

extrasystolic pauses can also result from retrograde conduction of ventricular ectopic beats to the atria, which causes a reset of the sinus node pacemaker.[3]

Ventricular ectopic beats may alternate with sinus beats, and less frequently, with atrial ectopic beats or ventricular paced beats. In ventricular bigeminy, the ventricular ectopic beat occurs every other heartbeat, while in ventricular trigeminy, it occurs every third beat. In the case of ventricular quadrigeminy, it occurs every fourth beat.[3] Three mechanisms have been proposed to explain bigeminal rhythms in different conditions, including reentry, modulated parasystole, and early afterdepolarizations.[25] Sequential occurrences of ventricular ectopic beats are possible. When two ectopic beats manifest consecutively, they are termed couplets, while a sequence of three ectopic beats in a row is known as triplets.



FIGURE 18.3. Ventricular bigeminy in a 7-year-old male Boxer. Notice the RR' morphology of the second QRS complex (arrow), suggestive of structural remodeling at the site of origin of the ectopy. Lead II; speed, 50 mm/s; calibration, 10 mm/1 mV.



FIGURE 18.4. Monomorphic ventricular tachycardia with left bundle branch block type morphology in a 12-year-old female English Bulldog with arrhythmogenic cardiomyopathy. Notice the presence of wide QRS complexes (100 ms) with a regular rate of 200 bpm, a negative V1 with a transition zone between V1 and V2, precordial lead discordance, and a normal QRS axis in the frontal plane (+60°). Left limb lead (II, III, aVF) polarity is concordant with left precordial lead (V2–V6) polarity, right limb lead (aVR) polarity is concordant with right precordial lead (V1) polarity, and lead I is positive. Based on the QRS polarity in the frontal and horizontal planes and the positive QRS complexes in lead I, the site of origin of the circuit is the posterior portion of the right ventricular outflow tract. Twelve leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6); speed, 50 mm/s; calibration, 5 mm/1 mV.

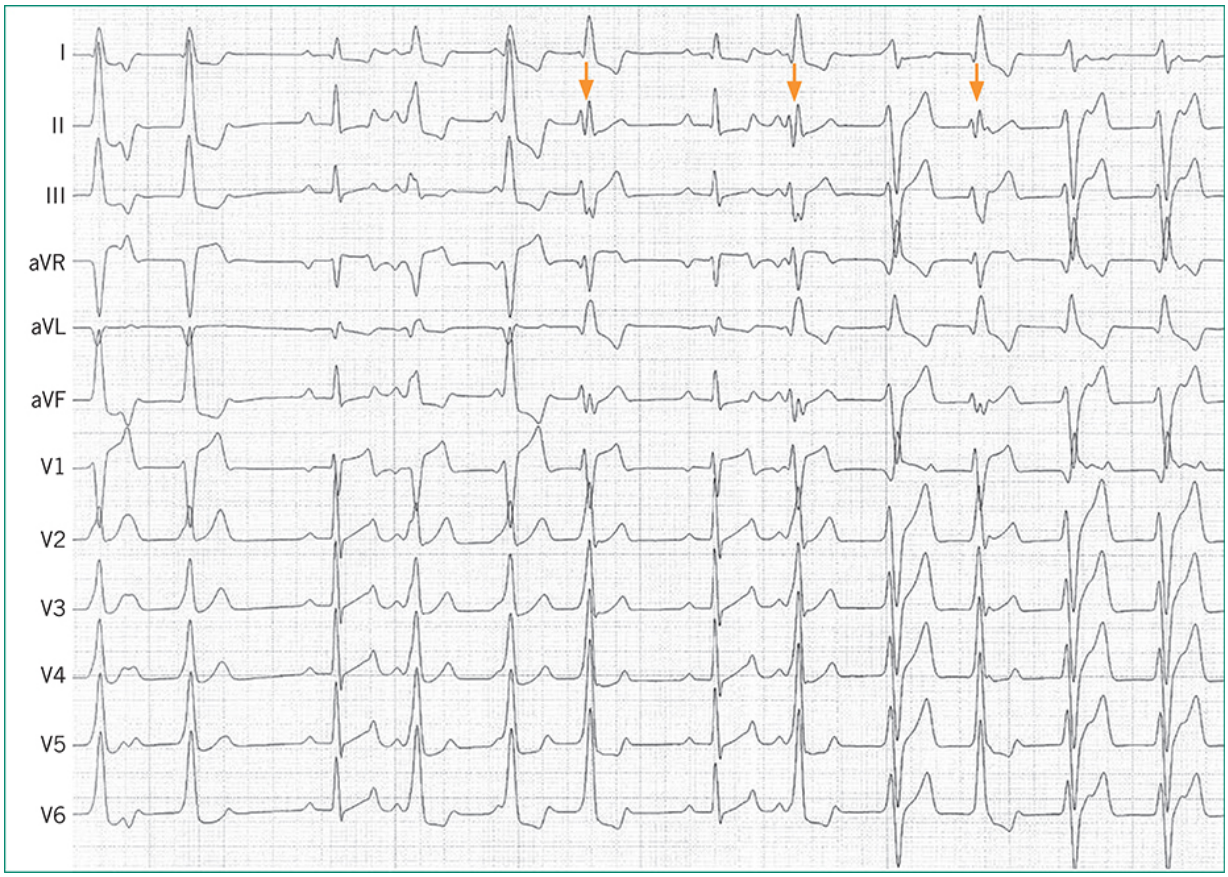


FIGURE 18.5. Multiform ventricular tachycardia in an 8-year-old male German Shepherd with gastric dilatation-volvulus. Notice the presence of multiform wide QRS complexes with left bundle branch block type morphology (1st, 2nd, 4th, and 5th) and right bundle branch block type morphology (9th, 11th, and 12th). Fusion beats with atrioventricular dissociation are also evident (arrows). Twelve leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6); speed, 50 mm/s; calibration, 5 mm/1 mV.



FIGURE 18.6. a) Ventricular premature ectopic beat with compensatory pause. b) Ventricular premature ectopic beat without compensatory pause. Notice the prolongation of the PQ interval post ectopy, a sign of ventriculo-atrial retroconduction. c) Interpolated ventricular premature ectopic beat. Lead II; speed, 50 mm/s; calibration, 5 mm/1 mV.

VENTRICULAR PARASYSTOLE

Ventricular parasystole is rare but becomes a potential consideration when an electrocardiogram displays monomorphic ventricular ectopic beats with varying coupling intervals. In an extended electrocardiographic tracing, the interectopic intervals are multiples of a common denominator. This occurrence signifies that the parasystolic focus, responsible for the ectopic beats, operates independently from the underlying sinus rhythm, leading to a lack of interference. Generally, the rate of the parasystolic focus tends to be slower than the regular heart rhythm, as it corresponds to a subsidiary pacemaker in the Purkinje fibers that is protected from being suppressed by the sinus node's overdrive due to an entrance block.[3] Fusion beats are also frequent. Diagnosis of parasystole can be complicated by the fact that it can be modulated. When parasystole is modulated, the coupling interval between sinus beats and ventricular ectopic beats remains variable, but no mathematical relationship between ectopies can be found. This is due to an incomplete entrance block, which allows the rate of discharge of the parasystolic focus to be influenced—either accelerated or delayed—by the surrounding tissue's depolarization caused by the dominant sinus rhythm.[26]

ACCELERATED IDIOVENTRICULAR RHYTHM

An accelerated idioventricular rhythm manifests on an electrocardiogram as a mostly monomorphic ventricular rhythm that competes with the predominant underlying rhythm, commonly the sinus rhythm. As the rate of the accelerated idioventricular rhythm is within 10% of the underlying sinus rate, fusion beats and capture beats are frequent.[9] An accelerated idioventricular rhythm can be overdrive-suppressed by the sinus node, and it is influenced by variations in autonomic tone (Fig. 18.7).



FIGURE 18.7. Accelerated idioventricular rhythm in a 12-year-old female Weimaraner with acute coronary syndrome. Notice the presence of wide QRS complexes (80 ms) with a regular rate of 150 bpm interrupted by an intermittent capture beat (arrow), a sign of atrioventricular dissociation. Lead II; speed, 50 mm/s; calibration, 5 mm/1 mV.

MONOMORPHIC VENTRICULAR TACHYCARDIA

Monomorphic ventricular tachycardia typically appears as a regular and fast rhythm featuring QRS complexes with a single morphology. The analysis of QRS complex morphology in the 12 leads is essential to try to define the site of origin. Monomorphic ventricular tachycardias are described as left bundle branch block–like when lead V1 is negative, and right bundle branch block–like when lead V1 is positive. The former very likely arises from the right ventricle and the latter from the left ventricle. However, further studies are needed in veterinary medicine to better localize ventricular tachycardia based on QRS complex morphology.

The second step of electrocardiogram interpretation in monomorphic ventricular tachycardia is to define the QRS complex axis in the frontal plane, R wave progression from V1 to V6, and the transition zone, i.e., the area where the QRS complex polarity changes from negative to positive or vice versa. Some variability in the cycle length has been observed in individuals experiencing monomorphic ventricular tachycardia due to a reentrant mechanism (Fig. 18.8). Volosin et al.[27] noted that this variability occurs at the onset of a tachycardia episode and tends to stabilize around the 40th or 50th beat in most cases. Additionally, a higher tachycardia rate correlates with less variability in cycle length. Factors contributing to this variability may involve the nature of the reentrant circuit, fluctuations in autonomic tone, and changes in hemodynamics.[27] Some variability in morphology is also possible during ventricular tachycardia episodes caused by reentry. Indeed, Josephson et al.[28] showed that a change in QRS configuration, known as pleomorphism, corresponds to a shift in the exit site from a single reentrant circuit or a change in the path of the electrical impulse around the same isthmic region.[29]

A challenge in electrocardiogram interpretation involves distinguishing between different types of wide QRS complex tachycardias. These encompass monomorphic ventricular tachycardias, supraventricular tachycardias that exhibit either anatomical or functional bundle branch

block, and rarely, preexcited supraventricular tachycardias. Various electrocardiographic criteria are available to assist in accurately diagnosing these arrhythmias:

- Atrioventricular dissociation. Identifying atrioventricular dissociation confirms the diagnosis of ventricular tachycardia. Look for sinus P waves that are not associated with the QRS complexes. The absence of a relationship appears as fewer P waves than QRS complexes, and a variable P wave position relative to the QRS complexes. P waves can be difficult to identify during tachycardia as they are often buried within the QRS complexes and T waves. Check lead II, where sinus P waves usually have a large positive amplitude (Fig. 18.9). Fusion beats and intermittent capture beats also indicate atrioventricular dissociation.
- If atrioventricular dissociation is not confirmed, assess the limb leads for a left or right bundle branch block pattern. Supraventricular tachycardias with wide QRS complexes typically exhibit these patterns due to anatomical or functional bundle branch blocks. The absence of such pattern favors the diagnosis of monomorphic ventricular tachycardia.
- When a bundle branch block pattern is present in the limb leads, verify its presence in the precordial leads; concordance between the left limb leads (II, III, aVF) and the left precordial leads (V2–V6), and the between right limb lead (aVR) and the right precordial lead (V1) supports the diagnosis of supraventricular tachycardia conducted with bundle branch block, while discordance leans towards monomorphic ventricular tachycardia. Rarely, ventricular tachycardia may show a bundle branch block pattern in both the limb and precordial leads, as seen in ventricular tachycardia originating from the right ventricular outflow tract region and displaying a left bundle branch block pattern (Fig. 18.10).
- Precordial concordance. All precordial leads showing the same polarity supports the diagnosis of ventricular tachycardia (Fig. 18.11) (see p. 48).



FIGURE 18.8. Monomorphic ventricular tachycardia in a 5-month-old male Boxer with chronic myocarditis. Notice, after the first sinus beat, the presence of a nonsustained run of monomorphic ventricular tachycardia with an initial RR interval of 160 ms (375 bpm), then a stable acceleration of

the rate to 430 bpm. A multiform ventricular bigeminy follows the run and it ends with a bidirectional couplet. Lead II; speed, 50 mm/s; calibration, 5 mm/1 mV.

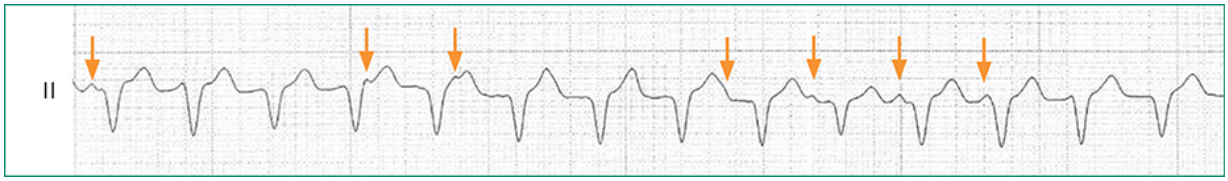


FIGURE 18.9. Monomorphic ventricular tachycardia with evidence of atrioventricular dissociation in a 13-year-old male mixed-breed dog with dilated cardiomyopathy. Notice the presence of wide QRS complexes (80 ms) with a regular ventricular rate of 215 bpm and the presence of P waves (arrows) dissociated from the QRS complexes. Lead II; speed, 50 mm/s; calibration, 5 mm/1 mV.

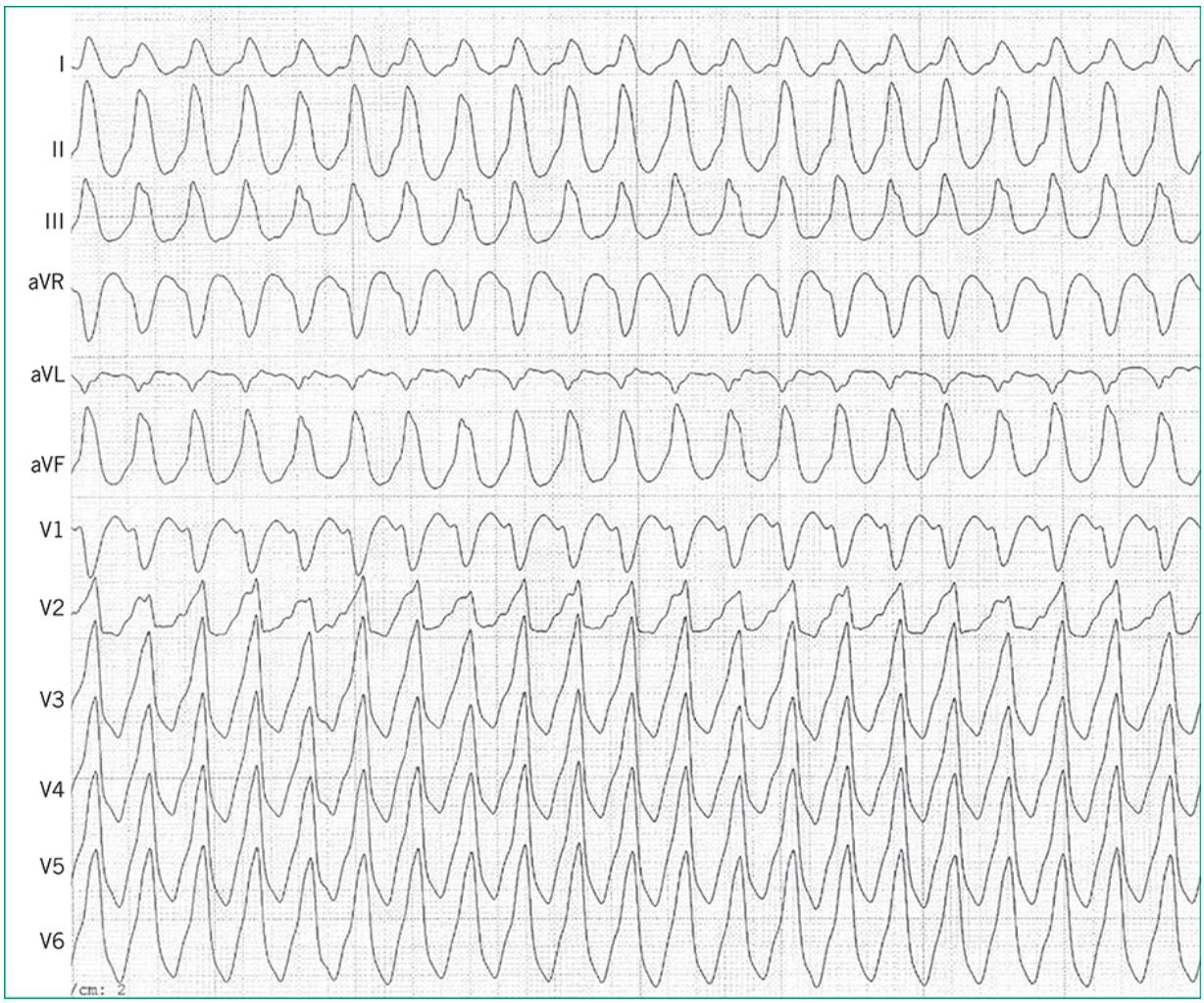


FIGURE 18.10. Monomorphic ventricular tachycardia with left bundle branch block–type morphology in a 10-year-old female English Bulldog with arrhythmogenic cardiomyopathy. Notice the presence of wide QRS complexes (80 ms) with a regular rate of 300 bpm, a negative V1 with a transition zone between V1 and V2, precordial lead discordance, and a normal QRS axis in the frontal plane (+60°). Left limb lead (II, III, aVF) polarity is concordant with left precordial lead (V2–

V6) polarity, right limb lead (aVR) polarity is concordant with right precordial lead (V1) polarity, and lead I is positive. According to the QRS polarity in the frontal and horizontal planes and the positive QRS complexes in lead I, the site of origin of the circuit is the posterior portion of the right ventricular outflow tract.

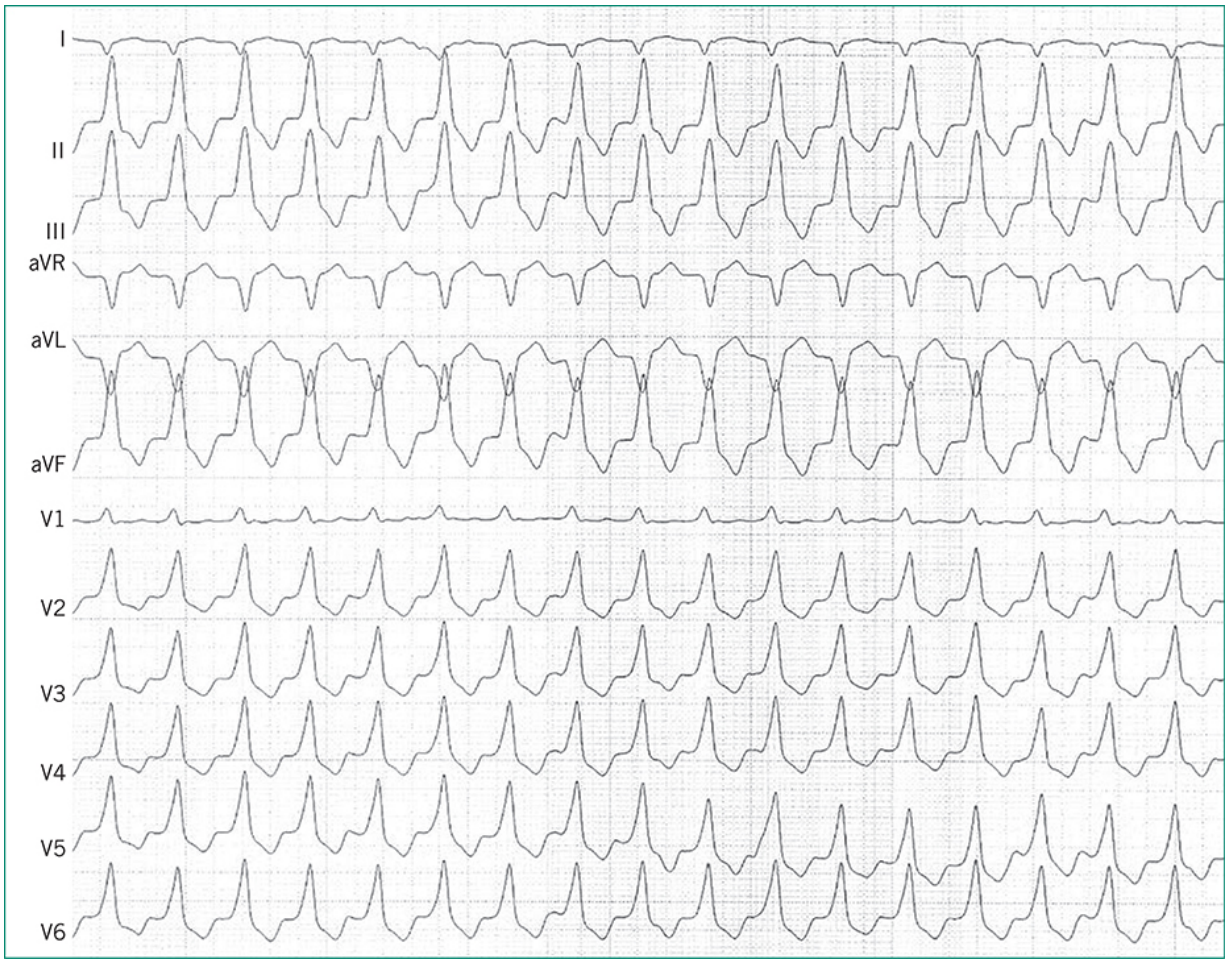


FIGURE 18.11. Monomorphic ventricular tachycardia with right bundle branch block–type morphology in a 6-year-old female mixed-breed dog with chronic myocarditis. Notice the presence of wide QRS complexes (75 ms) with a regular rate of 270 bpm, a positive V1 with no transition zone, precordial lead concordance, and right QRS axis shift in the frontal plane (+120°). Left limb lead (II, III, aVF) polarity is concordant with left precordial lead (V2–V6) polarity, right limb lead (aVR) polarity is discordant with right precordial lead (V1) polarity, and lead I is negative. Twelve leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6); paper speed, 50 mm/s; calibration, 5 mm/1 mV.

POLYMORPHIC VENTRICULAR TACHYCARDIA

Polymorphic ventricular tachycardia is distinguished by beat-to-beat variations in the configuration or axis of QRS complexes. One variant of this condition is bidirectional ventricular tachycardia, identifiable by

alternating polarity in QRS complexes. Digitalis toxicity can contribute to the occurrence of bidirectional ventricular tachycardia. Polymorphic ventricular tachycardia is typically not sustained, but there is a considerable risk of progression into ventricular fibrillation. When encountering polymorphic ventricular tachycardia, it is crucial to examine sinus beats for indications of prolonged QT intervals. The subtype of polymorphic ventricular tachycardia associated with a prolonged QT interval is termed "torsades de pointes". This tachycardia exhibits a distinctive pattern known as "twisting points", characterized by an oscillating pattern of the QRS complexes around the isoelectric baseline (Fig. 18.12).[2,6]



FIGURE 18.12. Ambulatory electrocardiographic recording from an 8-year-old female Boxer with arrhythmogenic cardiomyopathy. The initial part of the tracing shows a multiform ventricular tachycardia which degenerates first into torsade de pointes–like (horizontal line) and then ventricular fibrillation inducing sudden cardiac death. Lead Y; each line corresponds to 30 seconds. Paper speed, 7.5 mm/s; calibration, 2 mm/mV.

VENTRICULAR FIBRILLATION

Ventricular fibrillation is a life-threatening rhythm unless terminated by electrical cardioversion. It may start from a single ventricular ectopy, while in other instances a supraventricular or ventricular tachycardia can deteriorate into ventricular fibrillation. Electrocardiographically, ventricular fibrillation presents as rapid and erratic waveforms, exhibiting variable durations and amplitudes. In an experimental setting, the author determined the ventricular fibrillation rate to be around 600 bpm in dogs. During this

type of arrhythmia, discernable QRS complexes and T waves are notably absent. Instead, a chaotic and disorganized pattern dominates the electrocardiogram, reflecting the erratic electrical activity within the ventricles (see p. 335).

CLINICAL PRESENTATION

Apparently healthy adult dogs and cats have occasional ventricular ectopic beats, typically less than 25 to 30 ectopies over a 24-hour period.[30,31] Côté et al. reported that 96% of cats and 69% of dogs with ventricular tachyarrhythmias had evidence of structural heart disease on the echocardiogram. Approximately 40% of dogs with a normal echocardiogram were suspected to have arrhythmogenic cardiomyopathy.[32] Clinically significant ventricular tachyarrhythmias are associated with various forms of cardiomyopathies, myocarditis, and some congenital cardiac diseases. Young animals can have forms of idiopathic ventricular arrhythmias, which are not yet well described in veterinary medicine, and breed-specific juvenile ventricular arrhythmias likely associated with channelopathies.[33] Conversely, accelerated idioventricular rhythm is more commonly documented in animals lacking primary cardiac issues. It is a transient arrhythmia linked to systemic or cardiac ischemia–reperfusion injury, which occurs in situations such as gastric dilatation-volvulus surgery, splenic disorders, pancreatitis, systemic thromboembolism, and various other conditions. Accelerated idioventricular rhythm is also observed in animals with structural heart disease and other ventricular tachyarrhythmias.[2,34]

Ventricular arrhythmias may be detected during a routine physical examination. Clinical signs of ventricular arrhythmias include syncope, hemodynamic collapse, and heart failure. Identifying more subtle clinical signs in veterinary patients can be challenging. However, it is plausible that frequent ventricular arrhythmias might induce discomfort and adversely affect the quality of life in certain animals.[35] In some cases, sudden death might be the first and only manifestation of ventricular arrhythmias.

OTHER METHODS OF EVALUATION

ECHOCARDIOGRAPHY

Performing echocardiography becomes necessary for all animals displaying more than infrequent single ventricular ectopic beats, in order to detect the existence of a structural heart disease serving as the substrate for the arrhythmia. Discovering a phenotype of dilated cardiomyopathy might signify a primary cardiomyopathy or arrhythmia-induced cardiomyopathy, which could potentially regress if the arrhythmia is managed.

24-HOUR HOLTER MONITORING/IMPLANTABLE LOOP RECORDING

A Holter monitor is recommended when there are frequent single ventricular ectopic beats observed on an electrocardiogram, particularly in predisposed breeds, cases demonstrating evidence of structural heart disease, and situations in which clinical signs commonly linked with arrhythmias are present. Implantable loop recorders can be useful in identifying arrhythmias in animals with infrequent syncope (see p. 58) (Fig. 18.13).[36,37]

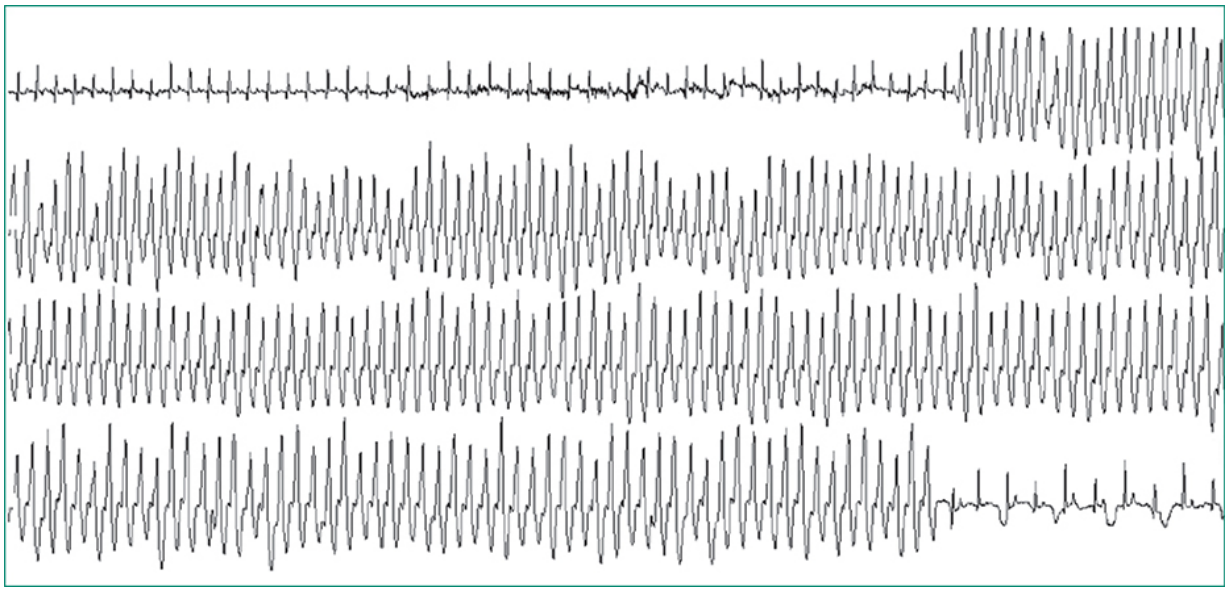


FIGURE 18.13. Implantable loop recorder tracing from a 7-year-old female German Shepherd with aortic stenosis. The initial part of the tracing shows a sinus tachycardia followed by a sustained monomorphic ventricular tachycardia lasting almost 90 seconds inducing transient loss of consciousness. Each line corresponds to 30 seconds. Paper speed, 7.5 mm/s; calibration, 2 mm/mV.

ELECTROPHYSIOLOGICAL STUDY

An electrophysiological study is indicated in ventricular arrhythmias that are suspected to rely on a reentrant mechanism and in focal ventricular arrhythmias. These studies have been used successfully to identify and ablate the isthmus of the reentrant ventricular tachycardia in English Bulldogs and Boxers with arrhythmogenic cardiomyopathy.[21] The integration of electroanatomic mapping technology further enhances the precision and scope of ventricular mapping. This technology facilitates the detailed mapping of extensive areas within the ventricles, thereby offering an advanced tool for managing ventricular arrhythmias. By providing a comprehensive visualization of the heart's electrical activity and structural anatomy, electroanatomic mapping aids in the identification of abnormal electrical pathways or arrhythmia-triggering foci. This technology is therefore poised to significantly contribute to the overall management and treatment of ventricular arrhythmias.[38]

THERAPY

DECISION TO TREAT

Three justifications exist for initiating therapy:

- Managing clinical manifestations linked to ventricular arrhythmias, such as frequent syncope and hemodynamic destabilization.
- Halting or reversing arrhythmia-induced cardiomyopathy and preserving systolic function.
- Preventing or postponing sudden cardiac death.

Clinical signs resulting from ventricular arrhythmias are influenced by three primary factors: heart rate, vasomotor reflex, and duration of the episodes. Rapid and sustained tachycardias are more likely to cause clinical signs. In dogs, the rate of ventricular tachycardia responsible for collapsing events typically approaches 300 bpm when vasomotor tone is not effective in preventing them.[36,37] Despite their rapid pace, occurrences such as couplets, triplets, and brief bouts of ventricular tachycardia do not elicit clinical signs. Similarly, accelerated idioventricular rhythm, with a rate near that of the underlying sinus rhythm, does not produce clinical signs, even if

it becomes the dominant rhythm for an extended duration. Whenever intermittent clinical signs, mainly syncope, could be secondary to ventricular tachyarrhythmias, it is important to try to confirm their cause via 24-hour Holter monitoring or the use of an implantable loop recorder. Indeed, bradycardia was shown to be the cause of syncope in dogs with cardiomyopathy and a high ventricular arrhythmia burden.[39] If the reason behind frequent yet sporadic clinical manifestations remain elusive, a treatment trial is warranted. If these signs resolve and there is a reduction in the number and complexity of the arrhythmias, it will substantiate the suspicion that the arrhythmia is the underlying cause of the clinical signs.[37] At times, animals experience critical ventricular tachycardia that leads to hemodynamic instability. These instances typically represent an "electrical storm", marked by recurring episodes of prolonged ventricular tachycardia within a brief timeframe. Most of these electrical storms stem from monomorphic ventricular tachycardia, a phenomenon frequently observed in veterinary medicine in Boxers and English Bulldogs suspected of suffering from arrhythmogenic cardiomyopathy.[21] Sustained ventricular tachycardia causing hemodynamic instability requires immediate intervention.

The decision to treat can also be based on the suspicion that an arrhythmia is responsible for structural cardiac changes or could negatively impact cardiac function over time. Arrhythmia-induced cardiomyopathy is discussed in Chapter 29 of this textbook. In brief, there are two variations of this condition: tachycardia-induced cardiomyopathy and premature ventricular complex-induced cardiomyopathy. Tachycardia-induced cardiomyopathy can arise in animals experiencing a high burden of hemodynamically well-tolerated nonsustained and sustained runs of ventricular tachycardia. On the other hand, premature ventricular complex–induced cardiomyopathy is a consequence of a high occurrence of single ventricular ectopic beats. In human cases, it is estimated that the burden of ventricular ectopy inducing systolic dysfunction typically exceeds 10%, often hovering around 20%, and mainly depends on the QRS morphology.[40] Additionally, interpolated ventricular ectopic beats, ectopic beats displaying variable coupling intervals, wide QRS complex beats, and epicardial ectopic beats elevate the risk of developing premature ventricular complex–induced cardiomyopathy.[40] Systolic dysfunction caused by ventricular

arrhythmias remains relatively understudied in veterinary medicine, resulting in a lack of defined criteria for guiding treatment decisions. Based on anecdotal observations, the author has noted instances of complete recovery in systolic function in specific Boxer dogs that experienced a high incidence of ventricular tachyarrhythmias and positively responded to antiarrhythmic therapy.

Deciding when to start treatment in an animal with ventricular arrhythmias but no apparent clinical signs is one of the most challenging aspects of arrhythmia management, despite being a common scenario. Usually, the rationale for initiating treatment revolves around attempting to minimize the risk of sudden cardiac death by lowering the frequency and complexity of the arrhythmia. It is crucial to note the uncertainty surrounding the potential of antiarrhythmic medications (the primary option for managing ventricular arrhythmias in animals) in decreasing the risk of sudden cardiac death. Veterinary medicine lacks significant clinical trials on this subject, and findings from human trials have generated ambiguous conclusions. The Cardiac Antiarrhythmic Suppression Trials (CAST) from the late 1980s highlighted a possible association between the use of antiarrhythmics and increased mortality. Subsequent research has demonstrated that merely diminishing the number of arrhythmias does not necessarily equate to effectiveness in reducing sudden cardiac death risk. Furthermore, when contemplating treatment, it is essential to consider the specific type of antiarrhythmic and the underlying disease linked to the arrhythmia as critical factors.[41] Electrocardiographic criteria including arrhythmia number and complexity are frequently used to guide the decision to treat. One proposed method for grading the complexity of a ventricular arrhythmia involves a scale from 0 to 4 with the following attributions:[42,43]

- 0 = no ventricular ectopic beat
- 1 = single ventricular ectopic beat
- 2 = bigeminy, trigeminy
- 3 = couplets and triplets
- 4 = R-on-T phenomenon or ventricular tachycardia.

A higher grade signifies a more severe and potentially dangerous arrhythmia that may warrant treatment. Variants of this classification, historically first proposed by Lown and Wolf in 1971, are used in veterinary

and human medicine.[6] In dogs with structural heart disease and ventricular arrhythmias, monomorphic and polymorphic ventricular tachycardia degenerating into ventricular fibrillation has been reported to be the most common mechanism of sudden death. This observation supports the assignment of grade 4 to ventricular tachycardia, and possibly initiation of therapy.[44] R-on-T phenomenon, which is characterized by a short-coupled ventricular ectopy superimposed on the T wave of a preceding beat, was initially identified as a major trigger of life-threatening arrhythmia in human patients with coronary heart disease. However, recent findings have not conclusively validated its use as a predictor for sudden cardiac death in more varied populations.[45,46] Rare instances of arrhythmic deaths induced by R-on-T ventricular ectopy have been documented in veterinary medicine. In 2017, Gunasekaran et al.[47] reported a case in a dog afflicted with severe subaortic stenosis, suggesting that myocardial ischemia might have initiated the arrhythmia. Santilli et al.[44] identified an R-on-T ventricular ectopy as the trigger for ventricular fibrillation in only 2 out of 19 dogs in which the arrhythmia responsible for sudden death was recorded.[44,47] Hence, relying solely on the presence of R-on-T ectopy to warrant the commencement of treatment raises questions.

The medical literature indicates that effective stratification of the risk for sudden cardiac death to guide therapy cannot solely rely on the electrocardiographic characteristics of ventricular arrhythmias. Likewise, relying on a solitary echocardiographic measure, such as the left ventricular ejection fraction, which was previously employed in identifying human patients with structural heart disease at heightened sudden cardiac death risk, is insufficient.[12] It is crucial to factor in the underlying substrate, triggers, and modulators for a comprehensive assessment. In dogs, in which specific inherited arrhythmias and cardiomyopathies are well documented within breeds, genetic factors likely have a greater impact on the clinical course of affected animals than the electrocardiographic features of the arrhythmia only. It is advised that all animals displaying ventricular arrhythmias undergo a comprehensive cardiac evaluation, including an echocardiogram. This thorough examination aims to provide a more accurate description of the underlying basis of the arrhythmia and potentially pinpoint causative factors, thus aiding in prognosis determination and guiding treatment choices.

MEDICAL MANAGEMENT

General principles on the management of ventricular arrhythmias will be discussed in this section. The reader is encouraged to explore the chapters focused on arrhythmias linked to specific conditions, as these chapters may offer insights into treatments tailored to them. The mechanisms of action, side effects, and dosages of antiarrhythmic drugs can be found in Chapter 7.

ACUTE TREATMENT

When dealing with an animal experiencing sustained ventricular tachycardia in an acute scenario, treatment selection often hinges on the animal's hemodynamic condition. If the animal remains stable despite the tachycardia, oral antiarrhythmic medications (e.g., sotalol, which is rapidly absorbed) are typically considered a viable option. Sotalol has shown to be beneficial for managing rapid monomorphic reentrant ventricular tachycardia with a short excitable gap.[48] In cases in which the animal is unstable, intravenous drugs may be administered. Veterinarians commonly have access to drugs such as lidocaine, procainamide, and premixed amiodarone HCl. Procainamide might be regarded as the preferred treatment for monomorphic ventricular tachycardia due to its capacity to modify conduction within the reentrant circuit's isthmus. Its effectiveness stems from possessing both sodium and potassium channel blocking properties. However, lidocaine, which is often less effective in humans due to its sodium channel–binding kinetics and its shortening effect on action potential duration, might be a more suitable option for dogs due to their considerably higher heart rate during ventricular tachycardia.[49] A review of the author's clinical database involving 20 dogs diagnosed with monomorphic ventricular tachycardia and treated using lidocaine showed successful cardioversion occurred in 17 instances. Lidocaine and procainamide have a limited effect on the hemodynamics of dogs with normal cardiac function, but potentially increase the risk of hypotension in animals experiencing heart failure.[50,51] In a series of cases reporting the use of premixed amiodarone HCl, ventricular tachycardia was effectively halted in 7 out of 9 instances. Amiodarone was consistently administered following unsuccessful attempts with lidocaine and/or procainamide to control the arrhythmia.[52] Antiarrhythmic medications can be concurrently

administered, potentially leading to synergistic effects. However, simultaneous administration of such drugs also raises the likelihood of encountering side effects, such as QT interval prolongation, particularly when combining multiple drugs that exhibit class III effects.[16] Polymorphic ventricular tachycardia with a normal QT interval is treated in the same way as monomorphic ventricular tachycardia.[53] However, tailored treatments can be recommended for particular arrhythmias (e.g., use of intravenous magnesium for torsades de pointes or pacing for bradycardia-dependent ventricular tachycardia, as observed in young German Shepherd dogs).[16,54]

If ventricular tachycardia persists despite initial intravenous drug administration, broader considerations in managing the arrhythmia involve mitigating elevated sympathetic system activity. This can be accomplished through the implementation of mild to profound sedation and anxiolysis. Another avenue involves using an antiarrhythmic drug possessing β-blocking properties, such as sotalol or amiodarone, or incorporating a β-blocker, provided that systolic function and blood pressure is within acceptable parameters.[16,55] Hemodynamic support, including cautious fluid therapy, may be needed. When inotropic support becomes necessary, prioritize medications with no proarrhythmic effects (e.g., pimobendan) over those that stimulate β-receptors.[56] Electrolyte imbalances, in particular hypokalemia and hypomagnesemia in animals on diuretics, should be corrected.[15]

Following chemical cardioversion of ventricular tachycardia, it is reasonable to persist with antiarrhythmic drug therapy to forestall any potential recurrence. It is crucial to acknowledge that even if an antiarrhythmic drug did not effectively halt the initial ventricular tachycardia episode, it might still be efficacious in preventing its reappearance.

CHRONIC TREATMENT

In animals that do not require immediate intervention, a thorough evaluation should be conducted to characterize the substrate of the arrhythmia and identify reversible triggers and modulators. Sotalol has demonstrated both effectiveness and good tolerance as a treatment for ventricular arrhythmias in Boxers with arrhythmogenic

cardiomyopathy.[43,57] Clinical observations suggest that this positive response extends beyond Boxers to encompass other breeds and forms of ventricular arrhythmias as well. At the author's institution, sotalol is the first-line drug for dogs undergoing treatment for ventricular tachycardia. In cases in which sotalol alone fails to yield the desired outcomes, anecdotal evidence suggests that combining mexiletine with sotalol can enhance the response in some instances, although efficacy may vary among individual dogs. Due to limited access to mexiletine in certain regions worldwide, there have been informal accounts indicating that flecainide has been utilized with satisfactory outcomes and minimal adverse effects either as a sole treatment or in conjunction with sotalol. Alternative therapeutic choices include the use of amiodarone. The initial administration of oral amiodarone appears to be well tolerated, even in animals diagnosed with heart failure. However, prolonged usage of amiodarone frequently results in elevated liver enzyme activity, particularly alanine aminotransferase. A two- to three-fold elevation in alanine aminotransferase activity typically prompts a reduction in dosage, and decisions to discontinue amiodarone are usually taken if alanine aminotransferase levels continue to rise or if clinical signs appear. Other side effects of amiodarone include thyroid dysfunction, anemia, neutropenia, thrombocytopenia, and ocular abnormalities.[58,59] Following initiation of treatment, serial 24-hour Holter monitoring is required to evaluate response to treatment and detect any evidence of proarrhythmic effect associated with the administration of antiarrhythmics. Drawing from insights into the day-to-day variability of ventricular arrhythmias in prevalent cardiac conditions, a favorable treatment response typically hinges on achieving a minimum 80% decrease in the ventricular ectopy count along with a decrease in arrhythmia complexity.[60]

NONMEDICAL MANAGEMENT

Nonpharmacological approaches to managing ventricular arrhythmias encompass procedures such as electrical cardioversion, implantation of a cardioverter defibrillator, and radiofrequency ablation. While in human patients with hemodynamically unstable ventricular tachycardia, electrical cardioversion stands as a primary therapy, in dogs it is typically reserved after injectable antiarrhythmic treatments have proven ineffective in

stopping the tachycardia, or in case of pulseless ventricular tachycardia.[15] This is because electrical cardioversion requires anesthesia, which has associated risks in hemodynamically unstable animals. Electrical defibrillation is the first-line therapy for ventricular flutter and fibrillation. Electrical cardioversion and defibrillation are detailed in Chapter 9.

In human medicine, implantable cardioverter defibrillators (ICDs) are suggested for those who survived cardiac arrest or face a high risk of sudden cardiac death. However, in veterinary practice, ICDs are not employed due to challenges in identifying high-risk animal candidates and programming human-designed devices to accurately detect arrhythmias.[61,62] ICD technology is discussed in Chapter 10.

Radiofrequency ablation is still not widely used for the treatment of ventricular arrhythmias. There are reports of this technique to manage ventricular arrhythmias originating from the right ventricular outflow tract in dogs with arrhythmogenic cardiomyopathy. The recent availability of three-dimensional electroanatomical mapping in some veterinary centers should allow the use of radiofrequency ablation to be extended to other types of ventricular arrhythmias.[21,61] Radiofrequency ablation is discussed in Chapter 11.

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SECTION V

BRADYCARDIAS

CHAPTER 19

Sinus bradycardia

Manuela Perego

DEFINITION

Sinus bradycardia is defined as a decrease in the sinus node discharge rate, with a heart rate below 60 bpm in dogs and below 140 bpm in cats. Sinus bradycardia is the result of a decrease in pacemaker cell (P cell) automaticity within the sinus node.[1]

ELECTROPHYSIOLOGICAL MECHANISM

The two key factors that can induce sinus bradycardia are a decreased depolarization rate of P cells in the sinus node and an imbalance of the autonomic nervous system.[2]

A decreased depolarization rate of P cells within the sinus node constitutes an intrinsic mechanism that induces sinus bradycardia, while the activation of the parasympathetic system and withdrawal of the sympathetic system are considered extrinsic mechanisms.[3]

The electrical impulse in the sinus node is generated by four major currents, the so-called "funny" or pacemaker current (I_f, an inward Na^+ current occurring during early diastolic depolarization), two Ca^{2+} currents (responsible for the late diastolic depolarization phase), and a K^+ current (responsible for phase 3 or repolarization phase).[4,5]

During the diastolic phase, myocytes in the working myocardium are relaxed, and there is a lack of electrical activity. Myocytes are in a normal resting state at hyperpolarized voltage levels.[4] The spontaneous diastolic depolarization of P cells is responsible for the generation of repetitive activity. Although the cellular processes that contribute, directly or indirectly, to the generation of an action potential are still a subject of investigation, there is a general agreement that the major role in the generation and control of the rate is played by I_f.[6]

The typical features of I_f currents include a hyperpolarization-induced activation, slow kinetics of activation and deactivation, a mixed Na^+ and K^+ ionic nature, and modulation by cyclic adenosine monophosphate (cAMP).[3] The voltage range at which diastolic depolarization occurs in P cells is mainly determined by the voltage range of I_f activation and its kinetics.[3] This explains, for example, why diastolic depolarization of P cells occurs at a more depolarized voltage in the sinus node than in the Purkinje fibers, in which the I_f activation range is normally tens of millivolts more negative than in the sinus node.[3] Even within the structure of the sinus node, the I_f activation range varies from cell to cell, shifting to more negative levels as we move from the central to the peripheral node.[7] Interestingly, the expression of I_f in the myocardium changes with age and in pathological conditions. In newborn rats, I_f is expressed at a high level and is activated at physiological voltages, but the activation threshold changes with adulthood.[8] In animal models of ventricular hypertrophy, adult I_f expression in the sinus node increases significantly when compared to the control group.[9] Typical mid-activation voltages of I_f currents in the sinus node P cells range from –60 mV to –70 mV. Sinus bradycardia induced by intrinsic factors is mediated by an increased conductance of external K^+ through I_f

channels, which results in a substantially decreased slope of diastolic depolarization and therefore in a decreased heart rate.[3]

Extrinsic causes of bradycardia refer to activation of the parasympathetic nervous system. The sinus node area is richly innervated by the autonomic nervous system, which exerts a direct control on sinus node activity.[3] Parasympathetic stimulation slows the heart rate through muscarinic receptors. The parasympathetic neurotransmitter acetylcholine mediates its physiological effects through two structurally distinct families of receptors: nicotinic and muscarinic receptors. Muscarinic receptors belong to the superfamily of G protein–coupled receptors and are classified, based on molecular and pharmacological criteria, into five subtypes (M1 through M5).[10] The M1, M3, and M5 receptors couple preferentially to G proteins of the Gq/G11 family, while the M2 and M3 receptors selectively couple to Gi/Go-type proteins.[10]

The activation of M2 muscarinic receptors by acetylcholine has been shown to shift the I_f activation threshold to more negative voltages, according to a process exactly opposite to that of β-adrenergic receptor stimulation and involving the G protein–dependent inhibition of cAMP synthesis. The gating modification of I_f channels in case of increased parasympathetic drive suggests that I_f currents play a major role in the negative chronotropic action of vagal activity. Another ionic mechanism has recently been identified and is consistent with an acetylcholine-activated K^+ current.[3]

Stimulation of the autonomic nervous system is also known to rapidly shift the location of the intranodal leading pacemaker to either superior (sympathetic drive) or inferior (parasympathetic stimulation) sites within the sinus node and to induce a preferential use of either superior or inferior exit pathways.[11]

Sinus bradycardia is often present in athletes. Several mechanisms have been studied to explain the physiological factors underlying sinus bradycardia in this population. Increased vagal tone has been considered the main modulator of sinus bradycardia. However, in humans, when vagus nerve activity is blocked with pharmacological agents (atropine), trained individuals still have a lower heart rate than those with a sedentary life.[12]

Other studies have shown that sinus bradycardia is not only due to increased vagal tone but can be also correlated with decreased sympathetic tone, which results in an overexpression of parasympathetic activity without simultaneously observing vagal hypertonia.[13,14]

Sinus bradycardia is also secondary to intensive trainings that induce cardiac remodeling.

The goal of cardiac remodeling in individuals who train intsensively is to increase stroke volume during exercise, ensuring a higher cardiac output. An increased stroke volume generates an increased blood pressure relative to the volume of a structurally normal heart.[15] The baroreceptors located at the level of the aortic arch detect the increase in blood pressure and, through a mechanism mediated by the autonomic nervous system, induce a reduction in the sinus node discharge rate. In athletes, a correlation between the severity of sinus bradycardia and the duration of the PQ interval was not found. This finding further validates the arguments against a purely parasympathetic pathophysiology.[16]

Sinus bradycardia, particularly when associated with chronotropic incompetence, is suggestive of sinus node dysfunction (see p. 271).[17]

Other causes of sinus bradycardia are sleep disordered breathing and endocrinological diseases.[18,19] Sleep disordered breathing has been described in Cavalier King Charles Spaniels and is characterized by multiple episodes of stertorous breathing, choking, and apnea during sleep associated with sinus bradycardia or sinus arrest due to autonomic nervous system imbalance.[18] Hypothyroidism may cause sinus bradycardia with a decreased resting, minimal, and maximal heart rate.[19]

Sinus bradycardia secondary to autonomic nervous system imbalances can be associated with extracardiac diseases such as hypothermia,[20] hypoglycemia,[21] hypoxia,[22] and intracranial lesions.[23]

Sinus bradycardia can also be secondary to drug administration; in this case, it is referred to as pharmacological bradycardia. Pharmacological sinus bradycardia is caused by inappropriate administration of drugs such as antiarrhythmic agents (e.g., sotalol,[24] calcium-channel blockers,[25–27] and β-blockers[27]).

Pharmacological sinus bradycardia may also be caused by incorrect administration of α-2-agonists,[28] morphine,[29,30] dexmedetomidine,[31]

methadone,[32] and xylazine,[33] as well as by marijuana poisoning[34] and hyperkalemia.[35,36]

Experimental studies in animals have demonstrated that a decrease in heart rate may increase life expectancy. A reduction in heart rate by 50% using digoxin increased lifespan by 20% in mice; however, these individuals also had a decreased body weight, which may also be related with a prolonged lifespan.[37] Another study demonstrated that selective sinus node inhibition with ivabradine was associated with a 14% reduction in heart rate and a 6% extension of the median lifespan.[38]

In addition to heart rate, resting heart rate is a fundamental parameter, and several trials in human medicine have assessed the effectiveness of heart rate lowering medications such as β-blockers and ivabradine.[39] A relationship between resting heart rate and longevity has been demonstrated across different species.[40] For instance, the mouse has a very fast heart rate (200–400 bpm) and a lifespan of a few years, while the whale has a lower heart rate (30–40 bpm) and a lifespan of several decades.[41] Since bigger hearts are normally characterized by a slower heart rate, the higher amount of fibrotic strands in the sinus node may play a role in the slower heart rate, in addition to other intrinsic cellular features.[42]

It has been theorized that low heart rate is correlated with basal myocardial oxygen consumption and for this reason also with longevity.[39] In human beings, the normal resting heart rate is 60–100 bpm.[43]

In healthy individuals, the resting heart rate is stable with age but is positively correlated with a higher blood pressure, a higher body mass index, poorer pulmonary function, and a lower level of physical activity.[39]

ELECTROCARDIOGRAPHIC FINDINGS

The electrocardiographic characteristics of sinus bradycardia include a heart rate below 60 bpm in dogs and 140 bpm in cats and atrial deflections compatible with P waves and characterized by a sinus axis (from –20° to + 90° in the dog and from ± 0° and + 90° in the cat) (Figs. 19.1 and 19.2). The PQ interval is usually normal (60–130 ms in the dog and 50–90 ms in the cat). The QRS complexes are usually narrow with a normal morphology, unless anatomical intraventricular conduction disturbances are already

present.[44] Nocturnal sinus bradycardia is common in both healthy and diseased animals, and more particularly in brachycephalic, young, and athletic dogs. In human beings, the frequency of nocturnal sinus bradycardia appears to decline in middle age and older individuals.[44] A 2021 study[45] showed that in normal dogs, the median heart rate over 24 hours was 81 bpm (70–101 bpm), while the median heart rate over a sleep hour with the lowest heart rate was 59.5 bpm (52–81 bpm). In most dogs, the 3 hours with the slowest heart rate occurred during late evening and early morning hours, between 11 p.m. and 7 a.m. In normal dogs, the median duration of the longest pause was 2.6 seconds (1.9–3.6 seconds). In a minority of dogs, the rolling average heart rate during sleeping hours was <40 bpm for more than 10 seconds. The rolling average is determined by averaging the beat-to-beat intervals over a designated number of heartbeats, then advancing one interval and re-averaging. The rolling average is calculated over a defined time interval. Based on the cumulative time of the rolling average rate, dogs spent 26.3% of the day between 70–90 bpm, while the time they spent with rates <65 bpm or >90 bpm represented approximately 30% of the day in both cases. If RR intervals vary depending on the respiratory phase, respiratory sinus arrhythmia can be diagnosed. Respiratory sinus arrhythmia is sometimes associated with wandering pacemaker, sinus pauses, junctional escape beats, and junctional escape rhythms with isorhythmic atrioventricular dissociation and type I or type II synchronization.[45]

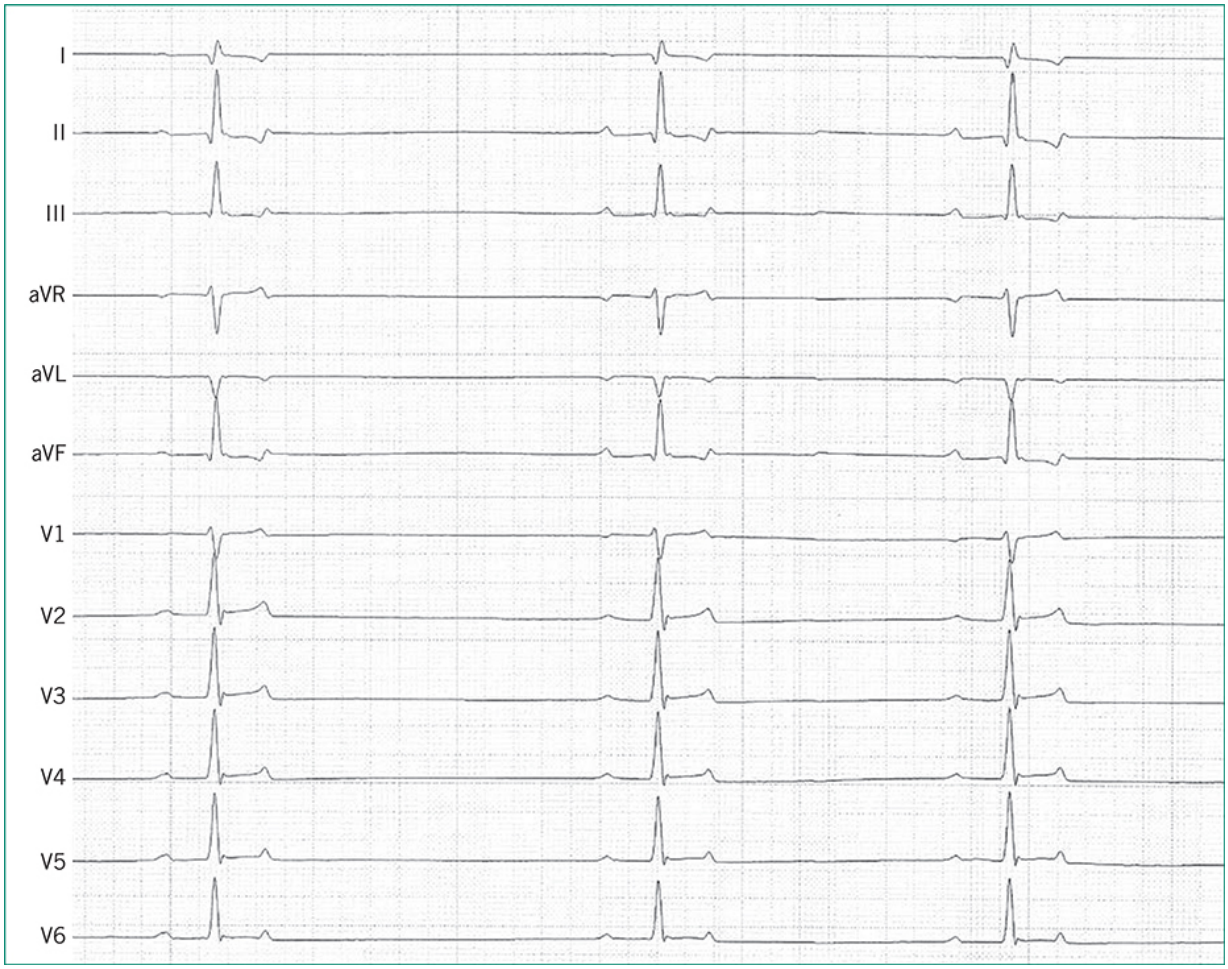


FIGURE 19.1. Sinus bradycardia in a 2-year-old female German Shepherd. Note the presence of atrial deflections that are positive in the inferior leads (leads II, III, aVF), isodiphasic in lead I, and more negative in aVR, with a rate of 43 bpm. P waves are followed by narrow QRS complexes with a normal morphology and a normal mean electrical axis in the frontal plane with a prolonged atrioventricular conduction time (first-degree atrioventricular block). Twelve leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6); speed, 50 mm/s; calibration, 5 mm/1 mV.



FIGURE 19.2. Sinus bradycardia in an 8-year-old female Persian cat. Note the presence of atrial deflections that are positive in the inferior leads (leads II, III, aVF), positive in lead I, and more negative in aVR, with a rate of 120 bpm. P waves are followed by narrow QRS complexes with a normal morphology and a normal mean electrical axis in the frontal plane, with a normal atrioventricular conduction time (normal and constant PQ interval). Six limb leads (I, II, III, aVR, aVL, aVF); speed, 50 mm/s; calibration, 10 mm/1 mV.

CLINICAL PRESENTATION

Most patients with sinus bradycardia are asymptomatic, while some may present with fatigue, exercise intolerance, transient loss of posture, worsening of a preexisting heart failure, or lethargy. Healthy athletes usually present with asymptomatic sinus bradycardia. Obtaining a thorough

history to relate the clinical signs of a patient with sinus bradycardia on an electrocardiogram is essential to reach the correct diagnosis. However, further investigations such as an echocardiographic examination, Holter monitoring, and laboratory testing (e.g., thyroid function and electrolytes) should be performed patients presenting with sinus bradycardia and clinical signs.[46]

THERAPY

Treatment should be aimed at treating the underlying disease associated with sinus bradycardia. Many dogs exhibit no clinical signs and require no antiarrhythmic treatment. In dogs without structural heart disease, heart rates as low as 40–60 bpm are still generally able to produce a normal cardiac output. If sick sinus syndrome is diagnosed, pacemaker implantation is suggested.[23]

Many drugs can be used to treat sinus bradycardia:

- Atropine is a parasympatholytic drug that blocks the muscarinic acetylcholine receptors. Atropine facilitates sinoatrial conduction and increases sinus node automaticity.[44]
- Isoproterenol is a nonselective β-adrenergic agonist with both positive chronotropic and dromotropic effects that enhances sinus node and atrioventricular node function associated with reduced vascular resistence.[44]
- Dopamine is a catecholamine with mixed α- and β-adrenergic and dopaminergic effects that depend on the dose, distribution, and metabolism.[44] In general, dopamine at low doses induces vasodilatory effects, while higher doses are required to reach a positive chronotropic effect. In addition, it must be used with caution because it can cause marked vasoconstriction and had proarrhythmic effects.[44]
- Epinephrine is a catecholamine with strong α-adrenergic and β-adrenergic stimulatory effects, which include increases in chronotropy, inotropy, blood pressure, and myocardial oxygen consumption.[44]

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CHAPTER 20

Sinus node dysfunction

Manuela Perego, Mara Bagardi

DEFINITION

First discovered by Keith and Flack in 1907,[1] the sinus node is a crucial component of the cardiac conduction system and is the dominant pacemaker of the heart. The sinus node has two equally important functions:

1. Producing repetitive electrical impulses responsible for the heartbeat, called normal sinus rhythm.
2. Accelerating or slowing the electrical impulse discharge to guarantee an optimal rate for the most effective cardiac output.

The signals allowing control of the heart rate fall into two main categories: those from the autonomic nervous system and those provided by substances delivered to the bloodstream through the sinus node artery, such as serotonin, histamine, nucleosides, and nucleotides.[2–11]

Normal sinus node function is essential in maintaining proper cardiac rhythm, which is correlated with cardiac performance.[2–11]

Sinus node dysfunction encompasses a range of disorders characterized by abnormal impulse formation and abnormal propagation of the impulse from the sinus node, which therefore cannot correctly perform its pacemaking function. Sinus node dysfunction is better conceptualized as a spectrum of disorders, rather than as a single entity, in which different pathophysiological mechanisms lead to a very similar disease phenotype. The nomenclature related to these disorders is still imprecise and

inconsistent in both human and veterinary medicine, even if some authors have suggested that the diagnosis of sick sinus syndrome requires the presence of clinical signs (most commonly syncope or transient loss of posture), and similar electrocardiographic findings in asymptomatic patients should be diagnosed as sinus node dysfunction rather than sick sinus syndrome.[2–11]

Sick sinus syndrome is associated with an atrial rate that does not meet the body's physiological requirements and may manifest as different types of arrhythmias including sinus bradycardia, sinus pauses or arrests, sinoatrial exit blocks, or alternating periods of tachycardia and bradycardia.[2–15] Sinus node dysfunction can be classified as primary or secondary. In human medicine, it has been established that primary sinus node dysfunction is related with intrinsic diseases of the sinus node and perinodal area, while secondary sinus node dysfunction can be the consequence of different systemic diseases.[2–15]

In human medicine and in the canine population, sinus node dysfunction is described to be more common in older adults, even if the disease can affect patients of all ages.[2–15]

In veterinary medicine, females seem to be more predisposed than males, and the disease is overrepresented in some breeds such as the West Highland White terrier, Miniature Schnauzer, and Cocker Spaniel, and in crosses.[11–15] Sinus node dysfunction is considered extremely rare in cats.[16]

ELECTROPHYSIOLOGICAL MECHANISM

The sinus node is considered the primary pacemaker in the heart; it is the source of intrinsic electrical activation driving the coordinated rhythmic contractions in the mammalian heart. The heartbeat is initiated within the sinus node through the combined action of pacemaker cells, which generate spontaneous depolarizations, and specialized conduction pathways, which are responsible for conducting the electrical impulse from the pacemaker cells to the adjacent atrial myocytes. The other function of the sinus node is to match the heart rate with the body's physiological demands, thus modulating cardiac function and cardiac output. Abnormal sinus node function can inappropriately accelerate or decelerate the heart rate, resulting

in fatal rhythm disturbances. Considering the crucial role of the sinus node in maintaining heart rate and cardiac output, understanding the complex mechanisms involved in sinus node dysfunction is of extreme importance in order to reach a correct diagnosis and establish the correct treatment.[2–15]

Studies in dogs and humans have demonstrated that in both species, the sinus node presents a unique three-dimensional heterogeneous structure characterized by small pacemaker cells enmeshed within fibrotic tissue, which partially insulates these pacemaker cells from aberrant and abnormal atrial myocardial activation.[17,18]

In both dogs and humans, the sinus node is typically described as a compact, slightly elongated three-dimensional intramural banana-shaped structure that is located at the junction of the cranial vena cava and right atrium. Within the intercaval region, the sinus node occupies the entire thickness between the endocardium and the epicardium in the rabbit and guinea pig; however, in people and dogs, a layer of atrial muscle is present between the sinus node and the endocardium. The atrial muscle within the intercaval region and the extensive connective tissue are thought to protect this important region against wall stress.[19–21] The sinus node is composed of different cell types, which include small pacemaker cardiomyocytes, fibroblasts, blood vessels, and nerves encased within fibrous and fatty tissue. In dogs, the sinus node has been reported to be about 11–29 mm long and 2–5 mm wide, with an intramural depth of 1–2 mm. From the structural point of view, the sinus node can be divided into different portions named head, center, and tail compartments (Fig. 20.1).[17–21] The head is usually closer to the epicardium, and the tail is tilted towards the endocardium. In both dogs and humans, the sinus node is characterized by dense fibrotic strands, unlike the atrial myocardium.

A typical characteristic of the sinus node is that is it composed of highly heterogeneous cells. In the center of the sinus node, the cells are poorly organized and described as interweaving. In dogs and humans, the center of the sinus node contains characteristic pacemaker cells (P cells) also called typical nodal cells. These cells are small and contain only few poorly organized myofilaments running in all directions and not organized in myofibrils. A gradual transition in cell type over several millimeters from the center to the periphery of the sinus node has been described, with no clear demarcation between the two tissues where the sinus node meets the

atrial muscle. From the center to the periphery of the sinus node, the shape and arrangement of the cells become progressively more regular, with more numerous and organized myofilaments. Transitional cells are present in addition to pacemaker or nodal cells. Different stages of transition have been described, with some cells more similar to nodal cells and others more similar to atrial myocytes. The transitional cells located between the pacemaker or nodal cells and the atrial myocytes have been proposed to have an important role in the conduction of the electrical impulse from the sinus node to the atrial myocardium.[17–21]

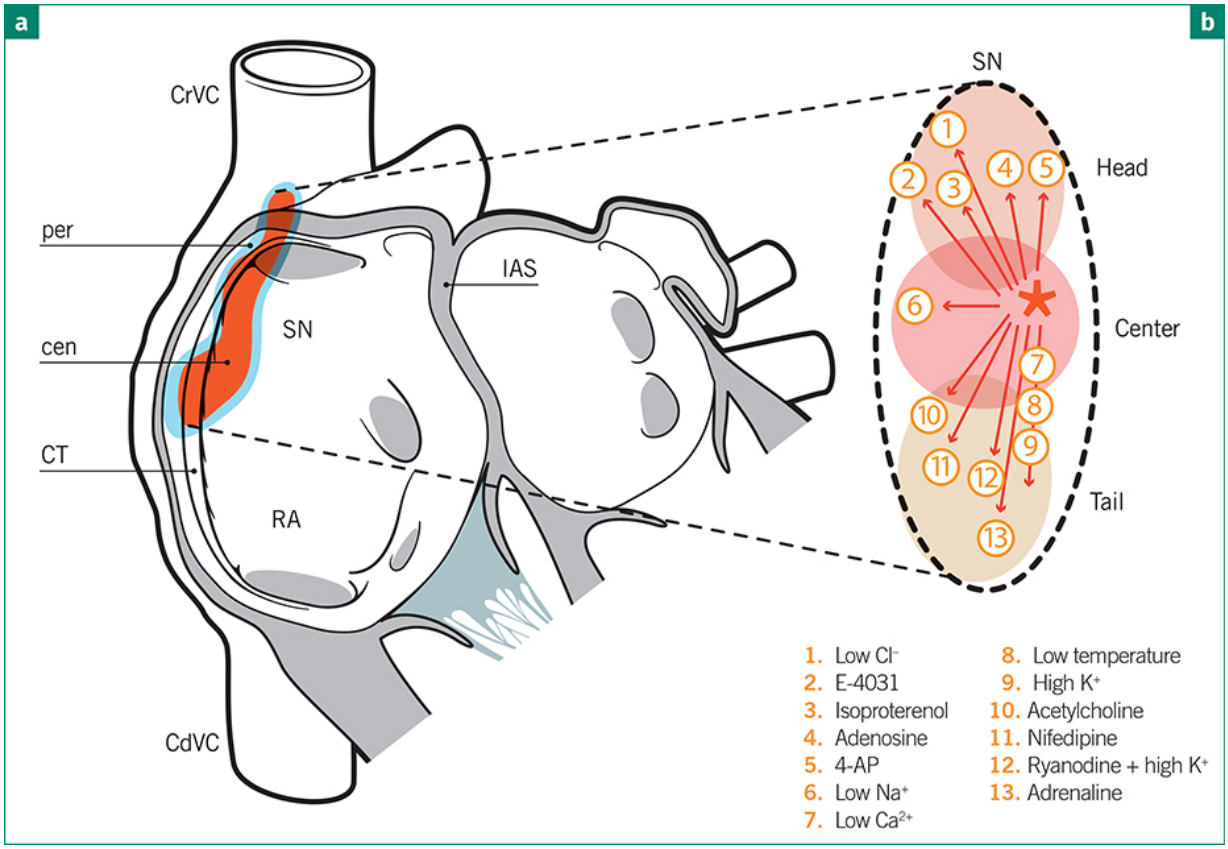


FIGURE 20.1. Anatomical representation of the sinus node (SN), a complex, dynamic, and extensive structure. The sinus node is located in the intercaval region of the right atrium and is characterized by a central area (cen) and a peripheral area (per) adjacent to the atrial myocardium. Note that the sinus node lies from the cranial vena cava to the crista terminalis and extends down to the caudal vena cava. Functionally, within the structure of the sinus node, there is a pacemaker shift, with the position of the leading pacemaker changing position according to different stimuli. CrVC, cranial vena cava; CT, cresta terminalis; CdVC, caudal vena cava; RA, right atrium; IAS, interatrial septum; E-4031, I_{Kr} blocker; 4-AP, 4-aminopyridine-sensitive current.

From the structural point of view, fibrosis and the presence of dense connective tissue are crucial features of the sinus node. The fibrotic strands, characterized by fibroblasts and collagen and elastin fibers, are aimed to increase the compactness of the sinus node structure. In general, the amount of fibrotic tissue is correlated with the heart dimensions, with smaller hearts (mouse) containing a relatively lower amount of fibrotic tissue compared to bigger hearts (whale). Since bigger mammalian hearts are described to have a lower basal rate, it has been postulated that higher levels of fibrotic tissue in the sinus node play a role in slowing the heart rate, in addition to other intrinsic mechanisms. The fibrotic content of the human sinus node is 35–55%, while it represents 20–30% of the heart in other mammals.[17–21] It has been proposed that these fibrotic strands help prevent the sinus node from hyperpolarizing the adjacent atrial myocytes, thus facilitating unidirectional conduction of the electrical impulse form the sinus node to the atrial myocardium. Furthermore, dense collagen fibers provide structural support to the sinus node, together with other components such as the blood vessels, nerve fibers, and other supporting cells. This dense collagen also provides mechanical protection of the sinus node against overstretching caused by strong contraction of the surrounding atrial myocardium. The collagen matrix has also been shown to have extensive direct connections with the adventitia of the central sinus node artery, and the rhythmical pulsation of the sinus node artery has been postulated to be part of the mechanism inducing the rhythmical discharge of pacemaker cells. It has been proposed that sinus node automaticity is an (at least in part) autoregulated process that depends on the stretch-receptor mechanism responding to changes in sinus node artery pressure below 20 mmHg in magnitude. Sinus node automaticity not only responds to small increases or decreases in sinus node artery pressure; the discharge rate of the sinus node may either increase or decrease in response to a particular change in the sinus node artery pressure, with the direction of the chronotropic response depending on the magnitude of the pressure-dependent change in the sinus node artery diameter.[22]

Both in humans and in dogs, pathological conditions such as heart failure and myocardial infarction are correlated with an increase in fibrosis within the sinus node and exit pathways. This pathological fibrosis has been described to interrupt the tight coupling between the sinus node and the atrial myocytes, thus affecting their mutual entrainment and often resulting in bradycardia, conduction blocks, and reentrant arrhythmias.[4,8]

Compared with atrial tissues, the sinus node has a higher expression of specific isoforms of different ion channel proteins, including hyperpolarization-activated cyclic nucleotide gated subunits, and a lower expression of the main gap junction protein connexin 43 (Cx43). Because these characteristics abruptly change between the sinus node and the atrial myocardium, it has been shown that they can be used as specific markers to identify the location of the nodal tissue.[4,8] The heterogeneous expression of ion channel and gap junction proteins within the sinus node pacemaker complex facilitates its automaticity and can protect it from rhythm failure.

When analyzing sinus node function, two important factors must be considered: the discharge rate of the pacemaker cells (intrinsic rate of the sinus node) and the time of conduction of the impulse from the sinus node to the atrial myocardium.

In canine hearts, the intrinsic heart rate has been reported to be 90–140 bpm. The first site of sinus node activation, also called leading pacemaker site, is typically located in the central part of the sinus node in both humans and dogs.[4–11,17–21] However, pacemaking in the intact sinus node is not limited to a single anatomical area; the leading pacemaker site has been shown to shift in response to physiological stimuli. This phenomenon is known as *pacemaker shift* or *wandering pacemaker*.[4–11,17–21] The pacemaker shift is likely responsible for the variations in P wave amplitude and polarity often seen in dogs. These changes in the leading pacemaker site are usually accompanied by either slower or faster rates. The variations in the PP interval are secondary to changes in the cycle length of the sinus pacemaker sites and the beat-to-beat variation in the sinoatrial interval for each automatic site. It has been proven that in conscious dogs, changes in the cycle length of the sinus pacemaker sites, in the sinoatrial interval, and in the location of the leading sinus pacemaker site could be explained by variations in autonomic tone.[23] The shift in the leading pacemaker site is correlated with a different pattern of activation of the atrial myocardium. Shifting of the pacemaker site to the head of the sinus node is correlated with a wavefront initially spreading along Bachmann's bundle rather than along the crista terminalis and middle and posterior internodal pathways. Shifting of the leading pacemaker site towards the tail of the sinus node causes the wavefront to spread down the crista terminalis before activating

Bachmann's bundle. These findings are consistent with sinus arrhythmia and wandering pacemaker (Fig. 20.2).[23]

Just like cell morphology, the shape of the action potential is not uniform within the sinus node. In the center of the sinus node, the action potential has a slow upstroke, a low overshoot (<10 mV), and a long duration (150 ms); the maximum diastolic potential is low (–60 mV to –70 mV). From the center to the periphery of the sinus node and then to the atrial muscle, there is a gradual increase in the action potential upstroke velocity and overshoot and maximum diastolic potential, and a gradual decrease in the action potential duration. Despite these findings, it should be underlined that the origin of the action potential in the sinus node is not static but dynamic and changes depending on the conditions.[21]

The sinus node is surrounded by an extensive paranodal area located within the crista terminalis, close to, but not continuous with, the sinus node. The paranodal area includes cells presenting a molecular and cellular architecture distinct but intermediate between that of the sinus node and that of the atrial myocardium. At present, the role of the paranodal area can only be supposed: this area may facilitate the passage of the electrical impulse from the sinus node to the atrial myocardium, or it may be involved in normal pacemaking, acting as a leading pacemaker. The paranodal area may also be responsible for impulse formation or conduction abnormalities that favor the genesis of cristal focal atrial tachycardia. The precise mechanism of how the electrical impulse exits from the sinus node is not yet fully understood. An area of functional medial block has been described in rabbits, and in dogs, the sinus node has been shown to be anatomically discontinuous with the atrial myocardium; it is continuous with the atrial muscle only at a limited number of discrete exit sites, located at the superior and inferior ends of the sinus node, called exit pathways. In both humans and dogs, the sinus node is anatomically surrounded by a loop of vessels and connective tissue that causes anatomical and physiological conduction block on both sides of the node, medially towards the interatrial septum and laterally towards the crista terminalis.[19–21] This arrangement may have some physiological advantages, such as a good electrical insulation from the surrounding hyperpolarized atrial myocardium, and some disadvantages, such as the fact that damage to the exit pathways will easily lead to sinoatrial block. However, the presence of discrete exit pathways is

considered functional rather than an anatomical phenomenon.[19–21] Conduction of the electrical impulse outside the sinus node can be affected by many factors, including sympathetic and parasympathetic agonists, antiarrhythmic drugs, and naturally occurring metabolites. These stimuli are known to induce rapid shifts in the location of the leading pacemaker to superior or inferior sites within the sinus node and induce a preferential use of either the superior or inferior exit pathways.[17,18] The shift in the preferential exit pathways has been described to be independent from intranodal leading pacemaker shifts, which could ensure a viable pathway when conduction through others is blocked.[17,18] In humans, it has been proven that the inferior pathway is preferred only during adenosine-mediated bradycardia and not at baseline, which suggests that in this species, the inferior exit pathway acts a backup pathway recruited to maintain conduction when other pathways are suppressed.[17,18] This backup mechanism has been proposed to provide a failsafe protection against sinus node arrest in diseased or aging hearts.



FIGURE 20.2. a) Respiratory sinus arrhythmia in a 12-year-old male Dachshund. The dominant rhythm is a respiratory sinus arrhythmia characterized by an increase in heart rate during inspiration and a decrease during expiration. Note the cyclic variations in the P wave amplitude, with an increased voltage when the rate is faster (shorter RR intervals) and a decreased voltage when the rate is slower (longer RR intervals). These electrocardiographic findings are defined as wandering pacemaker. Lead II; speed, 50 mm/s; calibration, 20 mm/1 mV. b) Respiratory sinus arrhythmia in a 9-year-old female German Shepherd. The dominant rhythm is a respiratory sinus arrhythmia characterized by an increase in heart rate during inspiration and a decrease during expiration. Note the cyclic variations in the P wave amplitude and polarity, which changes from positive to negative when the sinus node discharge rate decreases (longer PP interval). These variations in voltage and polarity of the P waves are called sinus node–atrioventricular junction wandering pacemaker. Lead II; speed, 50 mm/s; calibration, 20 mm/1 mV.

In addition to conduction, exit pathways are known to act as a low-pass filter preventing atrial activation of the sinus node by creating entrance blocks, thereby avoiding the overdrive suppression of the sinus node during fast supraventricular tachycardias or atrial fibrillation. The mechanism for entrance block is likely related to differences in refractoriness and excitability between the sinus node cells and the atrial myocytes.[17,18]

Several rhythm disturbances that depend on the type of sinus node function abnormality are common in both humans and dogs and include bradycardia, prolonged sinus pauses, tachy-brady arrhythmias, and sinus standstill. Although there are differences between human and canine medicine, similarities in the arrhythmias and major arrhythmic mechanisms (including sinus node exit blocks and reentry) seen in these two populations have been described.

FUNDAMENTALS OF AUTOMATICITY

Automaticity is the result of a gradual depolarization of the membrane potential in diastole, driven by a coupled system of trans-sarcolemmal ion currents and intracellular Ca^{2+} cycling.

The origin of the automaticity of firing from cardiac pacemaker cells lies in the fact that the membrane potential in the period between two consecutive action potentials is not constant. During this phase, called “diastolic phase”, the membrane slowly depolarizes until a threshold is reached and phase 0 of the action potential is initiated (Fig. 20.3). In order to completely understand the rhythmic generation of the electrical impulse from the sinus node, it is important to know not only the mechanism of diastolic depolarization, but also how pacemaker cells interact with the surrounding tissue, and how these interactions contribute to achieving a common and constant firing rate.[19–21]

It has long been established that the normal rhythm originates in the sinus node, but how and where the electrical signals are coordinated or synchronized among numerous cellular sites of spontaneous automaticity within the sinus node remains unclear. At least two morphological considerations should be taken into account when attempting to explain signal synchronization within the sinus node. First, normal pulsation of the sinus node artery produces a regular and repetitive mechanical event

favoring synchronization. Second, it has been proven that transitional cells in the sinus node not only connect pacemaker cells with the atrial myocardium, but also individual pacemaker cell clusters between each other.[21]

The sinus node cells have been described to show a unique profile of ion channels and receptors aimed to facilitate and support its specialized function. The most important ion channels in the sinus node are:[2–11]

1. The channels that mediate intrinsic automaticity, called hyperpolarization and cyclic nucleotide (HCN) isoforms.
2. Proteins and receptors that mediate intracellular Ca^{2+} cycling.
3. Cellular signaling pathways via metabolic ligands called adenosine receptor isoforms.
4. Transmembrane Na^{+} channels.
5. Proteins that forms the gap junctions between adjacent cells called connexin isoforms.

The hyperpolarization-activated cyclic nucleotide-gated (HCN) channels have been described to have an important role in the spontaneous generation of the action potential in the sinus node pacemaker cells. These channels are considered as voltage-gated cation channels and are responsible for conducting a mixed Na^{+}–K^{+} inward current. This current, commonly named "funny current" (I_f) has been shown to facilitate spontaneous diastolic depolarization in sinus node cells. The crucial role of I_f has been confirmed by the fact that blocking this current with ivabradine, a selective blocker of HCN channels, results in a decreased firing rate of the pacemaker cells. Furthermore, in human medicine, mutations leading to a loss of function in the *HCN4* gene have been shown to affect I_f and have been described to be associated with sinus node dysfunction, thus confirming the role of I_f in sinus node automaticity (Fig. 20.3).[8–10] Sympathetic nerve stimulation shortens the duration of the pacemaker potential and leads to an increased pacing rate. The HCN channels have been suggested to be central to this process because cAMP produced in response to β1-adrenoreceptor activation due to sympathetic stimulation modulates the electrophysiological properties of these channels.[2–11]

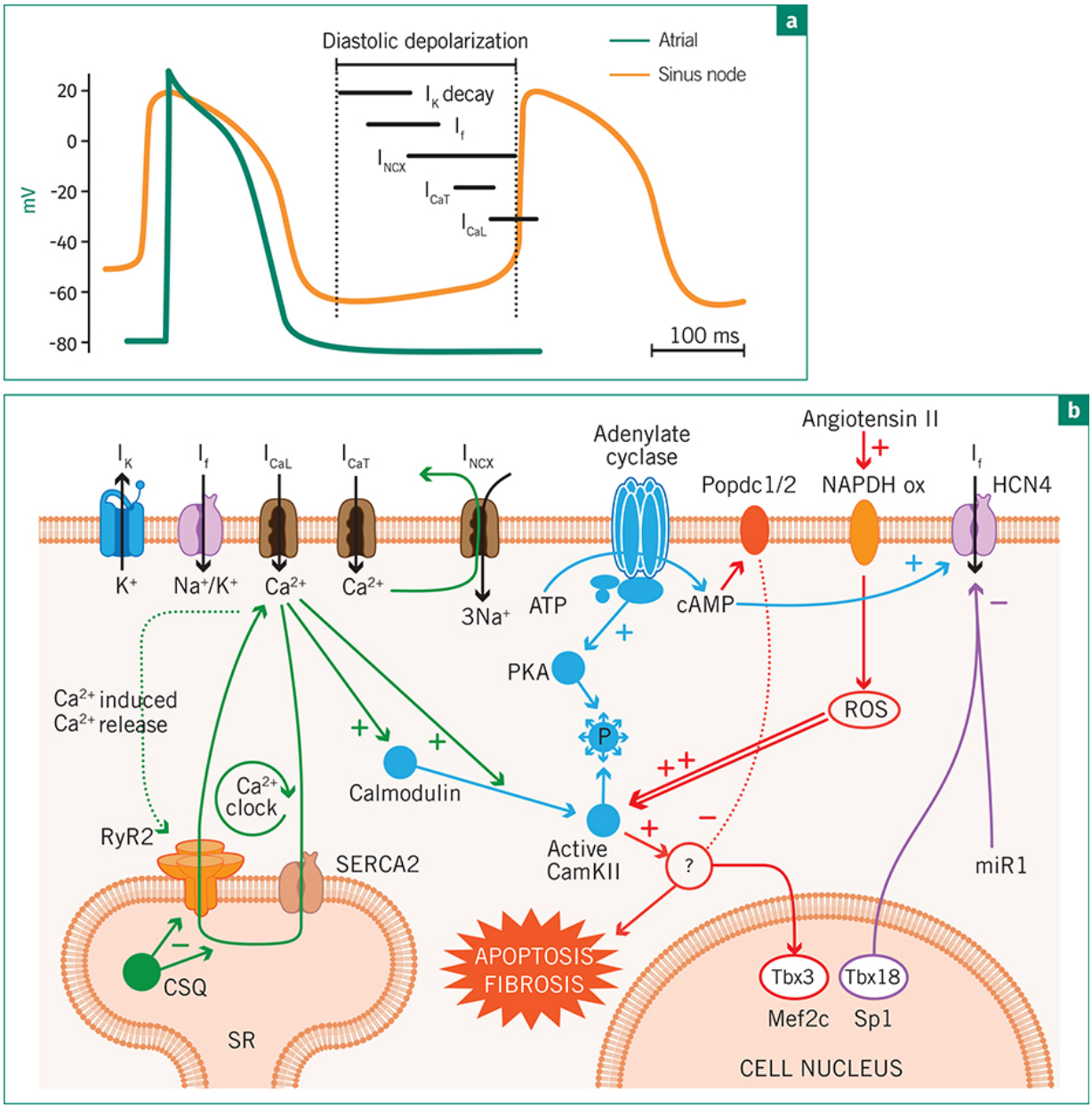


FIGURE 20.3. Molecular basis for sinus node automaticity and sinus node dysfunction. a) Schematic representation of the action potentials in the atrial myocytes (green) and the central portion of the sinus node (orange). The structure of the main membrane and calcium currents during diastolic depolarization are shown in black bars. b) Schematic representation of the sinus node cell at its central portion, with cyclic adenosine monophosphate (cAMP) and regulatory mechanisms. Pacemaking in the sinus node depends on the membrane clock (transmembrane channels) and on the Ca^{2+} clock (green symbols), which are shown at the left of the image. The funny current (I_f) and decay of the inward rectifier current (I_K) are primary responsible for the membrane clock and early spontaneous depolarization phase (phase 4 of the action potential). The influx of Ca^{2+} through the T-type Ca^{2+} channel (I_{CaT}) and the release of Ca^{2+} via ryanodine receptors 2 (RyR2s) from the sarcoplasmic reticulum (SR). Calsequestrine (CSQ) regulates Ca^{2+} release from the SR by binding Ca^{2+} and also by inhibiting RyR2s. The Ca^{2+} clock is reset by pumping of Ca^{2+} into the SR by the

sarco-endoplasmic reticulum Ca^{2+}-ATPase (SERCA2). Normal function of the sinus node depends on high levels of protein phosphorylation (blue symbols in center). On the right of the image, regulatory pathways are shown (afferent limb in red and efferent limb in purple). In particular, angiotensin II elevates reactive oxygen species (ROS) via activation of the nicotinamide adenine dinucleotide phosphate-oxidase (NADPH ox). This pathway is particularly influenced by cellular apoptosis, fibrosis and downregulation of HCN4. Popdc 1/2, Popeye domain containing 1 and 2; PKA, protein kinase A; CamKII, Ca^{2+}/calmodulin-dependent protein kinase II; miR1, micro-RNA 1; Tbx3, T-box transcription factor 3; Tbx18, T-box transcription factor 18; Mef2c, myocyte enhancer factor 2C; Sp1, transcription factor Sp1.

The diastolic spontaneous depolarization of pacemaker cells is also guaranteed by several key membrane ion channels, including voltage-gated Ca^{2+} channels, the sodium–calcium exchanger, and voltage-gated potassium channels. Since the activation and deactivation kinetics of these ion channels interact to sustain a self-perpetuating cycle, they have been proposed to constitute a "membrane clock". This cycle includes the spontaneous and rhythmic local release of Ca^{2+} from the sarcoplasmic reticulum via the ryanodine receptors in the diastolic phase, the subsequent massive release of Ca^{2+} from the sarcoplasmic reticulum coinciding with phase 0 of the action potential, and calcium reuptake by the sarcoplasmic reticulum. Since these events are self-perpetuating and cyclical, they are said to constitute the "Ca^{2+} clock". The membrane and Ca^{2+} clocks may be completely independent from each other or may interact during their spontaneous cycling. The interaction between the two coupled clocks helps maintain the flexibility and robustness of sinus node pacemaking by providing a mutual failsafe mechanism against automaticity failure. In canine hearts, it has been proven that the voltage and Ca^{2+} clocks cooperate to maintain normal function of the sinus node, both in basal state and during adrenergic stimulation. However, it has been found that blocking the Ca^{2+} clock in the canine sinus node does not affect the basal discharge rate of pacemaker cells. These findings suggest a greater relevance of the Ca^{2+} clock in sinus node increase discharge rate during β-adrenergic stimulation than in basal automaticity control (Fig. 20.3).[2–11]

Adenosine is an endogenous metabolite presenting a negative chronotropic effect on the sinus node. This metabolite is released by myocytes, in particular during metabolic stress, ischemia, and heart failure. The role of adenosine is to activate the potassium channels known as I_{KAdo} (also I_{KAch}). The activation of these channels leads to hyperpolarization and

action potential suppression in the pacemaker cells and in other specialized conduction system branches in the heart.[2–11]

Voltage-gated Na^+ channels and the correlated current called I_{Na} play a crucial role in facilitating rapid membrane depolarization through the influx of Na^+ ions into the cell, which generates the upstroke (or phase 0) of the action potential in the atrial and ventricular myocytes. The I_{Na} current in the sinus node has been suggested to protect against excessive vagal slowing of the heart rate.[2–11]

Electrical coupling of the pacemaker cells at the gap junctions appears to play an important role in sinus node function. Connexins form gap junctions between adjacent myocytes and are recognized to play an important role in the cell-to-cell propagation of the electrical impulse. Each gap junction comprises a cluster of serially linked hemichannels (connexons) that are contributed by the two opposing cell membranes, providing a path for small molecules to pass between the inside of the two cells. More than 20 connexin genes have been identified in different species. Of these connexins, the mRNA isoforms 40, 43, and 45 have been described in the mammalian heart. The differential expression of connexins could create regions within the sinus node with different conduction properties, thereby contributing to the nonuniform conduction properties typical of this tissue. Among the cardiac isoforms, Cx 43 represents the predominant isoform in the atrial and ventricular myocardium, even if its expression has not been detected in the central part of the sinus node in both canine and human hearts. In fact, three population of pacemaker cells have been described in the canine sinus node: 30–35% of cells express Cx 43, Cx 40, and Cx 45; about 55% express only Cx 40; and about 10–15% do not express any connexins.[2–11,24]

SINUS NODE RECOVERY TIME

The sinus node recovery time is used to assess the integrity of the automaticity of the sinus node following an attempted overdrive by rapid atrial pacing; it represents the most commonly used electrophysiological method for the evaluation of sinus node function. This test is based on the assumption that automaticity of the sinus node suppressed by overdrive

recovers less promptly when the sinus node is diseased than when it is functioning normally. The technique involves right atrial pacing at progressively faster rates, starting just above the sinus rate and gradually increasing to a maximum of 300 bpm (200 ms atrial cycle length). The interval from the last paced atrial deflection to the first spontaneous P wave is normally longer than the normal PP interval because of overdrive suppression of the sinus node by a period of rapid atrial pacing. The duration of the longest pause after the interruption of atrial pacing is considered as the sinus node recovery time, which in both humans and dogs does not usually exceed 1.5–1.7 seconds. An abnormally prolonged sinus node recovery time reflects an abnormality of the intrinsic properties of the sinus node.[25,26]

OVERDRIVE SUPPRESSION

It is well established that pacemaker cells are present in the sinus node, atrioventricular junction, and Purkinje fibers. In normal conditions, one pacemaker is dominant, and all the others are latent or subsidiary. The sinus node presents the higher discharge rate, and it acts as the dominant pacemaker. Pacemakers other than the sinus node are normally engaged in conducting impulses but may become active pacemakers in abnormal circumstances, which is why they are also referred to as latent or subsidiary pacemakers. They are meant to assume the function of electrical impulse formation when the dominant pacemaker fails to initiate the activation of the heart. However, latent pacemakers can potentially introduce disturbances in the regular sequence of cardiac activation. The dominant pacemaker can thus be defined as the pacemaker tissue that first succeeds in reaching the action potential threshold (i.e., with the highest discharge rate). The other pacemakers are subsidiary because their diastolic depolarization fails to reach the threshold before a propagated impulse reaches them.[27–30] This can be seen in episodes of sinus arrest, which are usually followed by a period of quiescence before a subsidiary pacemaker becomes active rhythmically at its own discharge rate. The pause is usually longer than the following RR intervals of the newly established latent or subsidiary rhythm. This finding suggests that latent or subsidiary pacemakers are suppressed in normal conditions. This form of inhibition is called overdrive suppression.[30]

For latent atrial pacemakers, it has been shown that overdrive suppression is mainly mediated by acetylcholine release. A different mechanism has been proposed for the ventricular Purkinje fibers, which involves the role of the Na^+/K^+ pump. The sinus node drives the latent pacemakers of the Purkinje fibers at twice their normal intrinsic rate. Because there is a net sodium influx with each upstroke, as the depolarization rate of the Purkinje fibers driven by the sinus node increases, the sodium ion concentration in these fibers increases, reaching a value that is approximately double that necessary for their latent pacemakers to spontaneously fire. Due to this increased amount of sodium ions to be expelled, the Na^+/K^+ pump becomes more electrogenic, thus shifting the membrane potential of the Purkinje fibers to a more negative value. In case of sinus arrest, the membrane potential of the Purkinje fibers is kept by the Na^+/K^+ pump at a negative value with respect to the threshold potential until the electrogenic extrusion of sodium ceases or is reduced.[27–30]

Overdrive suppression may also be seen when a faster rhythm than the sinus rate is present. This mechanism is correlated with a depression in the normal spontaneous depolarization of the sinus node. The Ca^{2+} loading associated with overdrive can contribute to overdrive suppression together with electrogenic Na^+ extrusion.[28,29]

In experimental canine models, it has been proven that prolonged rapid atrial pacing and ventricular pacing both cause atrial electrical remodeling. Changes in atrial electrical function are more pronounced after atrial pacing than after ventricular pacing. The electrical remodeling of the atria described also includes the sinus node, resulting in sinus node dysfunction after prolonged overdrive suppression. The remodeling was proven to be reversible and complete regardless of whether atrial or ventricular pacing was used.[31]

ATROPINE TEST

The atropine test consists in the subcutaneous administration of atropine at a dose of 0.04 mg/kg, followed by heart rhythm monitoring by electrocardiography 20–30 minutes later. The response is considered adequate if the sinus rate increases to >150 bpm and no episodes of sinus

arrest are observed. Partial response is characterized by a sinus rate that increases by >25% with respect to the preatropine rate but remains below 150 bpm and/or by the presence of persistent sinus arrest. The response is considered negative when the sinus rate fails to increase by at least 25%. Dogs affected by sick sinus syndrome are less likely to be atropine responsive than dogs with sinus node dysfunction, and atropine response is significantly associated with medical treatment success. Conversely, dogs with sick sinus syndrome and a negative response to atropine are more likely to require pacemaker implantation.[12,13]

SINUS NODE REMODELING AND SINUS NODE DYSFUNCTION

Sinus node dysfunction as a clinical entity includes a variety of disorders, and its frequency is expected to increase significantly with age. Its etiology includes structural abnormalities, drug effects, and pathological autonomic influences. The main intrinsic causes of sinus node dysfunction to be considered are familial or related to age, heart failure, or extreme physical training (Fig. 20.4).[2–11]

Familial sinus node dysfunction has been described in humans, and while this disease is more common in the elderly, it can also occur in fetuses, infants, children, and young adults. In patients who develop sinus node dysfunction at a young age with no clear structural reasons, a genetic etiology may be suspected. Mutations in the gene encoding Na^+ channels have been shown to lead to sinus node dysfunction. In humans, mutations in the gene encoding HCN4, one of the main channels for the I_f current, have been identified in patients with sinus node dysfunction. These mutations are thought to lead to slowing of the diastolic depolarization phase in sinus node cells. Mutations in Ca^{2+}–handling genes have also been associated with sinus node dysfunction, leading to an abnormal functioning of the Ca^{2+} clock.[2–11,32]

Aging is associated with sinus node dysfunction because it causes a decrease in the overall intrinsic heart rate and an increase in the sinus node conduction time. In humans, these findings appear to be preceded by a clinically silent atrial remodeling that is particularly evident in the region of

the crista terminalis and leads to slowing of conduction and voltage loss. Why this condition progresses in some patients to clinically overt sinus node dysfunction is still unknown.[2–11]

The histopathological abnormality that is consistently encountered in dogs with sinus node dysfunction is the total or partial destruction of the sinus node, characterized by a loss of nodal cells with a corresponding increase in fatty or fibrofatty tissue that interrupts the continuity between the sinus node and the surrounding atrial myocardium. Such alterations occur mainly in the head and body of the sinus node portions and to a lesser degree in the tail portion. The fatty or fibrofatty replacement of the myocardium usually also involves atrial myocytes to a variable extent, and sclerotic lesions of the intramural coronary arteries supplying the sinus node characterized by thickening of the vessel walls and a decrease in luminal size, can be frequently observed.[33] The reported histopathological lesions are correlated with reduced function of the nodal pacemaker cells and impaired conduction of the electrical impulse between the sinus node and the atrial myocardium. Some of the histopathological findings can also explain the presence of a reentrant mechanism inside the sinus node. Pathological upregulation of fibrosis within the sinus node may lead to tachycardia-bradycardia arrhythmias, possibly due to sinus node reentry and exit block.

In fact, interstitial fibrosis may lead to disruption of the continuity of electrically coupled myocytes, altering the delicate balance between depolarized cells and the resting tissue. In fact, it has been shown that excess fibrosis slows the activity of primary pacemaker clusters and enhances beat to-beat variability and atrial arrhythmias due to competition between primary and subsidiary or latent pacemaker clusters within and outside the sinus node pacemaker complex.[34] Furthermore, intramural optical mapping studies demonstrated that fibrosis could also lead to intranodal unidirectional conduction blocks and cause sinus node micro- and macroreentrant mechanisms. Interstitial fibrosis can also abnormally insulate latent atrial pacemaker clusters, thereby increasing their pacemaking properties.[34]

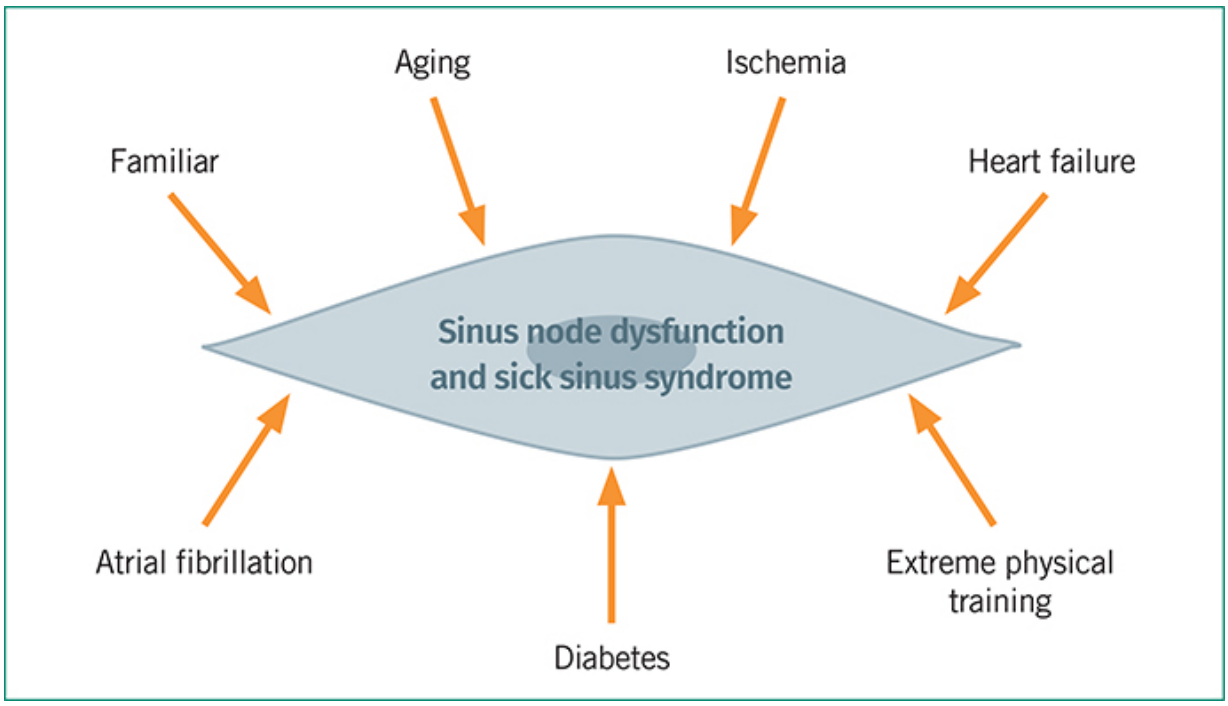


FIGURE 20.4. Schematic representation of the intrinsic and extrinsic causes of sinus node dysfunction.

Heart failure is a progressive condition that occurs when the heart no longer generates a sufficient cardiac output to meet the body's metabolic demands. Sinus node dysfunction occurs concurrently with heart failure development and is associated with abnormal automaticity due to structural remodeling of the mitochondria. In heart failure patients, an accumulation of damaged mitochondria at the sinus node has been demonstrated to be associated with a reduced ability to uptake Ca^{2+} when extramitochondrial Ca^{2+} levels increase, with a consequent reduction in energy generation.[35]

Resting bradycardia is a well-established phenomenon in athletes in both human and veterinary medicine. Historically, this phenomenon has been attributed to high vagal tone; however, more recent studies have shown that it is likely due to an irreversible mechanism involving ion channel remodeling.[2–11]

In human medicine, sick sinus syndrome has also been reported in association with myocarditis as a consequence of inflammation of the sinus node area.[6,36]

It has also been proven that patients with paroxysmal atrial fibrillation present regional remodeling in the right atrium near the sinus node area that

is associated with sinus node dysfunction. This atrial remodeling is responsible for slow conduction during sinus rhythm and lower electrocardiogram voltages in the sinus node region. However, these regional changes might be transient and reversible after the treatment of atrial fibrillation. Several mechanisms may explain the low-amplitude signals in the perinodal area in patients with atrial arrhythmias. Atrial fibrillation can lead to altered patterns of connexins, changes in myocyte cellular structure, interstitial fibrosis, and apoptotic atrial myocyte death. The nonuniform arrangement of atrial fibers in the diseased atrium may also enhance anisotropy and affect the conduction velocity in such a way that atrial fibers are activated asynchronously, thus explaining low-amplitude voltages. Diffuse atrial remodeling has also been described in patients with congestive heart failure in the presence of right atrial stretch, which could result in a reduced sinus node reserve.[37,38]

Because the sinus node is highly influenced by autonomic innervation, it is important to discriminate intrinsic from hypervagotonic sinus node dysfunction. Enhanced parasympathetic tone can be physiological (e.g., during sleep) or pathological. Pathological enhancement of parasympathetic tone may be triggered by gastrointestinal, genitourinary, pharyngeal, or other disorders involving tissues that are richly innervated by the vagal nerve; a different condition is characterized by normal reflexes such as the baroreceptor reflex associated with a disproportionate increase in vagal traffic.[40]

The extrinsic causes of sinus node dysfunction are systemic and include metabolic abnormalities (hyperkalemia, hypokalemia, hypocalcemia, hypothermia, hypothyroidism, hypoxia, diabetes), intracranial hypertension, systemic hypertension, drug-related (ivabradine, flecainide, propafenone, β-blockers, amiodarone, calcium-channel blockers, digoxin, cimetidine, phenothiazine) or toxins. Frequently, sinus node dysfunction due to extrinsic causes is considered reversible.[2–11]

ELECTROCARDIOGRAPHIC FINDINGS

Most of the diagnoses of sinus node dysfunction are based on a 12-lead electrocardiogram, which may show sinus bradycardia, sinus pauses (sinus arrest or sinus exit block), sinus standstill, and tachycardia-bradycardia or

bradycardia-tachycardia syndromes.[2–15] Electrocardiography is also useful in the evaluation of heart rate variability using 5-minute recordings. Changes in heart rate variability parameters can be recorded in patients with sinus node dysfunction and may facilitate the diagnosis and improve the accuracy of prognosis. In particular, the values of all time-domain heart rate variability parameters significantly exceed their reference limit; these findings were particularly evident for parameters directly linked to RR interval variability (SDNN, SDANN) (see p. 69) and the average RR interval duration.[40]

SINUS BRADYCARDIA

Sinus bradycardia is a common electrocardiographic finding in dogs affected by sinus node dysfunction.[12–15] A sinus rate of less than 60 bpm conventionally defines sinus bradycardia in dogs. Moderate degrees of bradycardia, with rates between 50 and 60 bpm, or even slower, are commonly found in athletes and in healthy individuals during sleep and at rest and do not necessarily constitute evidence of sinus node dysfunction or depressed cardiac performance. However, marked sinus bradycardia (<40 bpm), particularly if it is persistent and with little diurnal variability, is consistent with sinus node dysfunction.[2–15] Sinus bradycardia is characterized by regular RR intervals with cycle length irregularity, atrial deflections (P waves) with a superior-to-inferior and right-to-left axis (± 0°/+ 90°) that are positive in the inferior leads (II, III, and aVF), positive or isodiphasic in lead I, and with most negative in aVR. The atrioventricular conduction time is normal, and the PQ interval is usually normal and constant. The QRS complexes are normal in duration (≤70 ms in dogs), except if preexisting intraventricular conduction abnormalities and if escape beats or escape rhythm are present (Fig. 20.5).



FIGURE 20.5. Sinus bradycardia in a 14-year-old female West Highland White Terrier with sinus node dysfunction. The dominant rhythm is a sinus bradycardia (45 bpm) characterized by normal P waves (40 ms, 0,25 mV), normal PQ interval (100 ms), normal QRS complex (50 ms) and prolonged

QT interval (280 ms) due to the decreased heart rate. Lead II; speed, 50 mm/s; calibration, 20 mm/1 mV.

SINUS ARREST AND SINOATRIAL EXIT BLOCK

Sinus arrests and sinoatrial exit blocks denote a transient cessation of the sinus node impulse formation or a transient block of the electrical impulse from the sinus node to the atrial myocardium.[2–15]

Sinus arrest is characterized by a sinus pause appearing as a flat isoelectric line with no atrial depolarizations (Fig. 20.6); it is reported to be the most common electrocardiographic finding (80% of dogs with sick sinus syndrome reported). Concomitant atrioventricular conduction disturbances (first-degree atrioventricular block or second-degree atrioventricular block) are present in about 16% of dogs affected by sinus node dysfunction.

Due to the presence of sinus arrhythmia, it is very difficult to differentiate sinus arrest from sinoatrial block in dogs. In human medicine, sinoatrial blocks are characterized by pauses with a duration that is approximately a multiple of the preceding PP interval (type 2 sinoatrial block) or occur after gradual PP interval shortening in preceding PP intervals (type 1 or Wenckebach sinoatrial block). A high-grade or complete sinoatrial block results in a sinus pause that is indistinguishable from a pause secondary to sinus arrest.

In case of prolonged sinus pauses, slow ectopic atrial rhythms or junctional rhythms can be observed as subsidiary rhythms and are therefore markers of sinus node dysfunction (Fig. 20.7).[2–15]

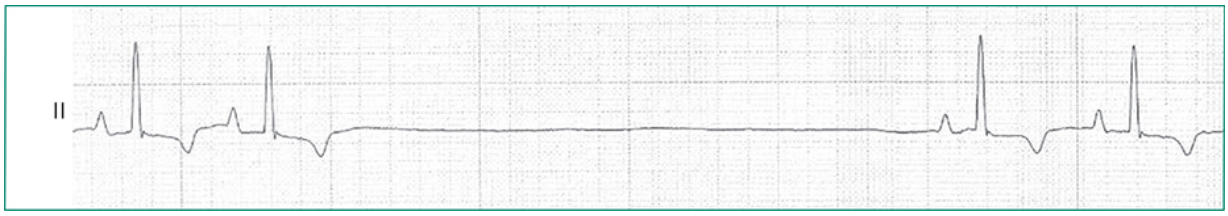


FIGURE 20.6. Sinus arrest in a 15-year-old male Jack Russell Terrier with sinus node dysfunction. Note the presence of two normal P-QRS-T complexes followed by a sinus pause lasting 2.4 seconds. The PP interval, which includes the sinus arrest is equal to 5.2 times the previous PP interval. After the sinus arrest, two normal P-QRS-T complexes are present. Lead II; speed, 50 mm/s; calibration, 20 mm/1 mV.

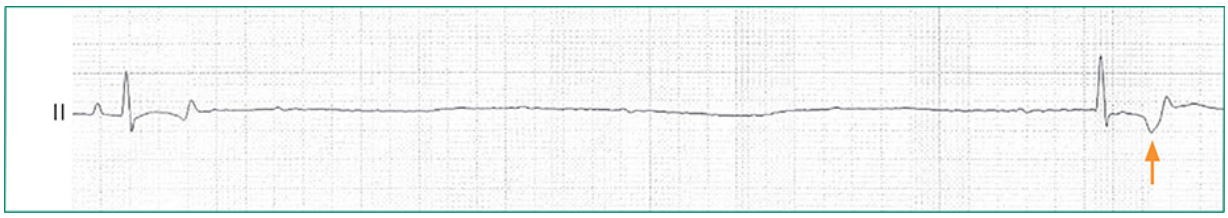


FIGURE 20.7. Sinus arrest in a 16-year-old female West Highland White Terrier with sinus node dysfunction. Note the presence of a normal P-QRS-T complex followed by a sinus pause lasting 3.36 seconds. After the sinus pause, an escape junctional ectopic beat is present. Note the absence of a P wave before the narrow QRS complex and the presence of a negative atrial deflection inscribed in the ST segment (arrow) characteristic of concentric atrial retroactivation. Lead II; speed, 50 mm/s; calibration, 10 mm/1 mV.

SINUS STANDSTILL

Sinus standstill is a persistent or prolonged sinus arrest during which the heart rhythm is maintained by junctional escape rhythms, and less commonly by atrial or ventricular escape rhythms.[2–15]

Sinus standstill is characterized by the absence of sinus P waves and a normal QRS complex duration (≤70 ms in the dog) and morphology if associated with a junctional escape rhythm, or wide QRS complexes (>80 ms in the dog) with an abnormal morphology if associated with a ventricular escape rhythm. The RR intervals are usually regular in both junctional and ventricular escape rhythms. Sinus standstill with a junctional escape rhythm or ventricular escape rhythm is usually associated with retrograde concentric atrial activation and a 1:1 ventriculoatrial conduction ratio. This is consistent with atrial deflections characterized by an inferior-to-superior axis (–80°/–100°) that are negative in the inferior leads (II, III, and aVF), isodiphasic in lead I, and equally positive in leads aVR and aVL. The atrial deflections, also described as pseudo-S waves, are observed just after the descending branch of the R wave or within the ST segment (Fig 20.8).

Based on the electrocardiographic findings, sinus standstill is impossible to distinguish from high-grade or complete sinoatrial block on the surface electrocardiogram, and endocardial mapping and programmed pacing are required to differentiate the two conditions.[41]

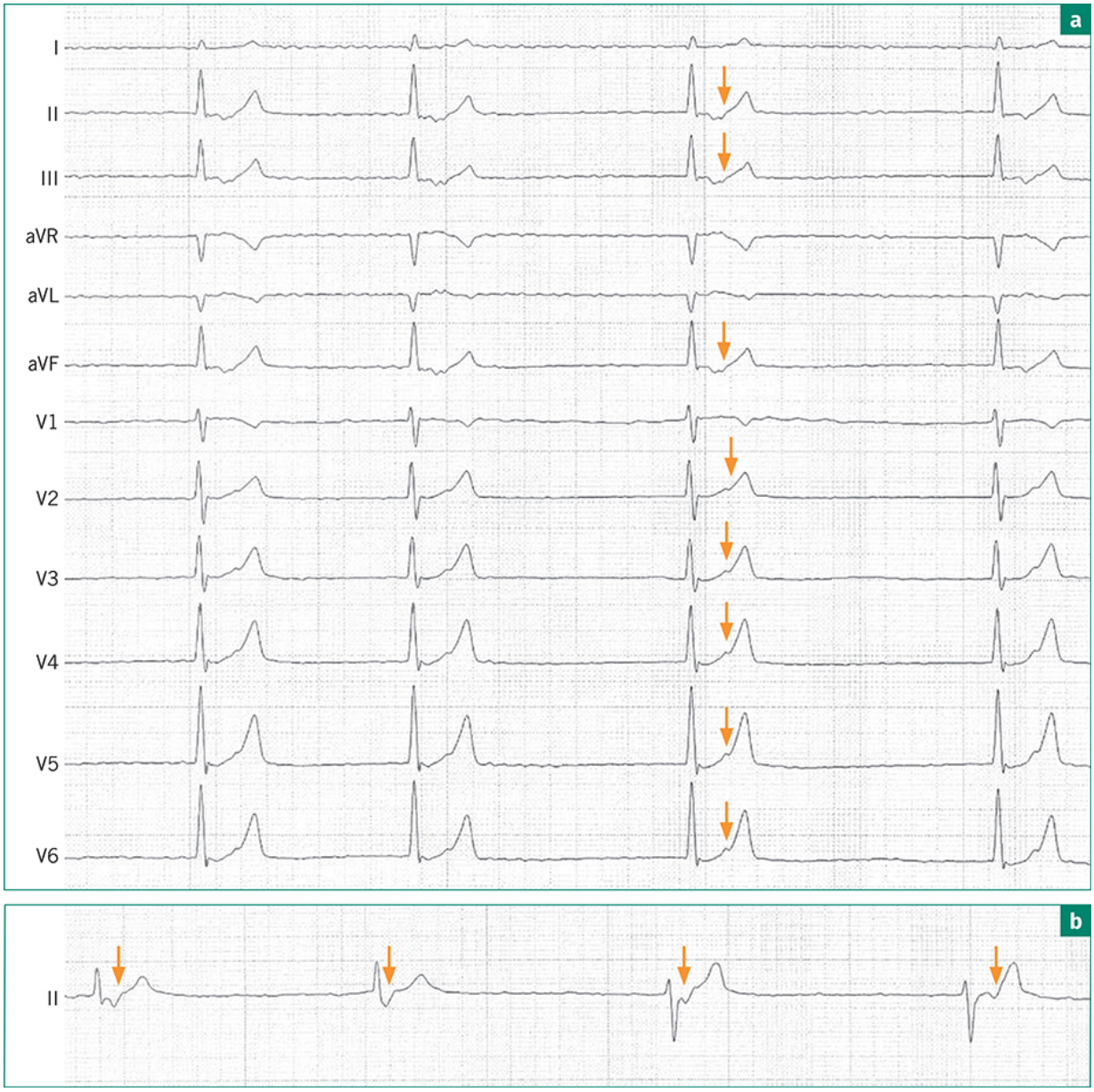


FIGURE 20.8. a) Sinus standstill with a junctional escape rhythm in a 12-year-old female Poodle with sinus node dysfunction. Note the absence of P waves and the presence of narrow QRS complexes (50 ms) originating from the atrioventricular junction. An atrial deflection inscribed in the ST segment is evident, with negative polarity in the inferior leads and positive polarity in the left precordial leads (arrows) characteristic of concentric retrograde atrial conduction with a 1:1 ratio. The RP' interval is long, which indicates atrial retroactivation occurred along a slow atrioventricular pathway. Twelve leads (I, II, III, aVR. aVL, aVF, V1, V2, V3, V4, V5, V6); speed: 50 mm/s; calibration, 5 mm/1 mV. b) Sinus standstill with a junctional escape rhythm and ventricular escape rhythm in a 14-year-old female West Highland White Terrier with sick sinus syndrome. Note the absence of P waves and the presence of narrow QRS complexes (50 ms) originating from the atrioventricular junction (1st and 2nd QRS complexes) and wide QRS complexes (80 ms) originating from the ventricle (3rd and 4th QRS complexes). An atrial deflection inscribed in the ST segment of both narrow and wide QRS complexes is evident; this atrial deflection has negative polarity (arrows), which is characteristic of a concentric retrograde atrial conduction with a 1:1 ratio. The RP' interval

is short in the first three beats, indicating atrial retroactivation occurred along a fast atrioventricular pathway, but becomes long in the last beat, indicating atrial retroactivation occurred after partial depolarization of the ventricular myocardium. Lead II; speed, 50 mm/s; calibration, 5 mm/1 mV.

TACHYCARDIA-BRADYCARDIA AND BRADYCARDIA-TACHYCARDIA SYNDROMES

The tachycardia-bradycardia variant of sinus node dysfunction is characterized by paroxysmal supraventricular tachycardia that terminates in long pauses (Figs. 20.9 and 20.10).[2–15] Senescence of the atrial muscle leading to increased atrial fibrosis constitutes the anatomical substrate for the supraventricular tachyarrhythmias typical of this variant.

The bradycardia-tachycardia variant of sinus node dysfunction is characterized by periods of sinus bradycardia followed by an idioventricular rhythm with a high firing rate, atrial fibrillation, or supraventricular tachycardia.[2–15] Persistent sinus bradycardia can strongly facilitate the conditions for atrial fibrillation and supraventricular tachycardias by increasing dispersion of refractoriness in the atrial myocytes, which is the main functional source for these rhythm disturbances.[2–11]

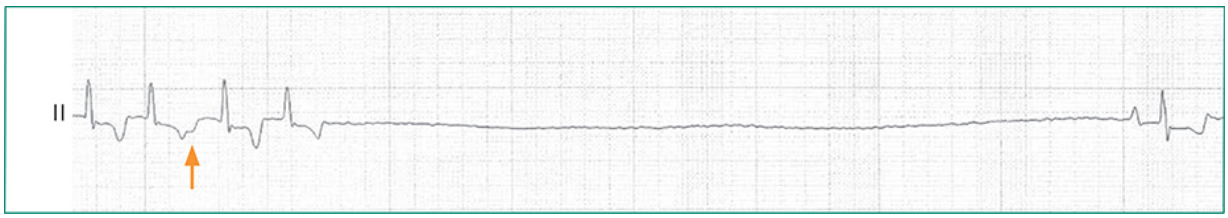


FIGURE 20.9. Tachycardia-bradycardia variant of sick sinus syndrome in a 13-year-old female mixed-breed dog. Note the presence of a supraventricular tachycardia in the first part of the tracing (214 bpm), characterized by narrow QRS complexes (50 ms) and an abnormal negative atrial deflection inscribed in the previous T wave (arrow). When the supraventricular tachycardia stopped, a prolonged sinus node recovery time occurred with a sinus arrest lasting 3.44 seconds, which was interrupted by a normal P-QRS-T complex. Lead II; speed, 50 mm/s; calibration, 10 mm/1 mV.



FIGURE 20.10. Tachycardia-bradycardia variant of sick sinus syndrome in a 11-year-old female mixed-breed dog. Note the presence of a normal P-QRS-T complex followed by a supraventricular ectopic rhythm in the first part of the tracing (166 bpm) characterized by narrow QRS complexes (50

ms) and abnormal negative atrial deflections. After the supraventricular ectopic rhythm, a sinus arrest interrupted by artificial paced wide QRS complexes is evident. Note the presence of the spikes (arrows) and the programmed hysteresis (the RR interval between the last intrinsic and the first paced beat is 1200 ms; the RR interval between two consecutive paced beats—the pacing interval set— is 800 ms). Lead II; speed, 50 mm/s; calibration, 10 mm/1 mV.

HOLTER FINDINGS

The 24-hour ambulatory electrocardiogram is used to better understand the spectrum of arrhythmias correlated with sinus node dysfunction. Holter monitoring is also useful to evaluate the type and discharge rate of escape beats and rhythms (junctional or ventricular).[12–15]

The criteria for the diagnosis of sinus node dysfunction based on Holter findings includes: a heart rate <65 bpm with a minimum of 35 bpm, more than 3000 pauses lasting more than 2 seconds, more than 5 pauses lasting more than 4 seconds, and the longest pause lasting more than 5.5 seconds.[42] The average heart rate on 24-hour monitoring is described to be statistically lower in dogs with sinus node dysfunction (45 bpm; range, 41.5–54) and in dogs with high parasympathetic and/or low sympathetic modulation (48.5 bpm; range, 45.8–51) than in normal dogs (64 bpm; range, 58.8–67). The minimum heart rate is reported to be statistically lower in dogs with sinus node dysfunction (26 bpm; range, 23.5–28.5) than in both dogs with high parasympathetic and/or low sympathetic modulation (33.5 bpm; range, 31.8–36) and normal dogs (46; range, 41–50).[42] The tachycardia-bradycardia variant of sinus node dysfunction is considered an exception since, due to the electrocardiographic characteristics, it may result in a higher average heart rate.[42]

In dogs with syncope, Holter monitoring is crucial to distinguish transient loss of consciousness or posture due to intrinsic sinus node dysfunction from neurally mediated syncope. Typically, the Holter findings consistent with neurally mediated syncope include sinus arrest preceded by progressive sinus bradycardia or initial sinus tachycardia followed by progressive sinus bradycardia until sinus arrest (Fig. 20.11). In case of intrinsic sinus node dysfunction, sinus arrest occurs with a sudden onset during sinus rhythm or persistent sinus bradycardia or after an episode of supraventricular tachycardia (Fig. 20.12).[43]

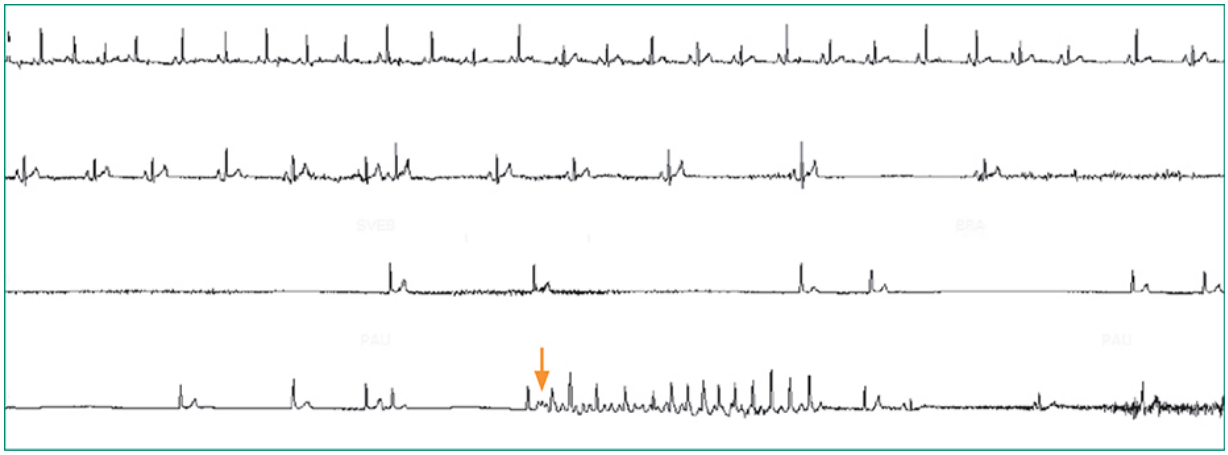


FIGURE 20.11. Ambulatory electrocardiographic recording of a type 1A neurally-mediated transient loss of consciousness in a 12-year-old female mixed-breed dog.[43] Note the presence of an initial sinus rhythm, followed by progressive sinus bradycardia and a prolonged sinus arrest interrupted by an ectopic junctional escape rhythm. In the last line, vagal functional atrial flutter can be seen (arrow), which spontaneously converted into sinus rhythm. Y lead; each line corresponds to 15 seconds. Speed, 18 mm/s; calibration, 5 mm/1 mV.

Poincaré plots and tachograms can be used to better evaluate sinus node function. Twenty-four-hour electrocardiograms allow not only the identification of arrhythmias but also provide an opportunity to analyze the pattern, triggers, and timing of arrhythmias over the course of the day and night. Tachograms displaying the RR interval duration over time can document changes in heart rate, while Poincaré plots can be obtained from the RR interval data. These plots display a short-term heart rate variability from the plotting of the RRn interval (x-axis) versus the RRn+1 interval, i.e., the immediate next interval (y-axis).[44]

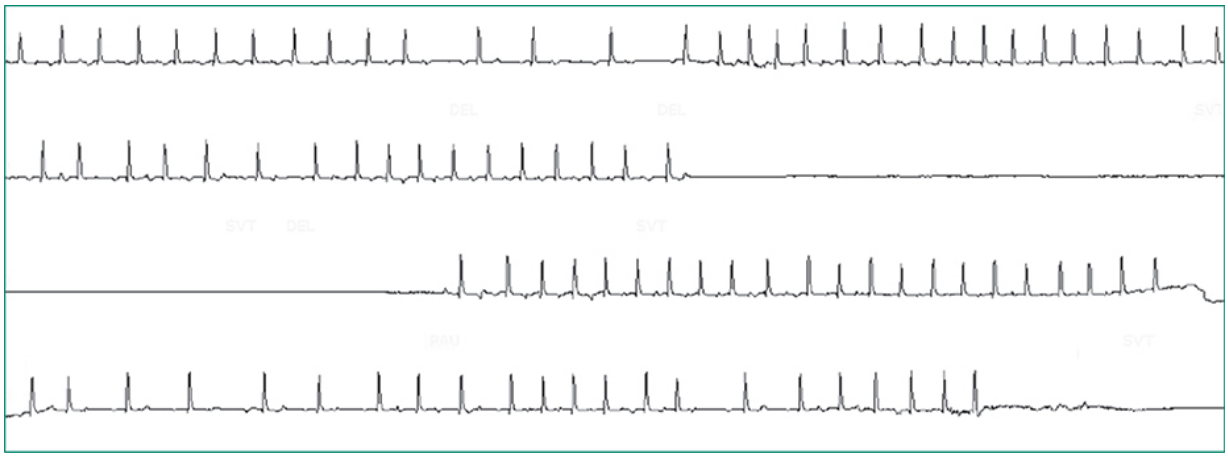


FIGURE 20.12. Ambulatory electrocardiographic recording of a sinus arrest due to sick sinus syndrome and inducing type 1D syncope[43] in a 13-year-old male Dachshund. Note the presence of an atrial ectopic rhythm with atrioventricular blocks followed by a sudden onset of sinus arrest. After the sinus pause, a normal P-QRS-T complex followed by a reoccurrence of atrial ectopic rhythm is evident. Y lead; each line corresponds to 10 seconds. Speed, 28 mm/s; calibration, 5 mm/1 mV.

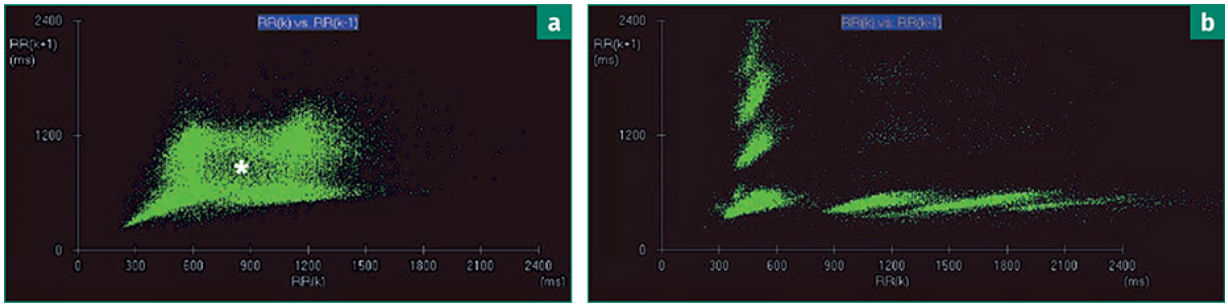


FIGURE 20.13. a) Normal Poincaré plot in the dog. This plot displays a short-term heart rate variability from the plotting of the RRn interval (x-axis) versus RRn+1 interval (y-axis), which is the immediate next interval. Note the normal distribution of the RR intervals with the zone of avoidance (*). b) Poincaré plot in a dog with sinus node dysfunction. Note the dispersion of dots grouped in different spots.

In normal dogs, dynamic Poincaré plots are described to show linear rate changes as intervals increase until a point of divergence (mean interval, 598.5 ms) called bifurcation interval. Dogs have also been shown to have a bimodal beat distribution during sleep, with slower rates and greater variability than during active. A slower heart rate during sleep hours suggests greater parasympathetic modulation, with a branched rather than clustered distribution. The abrupt bifurcation, zone of avoidance, and beat-to-beat patterning demonstrate the development of an exit block from the sinus node, with parasympathetic modulation influencing not only the oscillation of the pacing cells but also conduction to the atria (Fig. 20.13).[45]

Holter monitoring can be useful to document persistent sinus bradycardia (Fig. 20.14) with chronotropic incompetence. Chronotropic incompetence is described as the inability of the sinus node to adjust its rate appropriately in response to metabolic demand and represents a classical finding in dogs with sinus node dysfunction. Exercise testing is often considered to help identify such patients, even if it has never been described in veterinary medicine.[2–15]

Supraventricular tachycardias correlated with sinus node dysfunction usually show a pattern of RR interval bands with differing ratios of atrioventricular nodal block. This pattern is characteristic of sustained

supraventricular tachycardia, with RR intervals that result from 1:1, 2:1, 3:1, 4:1 or more atrioventricular block and are fairly consistent for each conduction ratio (Fig. 20.12).[44]

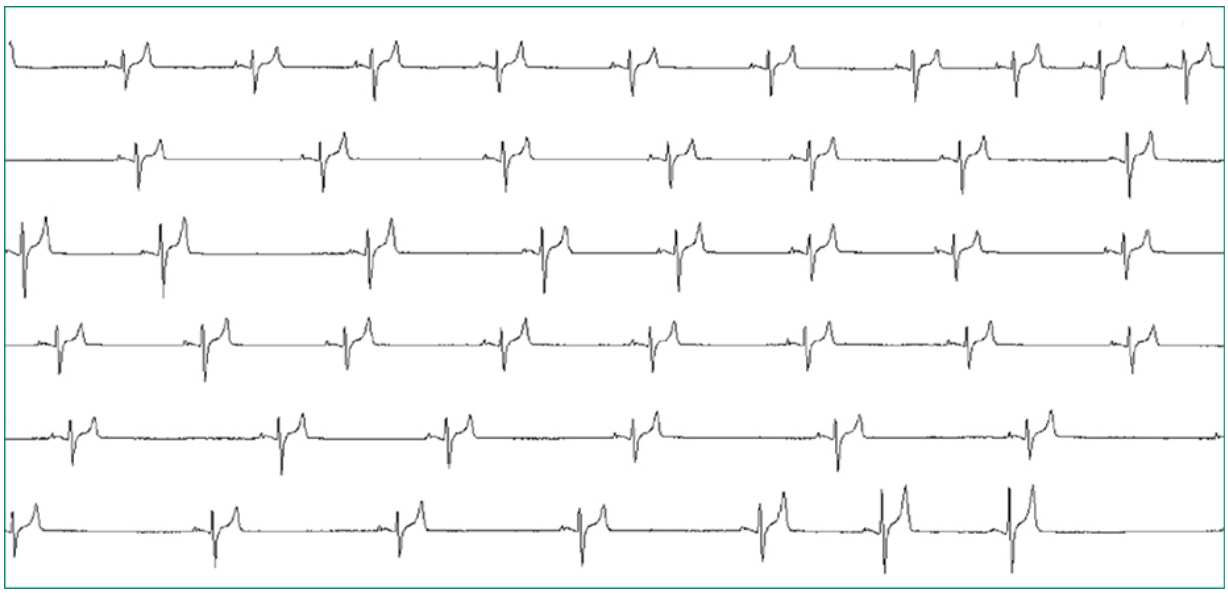


FIGURE 20.14. Ambulatory electrocardiographic recording of a sinus bradycardia associated with chronotropic incompetence in a 12-year-old male West Highland White Terrier. Note the presence of sinus bradycardia (ranging from 40 to 55 bpm) with no variations of the heart rate in response to metabolic demand during a 5-minute walk. This Holter finding is suggestive of sinus node dysfunction. Y lead, each line corresponds to 10 seconds. Speed, 28 mm/s; calibration, 5 mm/1 mV.

Cardiac event recording is suggested in the presence of clinical signs (transient loss of posture or transient loss of consciousness) with an electrocardiogram and Holter monitoring that are inconclusive. Usually, external cardiac event recording allows the identification of a period of sinus arrest during the transient loss of posture or consciousness.[12–15]

ECHOCARDIOGRAPHY

The echocardiographic examination is described to be unremarkable in 15% of dogs with sinus node dysfunction. Myxomatous degenerative mitral valve disease is a common concomitant structural heart disease considering the sinus node dysfunction population characteristics, and it is diagnosed as mild in 60%, moderate in 18%, and severe in 7% of dogs with sinus node dysfunction.[12,13]

CLINICAL PRESENTATION

Symptomatic sinus node dysfunction or sick sinus syndrome has a clinical presentation with variable degrees of clinical severity; clinical signs are often intermittent, extremely variable, and unpredictable. There are no specific signs for sick sinus syndrome, because they are observed in several other diseases. The average age at diagnosis has been reported to be 11±3 years (range, 2–16 years), and females are overrepresented. The average patient weight is 8.8±3.3 kg (range, 2.3–19.7 kg).[12] Commonly affected breeds are Miniature Schnauzers, West Highland White Terriers, Cocker Spaniels, and mixed-breed dogs.[12,13] The clinical manifestations of sinus bradycardia are due to a reduction in cerebral and peripheral perfusion and are usually subtle. They include lethargy, fatigue, and exercise intolerance. Syncope or transient loss of posture are considered to be caused by sinus arrests and the consequent drop in cerebral blood flow and are regarded as a typical sign of sinus node dysfunction. The median frequency of syncopal episodes at the time of presentation is one episode/day, with some patients experiencing as few as one single episode across their lifespan, and others experiencing up to 15 episodes per day.[12–15]

Physical findings in patients with persistent sinus bradycardias include pallor of the mucous membranes due to poor peripheral perfusion, a prolonged capillary refill time, inappropriately slow heart rate (mean heart rate at presentation, 87±33 bpm), and concomitant heart murmurs if myxomatous mitral and tricuspid valve disease is present. The femoral pulse can be hyperkinetic as a result of an increase in pulse pressure caused by the decreased heart rate.[12–15]

THERAPY

PHARMACOLOGICAL TREATMENT

Various medications have been used to increase the heart rate of patients with sinus node dysfunction, with disappointing results. In human medicine, slow-release theophylline has been shown to increase the resting heart rate by 33% and to prevent associated overt heart failure but not syncopal recurrences.[2–11]

Theophylline at a dose of 10–20 mg/kg PO every 24 hours has also been shown to increase the resting and exercise heart rates and to reduce cardiac pauses during follow-up. However, there is no direct evidence supporting the gross effects of aminophylline or theophylline in the setting of acute sinus node dysfunction in both humans and dogs.[2–15]

Other described oral positive chronotropes include propantheline bromide at a dosage of 0.5–2 mg/kg PO every 8 hours[12,13] and extended-release hyoscyamine at a dosage of 0.01 mg/kg PO every 12 hours.[46] Side effects have been reported with positive chronotropic agents in 6% of dogs and consisted in anxiety, hyperactivity, or diarrhea.[12]

Cilostazol is an oral selective phosphodiesterase type III inhibitor, used in Japan as an antiplatelet and antithrombotic agent for patients with peripheral arterial occlusive diseases. It has been demonstrated to have a positive chronotropic effect and has been used in human medicine to treat bradyarrhythmias such as sick sinus syndrome and atrioventricular blocks. The mechanisms of action of this drug include vasodilation resulting in a reflex increase in heart rate, suppression of parasympathetic tone leading to improved sinus node function, coronary artery dilation with a consequent increase in blood flow to the sinus node, and increased sinus node intracellular cyclic adenosine monophosphate. Cilostazol has been reported to increase heart rate in experimental dogs and in the clinical setting with a prolonged follow-up at the dosage of 10 mg/kg PO every 12 hours.[47,48]

Antiarrhythmic therapy in combination with pacemaker implantation is necessary to control supraventricular tachycardias in the tachycardia-bradycardia variant of the disease.[2–11] Supraventricular tachycardias have been described to be treated with propranolol at the dosage of 0.25 mg/kg PO every 8 hours.[13] In the author's experience, ivabradine at a dosage of 0.4–0.6 mg/kg PO every 12 hours can be used in dogs with sinus node dysfunction and supraventricular tachycardias after permanent endocardial pacemaker implantation.

CARDIAC PACING

Permanent endocardial pacemaker implantation is the first-line treatment for patients with confirmed sick sinus syndrome. However, in both human and veterinary medicine, pacemaker implantation has not been proven to

increase survival time, and its primary goal is to relieve clinical signs and improve quality of life.[2–13,49–51] Different studies in human medicine have shown that physiological pacing (atrial or dual-chamber pacing) is definitely superior to VVIR pacing, with the former technique resulting in a better quality of life, a lower frequency of overt heart failure, a better cardiac performance, and a lower risk of developing atrial fibrillation. Furthermore, in dogs with normal conduction at the atrioventricular node, ventricular pacing can be associated with ventriculoatrial conduction and correlated echo-beats after each artificial paced beat. Atrial-based pacing (AAI pacing) has been described in veterinary medicine.[49–51] In dogs, clinically important atrioventricular blocks do not appear to occur in the long-term follow-up in dogs with sick sinus syndrome, and AAI pacemakers are usually suggested to guarantee physiological atrioventricular synchrony. In human medicine, the effect of pacing mode on survival time is still debated. While some old case-control studies concluded that physiological pacing was able to improve survival time in patients with congestive heart failure, more recent large randomized trials have failed to confirm these findings, even though a trend towards a higher survival time was still observed.[2–11] Dual-chamber pacing (DDD pacing) seems to be more adequate but causes asynchronous interventricular septum contraction, which results from pacing at the apex of the right ventricle and constitutes a potential hemodynamic disturbance. Programming a long atrioventricular interval (longer than the spontaneous PQ interval) to maintain a normal sequence of ventricular activation and avoid right ventricular pacing is often useful.[2–11]

PROGNOSIS

The mean survival time in dogs affected by sick sinus syndrome from the time clinical signs are first noticed is reported to be 18–25 months,[12,13] with most dogs being euthanized for noncardiac causes. The survival time does not differ between symptomatic and asymptomatic dogs, or between dogs receiving pacemaker implantation and those treated medically. In dogs receiving positive chronotropic agents, clinical signs are controlled long term (>1 year or until death due to noncardiac causes in 54% of dogs).[12]

About 20% of dogs present an initial positive response to positive chronotropic agents but then experience subsequent worsening of the clinical signs requiring pacemaker implantation.[12] Medical management with positive chronotropic agents therefore appears to be a viable treatment strategy, which can be offered safely to the owners who refuse pacemaker implantation.[12] The specific positive chronotropic agents used (theophylline, propantheline, hyoscyamine, terbutaline) does not appear to affect the response to treatment and prognosis.

Permanent endocardial pacemaker implantation is correlated with relief of clinical signs, and the survival time in these dogs is reported to be 8–26 months from the onset of the clinical signs.[12]

Sudden cardiac death does usually not occur in dogs with sick sinus syndrome.[12]

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CHAPTER 21

Atrial standstill

Romain Pariaut

DEFINITION

Atrial standstill is a bradyarrhythmia defined by the absence of electrical and mechanical atrial activity.[1] Atrial standstill can be described as transient or persistent. It is called transient when atrial standstill is interrupted by periods of sinus rhythm or when it can be terminated by treating an underlying cause.[2] Identified causes of transient atrial standstill include cardiac glycoside intoxication, hyperkalemia, hypoxia, and myocardial ischemia in people.[3] The persistent form of atrial standstill is a rare bradyarrhythmia that represents approximately 3–5% of the indications for pacemaker implantation in dogs.[4,5] Causes of persistent atrial standstill include long-standing progressive cardiac disease, myocarditis, neuromuscular disorders with atrial involvement, but more commonly it is attributed to an idiopathic atrial myopathy.[1,2,6–8] This condition has also been described as an atrioventricular muscular dystrophy.[9] Pale and variably thin atrial walls are the most obvious necropsy findings in cases of idiopathic atrial standstill.[10] The reduction in thickness of the atrial wall is the result of partial to almost complete fatty and fibrofatty replacement of the myocytes. Lesions seem to first affect the subepicardium and midmyocardium of the upper regions of the atria and progressively extend transmurally and downwards towards the lower regions of the atria. A small number of mononuclear inflammatory cells might be observed but are probably not involved in the disease process (Fig. 21.1).[10] Dogs diagnosed

with persistent atrial standstill are more commonly young adults, although they can, on rare occasions, be as young as 5 months.[9,11] English Springer Spaniels and Labradors are overrepresented, and a female predisposition is suspected.[11,12]

Atrial standstill can also be described as total or partial, when some portions of the atria remain electrically active. In cases of partial atrial standstill, although no P waves are visible on the surface electrocardiogram, portions of the atria remain electrically active and can be stimulated with an electrophysiological catheter or a pacemaker lead.[2,13]

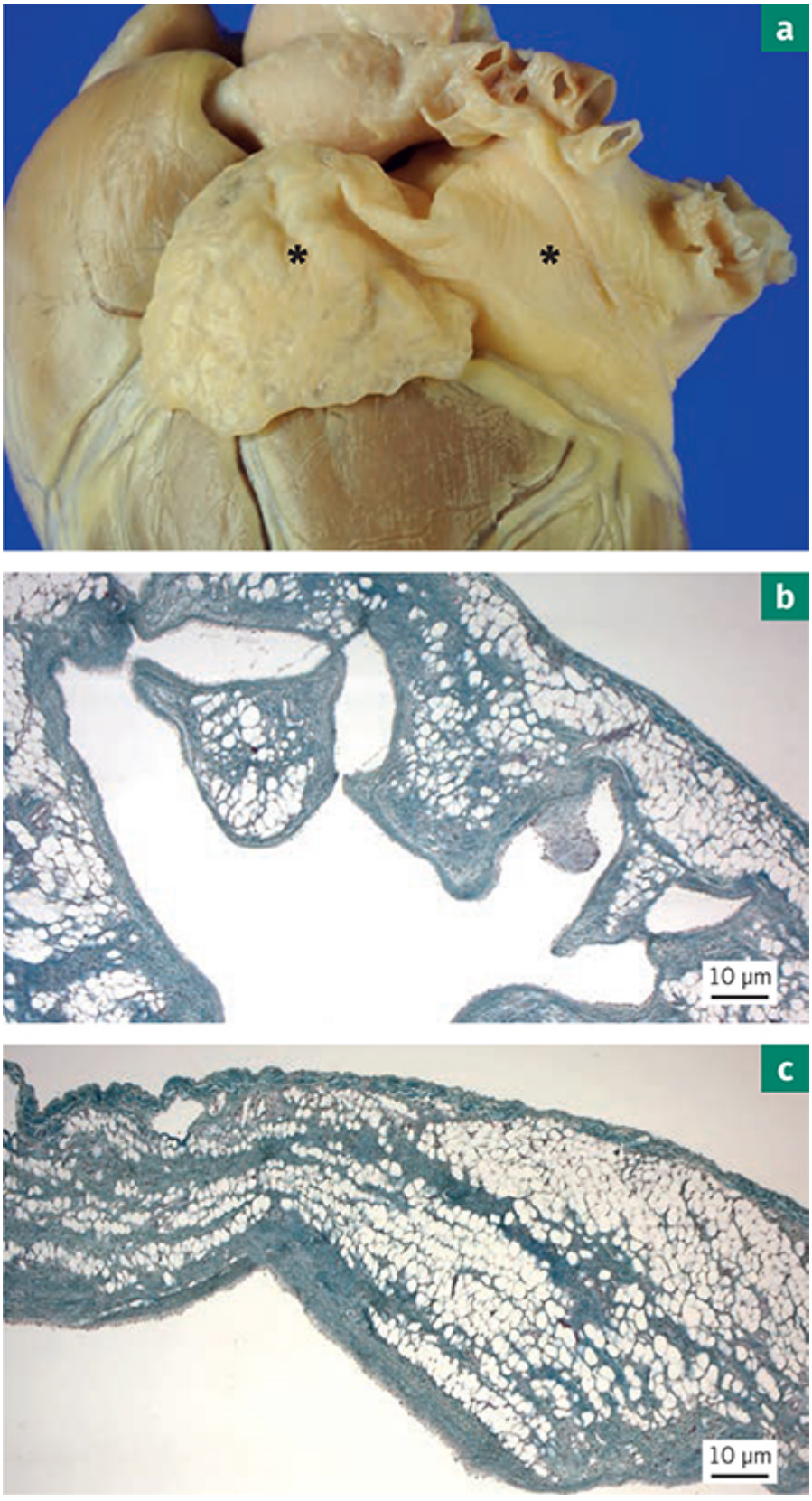

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b
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FIGURE 21.1. Gross and histopathological findings in a 4-year-old female Greyhound with persistent atrial standstill. a) Left side of the heart. Severe dilatation of the left auricle and atrium, diffuse white to yellow discoloration (*). b) Histological image of the left auricle: diffuse, severe transmural fibrofatty replacement (Masson's stain). c) Histological image of the left atrium: diffuse, severe transmural fibrofatty replacement (Masson's stain). Pictures courtesy of Dr Massimiliano Tursi, University of Turin, Italy.

Persistent atrial standstill has rarely been reported in cats.[14]

ELECTROPHYSIOLOGICAL MECHANISM

The absence of atrial depolarization and the inability to stimulate the atrium is due to the loss of atrial myocytes combined with the extensive replacement fibrosis that forms obstacles to electrical impulse conduction. Electrophysiological studies in people suggest that the fibrotic process frequently extends to the sinus node and atrioventricular junction.[3]

ELECTROCARDIOGRAPHIC FINDINGS

Atrial standstill is characterized by the absence of P waves on any lead of the surface electrocardiogram and a regular junctional or ventricular escape rhythm (Figs. 21.2 and 21.3) Ideally, the electrocardiographic diagnosis should be confirmed by intracardiac electrophysiological testing, and the absence of mechanical atrial activity should be demonstrated on echocardiography.[15] In the human pediatric population, in which persistent atrial standstill is frequently associated with mutations of the sodium channel encoded by the *SCN5A* gene, periods of atrial arrhythmias, including atrial tachycardia, atrial flutter and fibrillation are common. Ventricular arrhythmias are also frequently documented in people.[2]

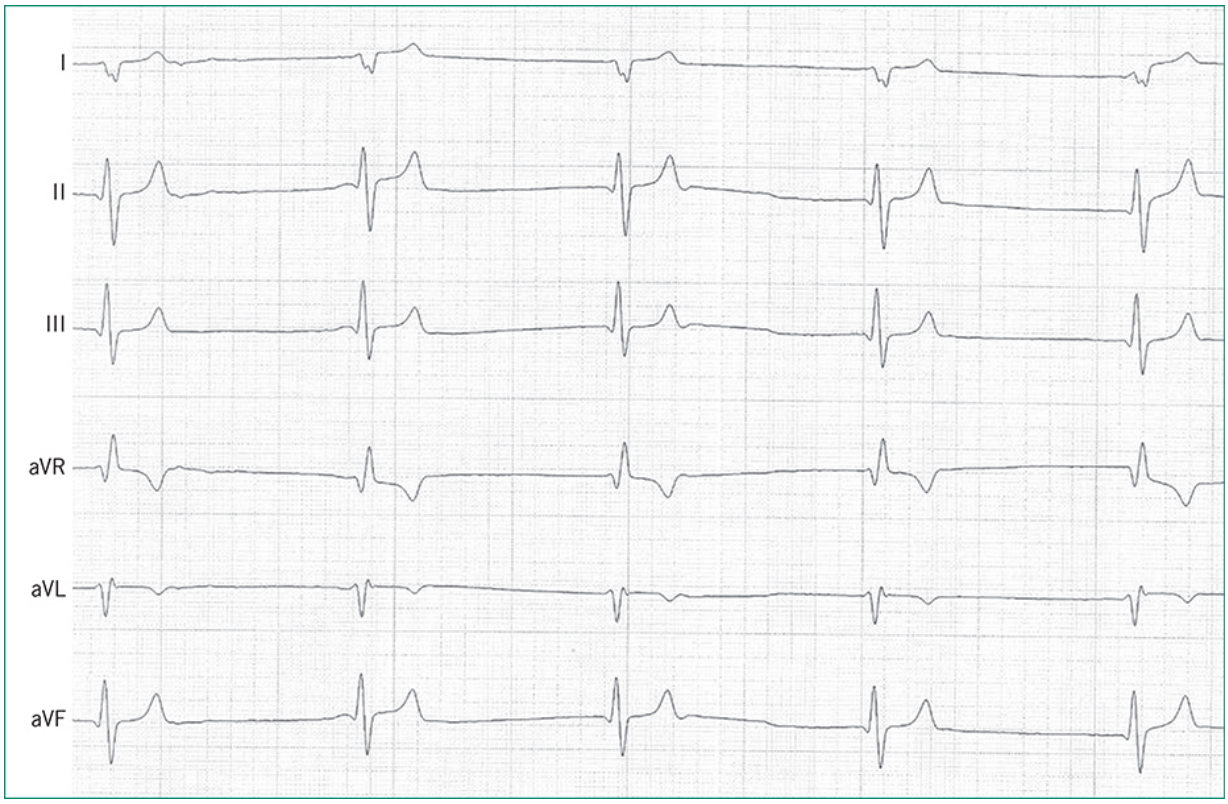


FIGURE 21.2. Atrial standstill in a 4-year-old male Labrador Retriever with persistent atrial standstill. Note the presence of a wide QRS (80 ms) rhythm with a ventricular rate of 60 bpm and the absence of atrial activation. Six limb leads (I, II, III, aVR, aVL, aVF). Speed, 50 mm/s; calibration, 5 mm/1 mV.

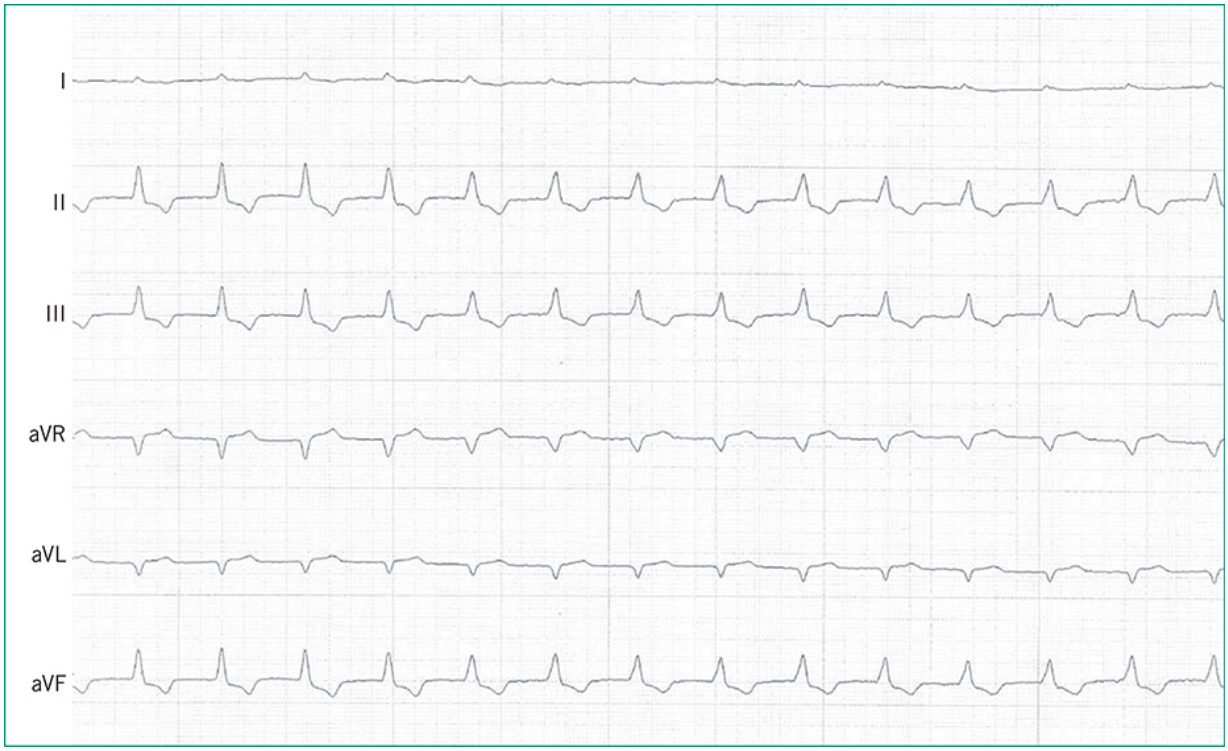


FIGURE 21.3. Atrial standstill in a 6-year-old male domestic shorthair cat with persistent atrial standstill. Note the presence of a wide QRS (60 ms) rhythm with a ventricular rate of 180 bpm and the absence of atrial activation. Six limb leads (I, II, III, aVR, aVL, aVF). Speed, 50 mm/s; calibration, 5 mm/1 mV.

CLINICAL PRESENTATION

The clinical signs at presentation include congestive heart failure (pulmonary edema, pleural effusion and ascites), syncope and exercise intolerance/lethargy.[11,16] The physical examination reveals bradycardia. Systolic murmurs secondary to atrioventricular valve insufficiencies are common.[10,13]

EVALUATION METHODS

Atrial standstill should be differentiated from sinus arrest, sinoatrial block, and permanent atrial fibrillation with complete atrioventricular block. In atrial standstill, low-amplitude fibrillatory waves are not always visible on the surface electrocardiogram. Intracardiac electrophysiological testing is

required to confirm the absence of fibrillatory waves. Lack of atrial capture even with high-output stimuli of up to 25 mA confirms that the absence of P waves is not solely due to sinus arrest or sinoatrial block (Fig. 21.4).[17] This test is usually limited to the right atrium using an electrophysiological catheter or a pacemaker lead at the time of pacemaker implantation.[3] In some cases, it is possible to test left atrial capture by inserting an electrophysiological catheter into the coronary sinus.[3]

Hyperkalemia should be ruled out when atrial standstill is suspected. Cardiac troponin-I (cTnI) is expected to be mildly to moderately elevated in most dogs with atrial standstill.[12] A marked elevation in cTnI should raise the suspicion of myocarditis as the cause for the arrhythmia and might be associated with a worse outcome.[18]

Echocardiographic evaluation typically reveals immobility of the atria, right atrial and ventricular enlargement, and various degrees of left atrial and left ventricular enlargement with preserved systolic function.[16] Spectral Doppler signals of mitral and tricuspid inflows do not have an A wave due to the absence of atrial contractions (Fig. 21.5).[2]

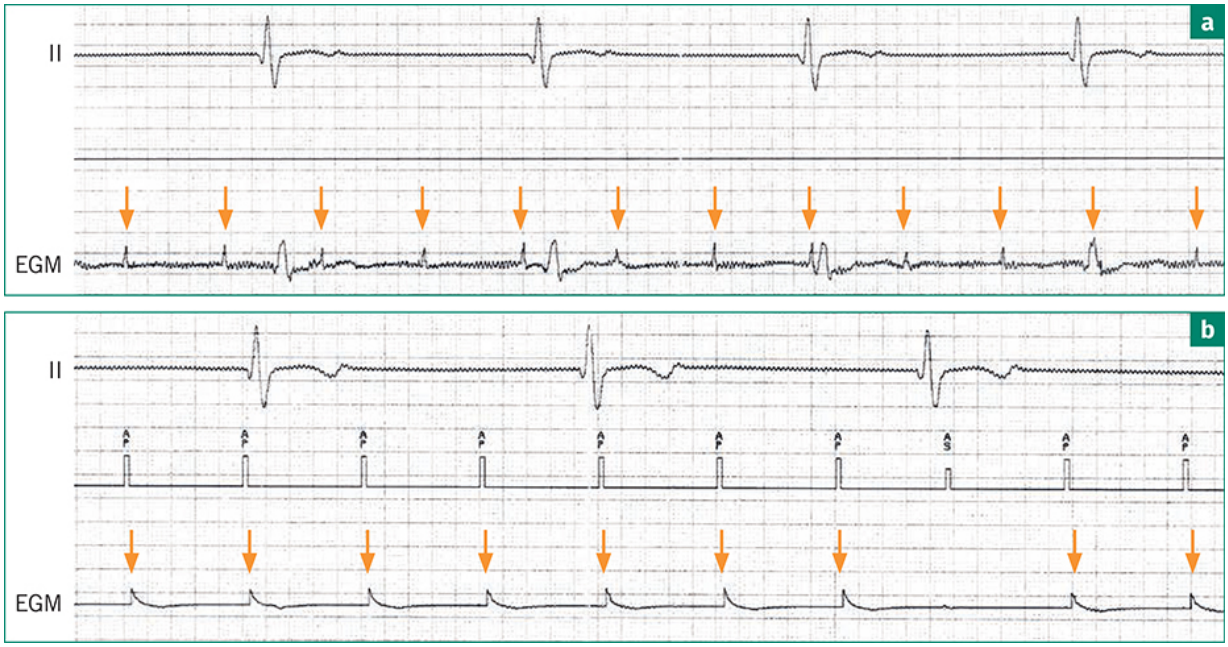


FIGURE 21.4. Endocardial mapping strips performed with a ventricular pacemaker lead in a 5-year-old female Labrador Retriever with partial atrial standstill. a) The upper tracing shows a wide QRS rhythm without atrial activity (lead II, 50 mm/s, 1 mm/0.2 mV) while the lower tracing is an atrial electrogram (EGM) at the entrance of the cranial vena cava into the right atrium (50 mm/s, 1mm/1 mV). Note the presence of atrial electrograms (arrows) that do not induce atrial depolarization,

therefore leading to the absence of visible atrial P waves on the surface lead. b) The electrode was then pushed into the right atrium to map the lateral wall of the cardiac chamber. As no atrial electrograms were seen, atrial pacing (AP) was performed up to 25 mA. Atrial spikes can be seen (arrows) in the lower tracing (50 mm/s, 1mm/1 mV), with no atrial capture and therefore no P wave on the surface lead (lead II, 50 mm/s, 1 mm /0.2 mV). The last QRS complex is sensed by the pacemaker (AS) and therefore no atrial spike is recorded.

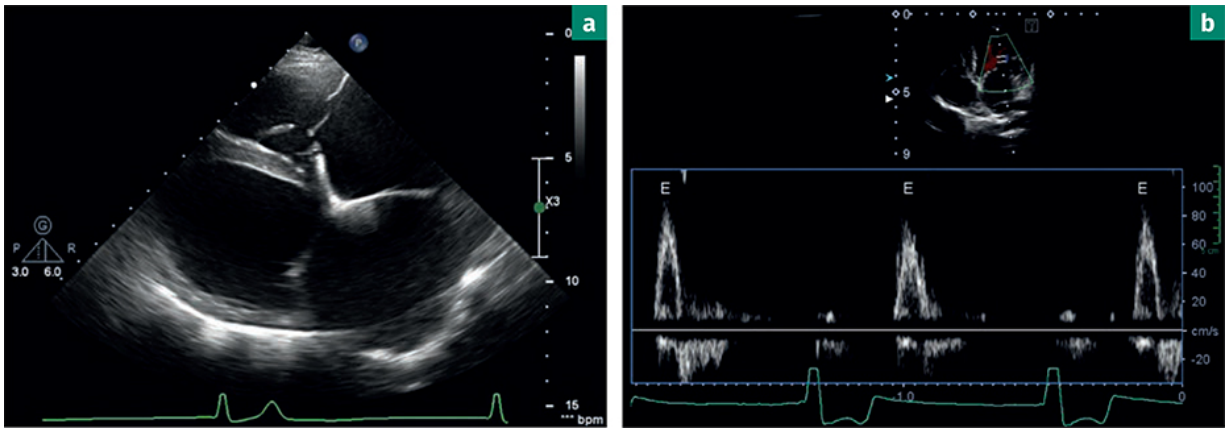


FIGURE 21.5. Echocardiogram in a 7-year-old female Labrador Retriever with persistent atrial standstill. a) Right parasternal four-chamber view showing severe enlargement of all four cardiac chambers. Left ventricular systolic function was preserved in this dog. b) Pulsed-wave Doppler interrogation of mitral inflow from a left apical four-chamber view. Note the absence of A waves after the E waves (E) indicating the absence of atrial contraction at the end of diastole.

THERAPY

Although pacemaker therapy is not expected to stop the progression of the underlying cause, which can lead to extensive myocardial fibrosis, it is the recommended treatment for the management of persistent atrial standstill.[16] Reports indicate that 50% of dogs with atrial standstill are expected to live more than 2 years after being diagnosed, which does not markedly differ from other bradyarrhythmias managed with pacemaker therapy.[4,5,11] Survival time beyond 10 years after diagnosis has been reported.[16] Congestive heart failure is common during the course of the disease but does not appear to negatively impact the long-term outcome with optimal medical management.[11] Sudden cardiac death has been reported even after pacemaker implantation.[11]

Single-chamber ventricular pacing (VVI, VVIR) is typically elected in dogs with atrial standstill, as atrial fibrosis prevents atrial

capture.[4,11,12,16,19,20] However, it has been shown in some human patients that detailed electrophysiological testing may reveal partial atrial standstill and areas of healthy atrial myocardium allowing the use of dual-chamber pacing (DDD).[2,3]

Thromboembolic events in the form of strokes occur at a relatively high rate in the human population with total atrial standstill. The risk is likely lower when atrial standstill is partial or transient and when atrial pacing is possible.[2] This complication has not been recognized in pets with atrial standstill. It is therefore unknown if antithrombotic therapy would be beneficial in this population.

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CHAPTER 22

Conduction disturbances

Roberto Santilli

DEFINITION

Cardiac conduction is the process that allows electrical activation to travel from the sinus node to the atria and, via the His–Purkinje system, to the ventricular myocardium, from one myocyte to the other, promoting their synchronous contraction and the pumping motion of the heart.[1] Atrial conduction abnormalities can lead to atrial fibrillation, while atrioventricular and intraventricular conduction abnormalities can lead to malignant ventricular arrhythmias, heart failure, and/or sudden cardiac death.[2–4]

Conduction involves the sequential depolarization of contiguous myocardium with a velocity that depends on several factors, such as the maximal rate of initial depolarization, the magnitude of depolarization, the threshold level of the membrane potential, and membrane resistance and capacitance. Velocity of conduction is the primary parameter to evaluate the spread of electrical activity within the conduction system and the myocardium; its value is crucial to evaluate uniformity of conduction in the space and to differentiate normal from abnormal tissues.[1,5]

Myocardial tissue works as a cable or a conductor that forms a syncytium linked by resistive routes called *gap junctions* and adhesive intercellular connections (*desmosomes* and *adherent junctions*), which provide further open channels for electrical communication in addition to structural stability.[6]

Gap junctions are composed by two hemichannels (connexons), one for each contiguous cells, which assemble with the contribution of cell adhesion proteins. A connexon is formed by six connexin (Cx) subunits; in the myocardium and intercalated discs, these are predominantly Cx40 (high conductance), Cx43 (medium conductance), and Cx45 (low conductance).[6] Due to the heterogeneous conformation of the atrial and ventricular sarcomeres, although the myocardium is considered a syncytium, conduction through it is uniformly anisotropic, with a prevalently lengthwise direction and end-to-end coupling (ratio of longitudinal to transverse conduction velocity >3). In normal patients, the electrical current decays more slowly along the long axis than along the short axis; this is due to the shape and size of the cells, the function and distribution of gap junctions, and the presence of interstitial fluid between the cells. In addition to gap junctions, sodium channels (NaV 1.5), and different potassium channels located in the intercalated discs participate in modulating the velocity of conduction.[1]

Changes in myocyte geometry with aging due to alterations in cell composition and size, number of gap junctions, and myocardial fibrosis can affect the electrical resistance of cardiomyocytes and therefore alter conduction anisotropy (*nonuniform anisotropic conduction*).[7]

Fibroblasts play an important role in providing structural support to sarcomeres, but in pathological situations they can modulate conduction (inflammation), or, in case of excessive deposition of extracellular collagen, they can create barriers to conduction, thereby changing the anisotropic pattern.[1] Moreover, remodeling and redistribution of connexins and a reduction in their expression during heart failure (particularly expression of Cx43, a connexin that predominates in the ventricular myocardium) has been considered an important marker of conduction slowing, aberrant ventricular conduction, and propensity to arrhythmias.[8]

Conduction is also a result of dynamics such as the strength of the electrical impulse (source) and the electrical load of the tissue (sink). Since, on average, one myocyte is coupled with 11 ± 3 others, the interplay of the source with the architecture of the myocardium, the fiber orientation, and the tissue geometry can induce, in pathological situations, an exacerbation of the source–sink mismatch.[7]

To understand conduction disturbances, it is important to have adequate knowledge of the anatomical features and electrophysiological properties of the sinus node complex, the internodal and interatrial connections, the atrioventricular junction, and the His–Purkinje system, and of the effect of the autonomic nervous system on these structures.

SINUS NODE COMPLEX

The sinus node is the dominant pacemaker of the mammalian heart. It is located 1–2 mm below the epicardium of the terminal sulcus, which corresponds to the endocardial crista terminalis, at the junction of the cranial vena cava and right atrium.

The sinus node complex is composed of the *compact sinus node,* at least two *sinus node exit pathways* and a *transitional region*.[9,10]

The *compact sinus node* is made up of around 20–30% of fibrous tissue strands in dogs (27% in cats), although this percentage varies with age depending on the amount of fatty deposit, fibroblasts, blood vessels, nerves, pacemaker (P) cells and transitional (T) cells.

Sinus node cells are differentiated according to the expression of high-conductance connexins and hyperpolarization-activated cyclic nucleotide-gated (HCN) subunits.

P cells do not express Cx43 but HCN4; however, some studies have shown that in the canine sinus node, 30–50% of P cells express Cx43, Cx40, and Cx45, 55% only Cx40, and 10–15% no connexins.[11] P cells are grouped into several major clusters, located at the level of the head (superior), center, and tail (inferior) with different dominant frequencies, which alternatively take control of the heart rate, and synchronization of the clusters depends on the influence of the autonomic nervous system, drugs, or pathological processes. The leading pacemaker site is the central cluster, with an intrinsic rate in dogs of 90–140 bpm.[10] P cells can be rhythmic, dysrhythmic, or dormant; the latter can become rhythmic under sympathetic stimulation.[12]

The superior P cell cluster and peripheral sinoatrial zone seem to be dependent on Ca^{2+}–driven depolarization (calcium clock), while the inferior P cell cluster depends more on I_f and voltage-gated K^+ channel–driven

depolarization (membrane clock). However, studies on the role of clocks in the canine and human sinus nodes have led to conflicting results. An intranodal heterogenicity in the expression of K^+ channels and the adenosine-dependent potassium channel (I_{KAdo}) that can influence conduction has also been described: I_{to} is more prominent in the periphery and inferior area of the sinus node, I_{kr} is more prominent in the central and inferior areas, and I_{KAdo} is more prominent in all regions of the compact sinus node and less in the surrounding atrial myocardium.[10]

T cells are either Cx43 positive or negative and HCN4 negative; they are located in the *transitional region*, an area with a mixture of cells (including atrial myocardial cells) located at the periphery of the nodal structure (Fig. 22.1).[13] Details on the anatomy and electrophysiology of the sinus node complex can be found in Chapter 20.

The compact sinus node is anatomically and functionally isolated from the atrial myocardium, which is rich in Cx43, by conduction barriers that create an extended conduction block. These conduction barriers include the connective tissue surrounding the nodal structure, fat, and sinoatrial arteries; a progressive reduction in Cx43 expression is observed from the nodal cells to the transitional and ultimately the atrial cells.[12,14] This insulation protects the weak sinus P cell depolarization current source (resting potential, –60 mV) from the high resistance adjacent atrium (resting potential, –85 mV). In physiological situations, the velocity of conduction within the sinus node is around 9 cm/sec; the electrical activation travels superiorly and inferiorly and is blocked laterally.[10]

The only connections between these anatomical structures are two or more *sinus node exit pathways*, which are muscular bundles formed by elongated branching fibers of T cells—with a progressive transition in connexin expression from Cx43 negative to Cx43 positive and negative to HCN4—and collagen. Depending on the location they are categorized as superior (cranial vena cava), middle (lateral), and inferior (septal) (Fig. 22.1).

The presence of these exit pathways increases the size of the sinus node area, which is located at the junction of the crista terminalis with the openings of the cranial and caudal venae cavae, and explains the different atrial ectopic foci during wandering pacemaker and the response of the

sinus node to supraventricular arrhythmias.[9,10,12–14] The location of the exit pathways is strictly correlated with pacemaker shifts during different physiological or pathological conditions from the central sinus node region: superior shift (superior leading pacemaker during high sympathetic drive), inferior shift (inferior leading pacemaker during high vagal drive), or lateral shift (during electrolytes imbalances, e.g., low Na^+ or Ca^{2+}) to reach the superior, inferior, or septal sinus node exit pathways, respectively.[12] However, the leading pacemaker shift is not strictly correlated with the closer sinus node exit pathway to protect conduction in case of temporary block of this circuit.[10]

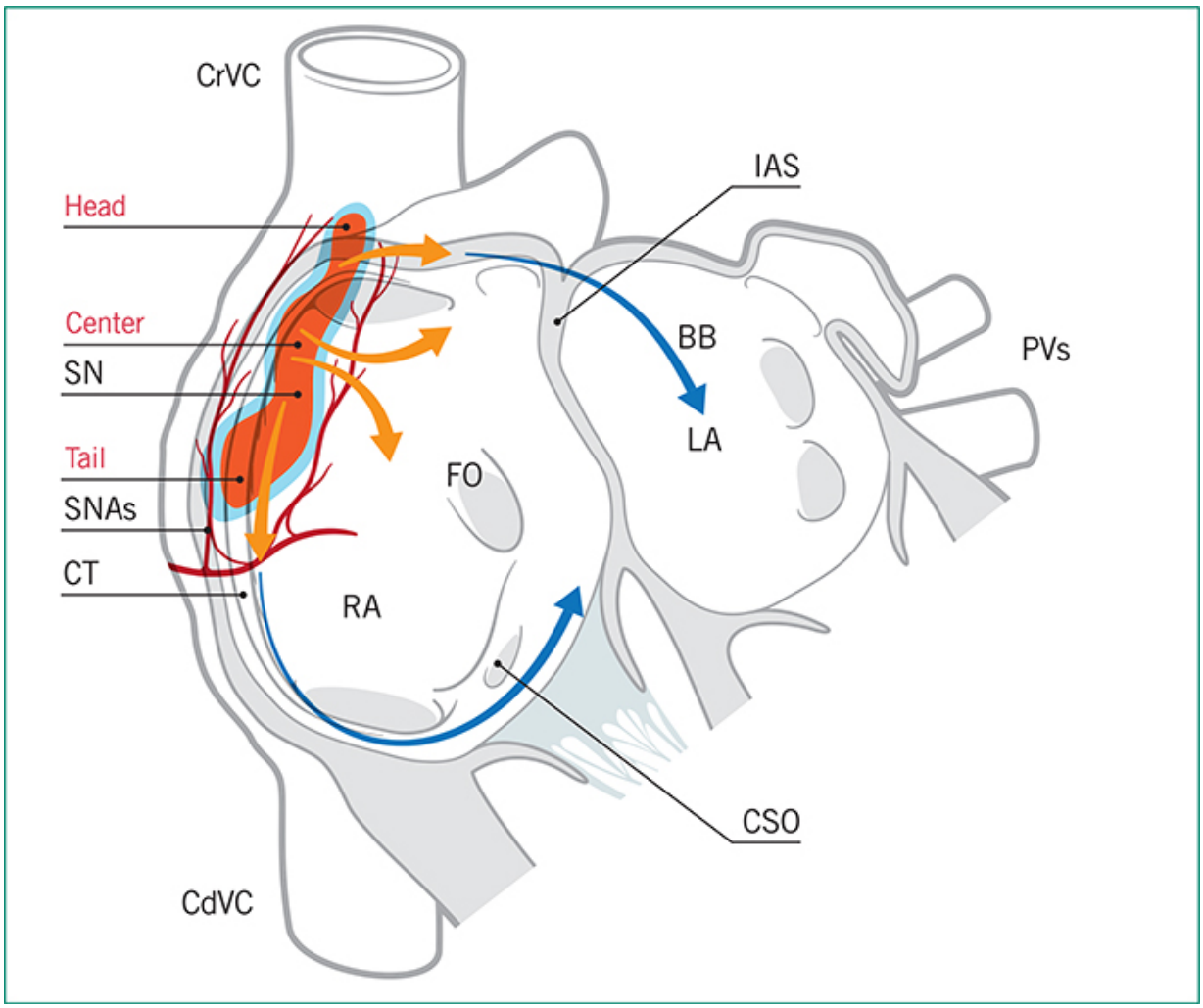


FIGURE 22.1. Schematic representation of the sinus node complex. CrVC, cranial vena cava; SN, sinus node; SNAs, sinoatrial arteries; CT, crista terminalis; CdVC, caudal vena cava; RA, right atrium; FO, fossa ovalis; CSO, coronary sinus ostium; IAS, interatrial septum; BB, Bachmann's

bundle; PVs, pulmonary veins; LA, left atrium. Blue area, transitional area of the sinus node; orange arrows, sinus node exit pathways; blue arrows, possible wavefronts of atrial activation.

INTERATRIAL AND INTERNODAL CONNECTIONS

Activation of the entire atrial myocardium requires in average 40 ms in the dog and 35 ms in the cat. Atrial action potentials exhibit regional heterogeneity with variations in duration and morphology, due to variations in ion channel expression that can affect the depolarization time. The crista terminalis has the longest action potential duration with the largest I_{CaL} current, whereas the atrioventricular ring cells have the shortest action potential duration. I_{Kr} is also distributed differently within the atrial cells and induces a shorter action potential duration in the left atrial cells than in the right ones.[15]

The rapid spread of atrial activation is mediated by preferential interatrial and internodal pathways.[16–20] There has been great debate in the literature as to the definition of preferential pathways; newer hypotheses consider these anatomical structures are not formed by specialized conduction tissue but are muscle fascicles that differ from the rest of the atrial myocardium due to the anisotropic orientation of their fibers.[17,18] Muscle fascicles are indeed defined as longitudinally parallel aligned myocytes and are called *bundles* when presenting the same orientation and course. Muscle fascicles are defined as circumferential when they are parallel to the atrioventricular valve annulus, and longitudinal when they are perpendicular to it. Unlike ventricular bundles, most interatrial and internodal bundles are not surrounded by a fibrous tissue sheath. Preferential interatrial pathways do not show decremental conduction properties and present different conduction velocities depending on fiber orientation.[17,18]

Interatrial preferential pathways described in dogs include Bachmann's bundle, anterosuperior and posterior septal connections, and the coronary sinus musculature (also termed inferior interatrial fascicle). In humans, another interatrial connection has been described and named septopulmonary bundle.[17–20]

The preferential interatrial connection in dogs is Bachmann's bundle, which is located in the subepicardial area, with electron microscopy characteristics and an orientation that differ from those of the underlying atrial myocardium. Bachmann's bundle is formed by myofibril-rich cells, myofibril-poor cells, transitional cells, and P cells; it has rapid nonuniform anisotropic conduction (0.92–1.67 m/sec) properties, due to the presence of surrounding collagen septa, compared to the slower adjacent atrial myocardium (0.4 m/sec).[21,22]

Bachmann's bundle extends from the right to the left auricles; it starts close to the sinus node, then runs along the anterior roof of the right atrium, crosses the interatrial groove, and bifurcates encircling the left auricle. These extensions then join again to form a single bundle that courses along the lateral and posterior left atrial wall.[18,20,22]

The *anterosuperior septal connection* is confined to the floor of the fossa ovalis and its anteroinferior rim, while the septal *posterior bundles* run superiorly at the level of the right atrium/cranial vena cava and inferiorly at the level of the posterior right atrial wall.[17,23]

The *coronary sinus musculature* connects the right atrial with the left atrial myocardium at the level of the coronary sinus ostium, up to 20–30 mm from its beginning, since the great cardiac vein has no musculature.[16] This preferential pathway has slower conduction compared to Bachmann's bundle due to the propagation of the impulse along an inhomogeneous tissue and the presence in this area of several barriers.[17]

The *septopulmonary bundle* has been described in humans. This bundle originates at the anterosuperior part of the interatrial groove and then runs to the roof of the left atrium, in between the pulmonary veins.[18]

Activation of the right and left atria depends on the origin of the impulse and on autonomic tone. In sinus rhythm with superior sinus node exit, the electrical wavefront is slowed or blocked at the crista terminalis interface, and Bachmann bundle conduction is therefore favored. In case of inferior sinus node exit, because there is no interference at the crista terminalis, the electrical wavefront runs along the posterior bundles.[23]

During atrial ectopic rhythm, conduction patterns along the interatrial pathways vary according to the site of origin of the impulse and the distance to the closest interatrial pathway. Bachmann's bundle is the preferential pathway for impulses originating from superior atrial foci, but also for those

originating from lower atrial foci in half of the animals, despite the vicinity of the coronary sinus musculature and the interatrial septal connections due the slower conduction of these areas. For impulses originating from left superior pulmonary vein foci, the preferential pathway can either be the coronary sinus musculature or Bachmann's bundle, while for impulses from right superior pulmonary vein foci it is either Bachmann's bundle or the anterosuperior septal connection. Finally, the preferential pathway is Bachmann's bundle for impulses from the superior septum, and it is the anterosuperior septal connection and coronary sinus musculature for impulses from inferior septal foci.[17]

Ongoing debate exists on the existence of *internodal tracts,* which has been postulated since canine experimental studies in vivo and in vitro during hyperkalemic sinus arrest showed the presence of excitable connections between the sinus node and the atrioventricular node.[22]

Three internodal preferential connections have been described: anterior, middle (Wenckebach), and posterior (Thorel). All internodal tracts arise from the sinus node; the anterior tract and, when present, the middle tract runs in the anterior limbus of the fossa ovalis, allowing the sinus node wavefront starting from the high crista terminalis to reach Bachmann's bundle. The posterior internodal tract runs along the crista terminalis and inferior limbus of the fossa ovalis to the posterior interatrial septum, allowing the sinus node wavefront starting from the crista terminalis to reach the Eustachian valve.[24]

ATRIOVENTRICULAR CONDUCTION AXIS

The atrioventricular conduction axis is composed of the atrioventricular junctions, the His bundle, the right and left bundle branches, and the cardiac conduction fibers or Purkinje fibers.

The *atrioventricular junctions* and their extensions connect the sinus node and atrial myocardium to the His–Purkinje system and ventricular myocardium. In these areas, the atrial musculature inserts into the annuli of the tricuspid and mitral valves. At the left atrioventricular junction, the leaflets of the mitral and aortic valves are in direct continuity; on the posterior aspect of this junction, the ventricular myocardium is only continuous with the posterior mitral valve leaflet, while on the anterior

aspect, the atrial myocardium inserts into half of the noncoronary aortic leaflet, since the remaining part in dogs is continuous with the septal structure. The right atrioventricular junction is the area around the tricuspid valve where the atrial and ventricular myocardium can, in pathological situations, potentially be in continuity, except for the small area formed by the membranous septum, where the His bundle is located. The atrioventricular annuli electrically insulate the atrial myocardium from the ventricular myocardium, thanks to the fibrous elements of the cardiac skeleton.[25,26]

The atrioventricular junction can be divided into three distinct anatomical regions (Fig. 22.2):[27]

1. Transitional cell zone
2. Atrioventricular node or compact portion
3. Nonpenetrating portion of the distal atrioventricular bundle

Due to the complex anatomy of the junctional areas, there is ongoing debate as to the definition of the *transitional zone* from the atrial myocardium to the compact atrio-ventricular node. Different theories have been postulated over the years since no anatomical landmarks could be found by all the authors to delimit the atrionodal bundles: one theory supports the existence in dogs of an atrionodal component and an internodal component,[28] while another theory is the presence of extensions of transitional cells arising from the atrial working myocardial cells and then merging into the compact atrioventricular node.[25]

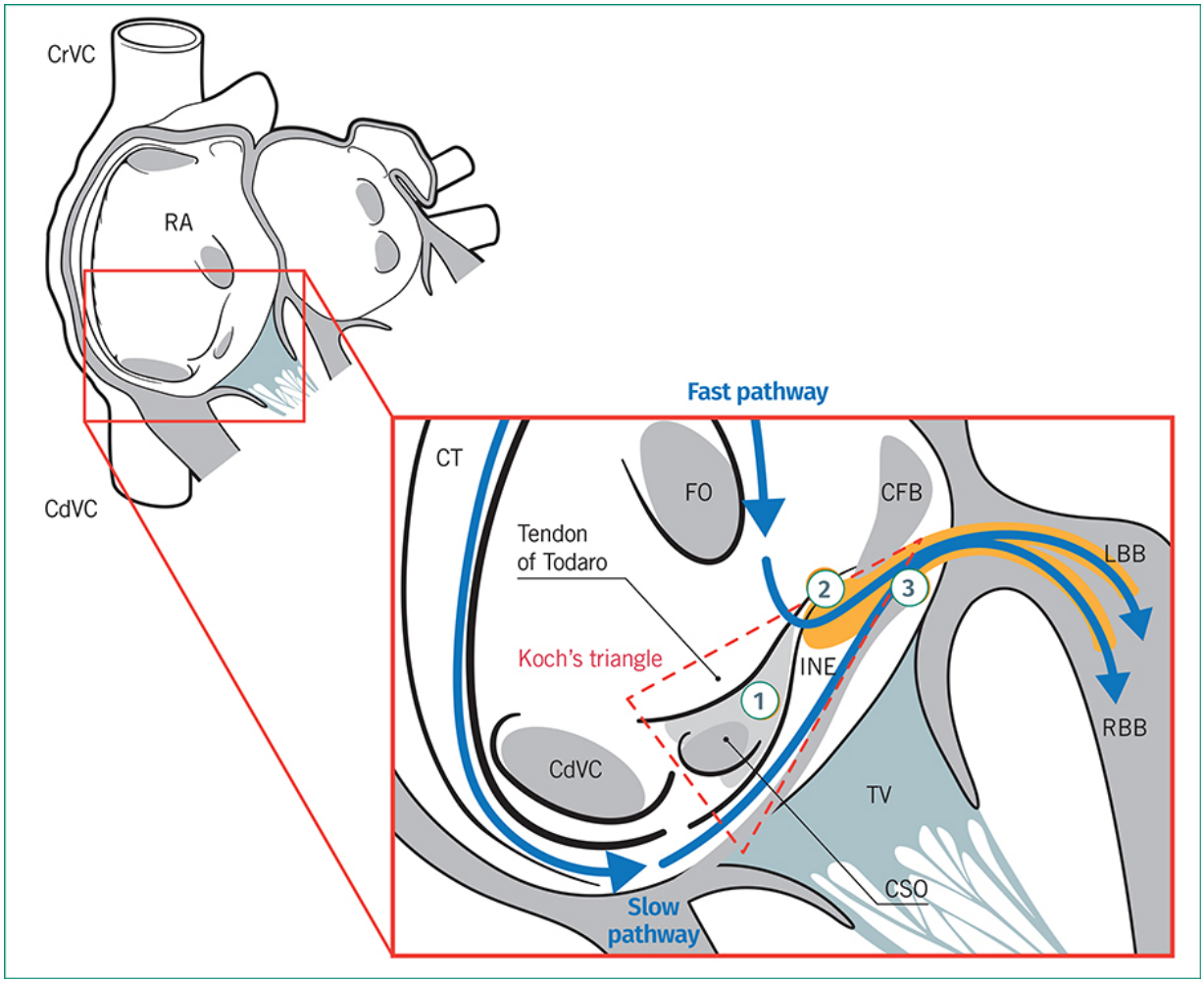


FIGURE 22.2. Anatomical and schematic representation of the atrioventricular junction. CrVC, cranial vena cava; RA, right atrium; CdVC, caudal vena cava; CT, crista terminalis; FO, fossa ovalis; CFB, cardiac fibrous body; LBB, left bundle branch; RBB, right bundle branch; INE, inferior nodal right extension; TV, tricuspid valve; CSO, coronary sinus ostium; 1, transitional tissue; 2, compact atrioventricular node; 3, His bundle.

Racker et al. described the transitional zone as discrete atrionodal bundles (superior, medial, and lateral), which, together with the right medial atrial wall, act as nodal approaches to the proximal atrioventricular bundle, which then merges into the compact atrioventricular node and finally into the nonpenetrating and penetrating portions of the distal atrioventricular bundle.[28]

Other studies described the transitional zone as node-like tissue extensions of the compact atrioventricular node in humans and animals: the vestibule extension, which runs around the tricuspid and mitral valves

(rightward [inferior nodal] and leftward extensions), and the septal extension (retroaortic node).[26,29,30]

The *inferior nodal extension*, also termed rightward extension, is found in the septal isthmus, an area along the septal leaflet of the tricuspid valve below the coronary sinus, which is a continuation of the cavotricuspid isthmus. In human and murine hearts, a leftward extension has been described, which runs around the vestibule of the mitral valve and then merges into the compact atrioventricular node and rightward extension forming the retroaortic node.

The *retroaortic node*, which has been described in humans and dogs, is located in the anterior septum at the level of retroaortic area, where a large connection with the atrial myocardium is possible due to a lack of fibrous tissue.[30]

The nodal extensions structurally and anatomically compartmentalize the atrioventricular junctional area, thereby creating the basis for the longitudinal dissociation and the dual pathway electrophysiology of the atrioventricular junction and His bundle.[29,30] Most authors consider the inferior nodal extension as Cx43 positive, like the His bundle, while the leftward extension is considered Cx43 negative. There is general agreement on the inferior nodal extension being the substrate for the *slow atrioventricular pathway*; however, there is still debate regarding the substrate for the *fast atrioventricular pathway,* which for some authors is the retroaortic node.[29,30]

In dogs, the *compact atrioventricular node* is delimited by the inferior nodal extension on the right side of the atrial septum and by the site of attachment of the aortic leaflet of the mitral valve, where the penetrating portion of the His bundle is found. The His bundle is separated from the atrial myocardium and passes through the area of fibrous continuity between the leaflets of the mitral and tricuspid valves.[26]

The His bundle lies 1 mm beneath the endocardium, just anterior to the coronary sinus ostium and above the septal leaflet of the mitral valve, in the anatomical landmark named Koch's triangle or pyramid of Koch (Fig. 22.3).[31,32] Koch's triangle is delimited anteriorly by the septal leaflet of the tricuspid valve and posteriorly by the tendon of Todaro; the membranous septum is located at its apex, while the coronary sinus ostium is found at its base. The floor of the triangle is formed by the right atrial septal

myocardium, which is separated from the underlying muscular ventricular septum by fibrofatty tissue which occupies the inferior pyramidal space.[25,32–34]

The compact atrioventricular node is completely insulated from the surrounding atrial myocardium by a capsule of irregular dense connective tissue, except for the areas where the inferior nodal extension and the retroaortic node merge into it.[29,33] In dogs, the compact atrioventricular node has a spindle shape and is richly innervated at its periphery; the cell population is abundant and surrounded by scarce connective tissue. It is composed of large P cells clustered in the central region and elongated or basket-shaped T cells located at the periphery, which are often organized in a linear fashion with other transitional cells to form extensions. In dogs, the compact atrioventricular node is 2 mm long, 2 mm wide, and 0.5–1 mm thick. Its arterial supply is dual, coming from the circumflex artery and the septal branch.[33]

The compact atrioventricular node and its inferior extension have nodal-like myocytes with an ion channel expression and resulting action potential that are very similar to those of the central sinus node. In this area, the action potential duration is long and mediated by the slow I_{CaL} current, and there is a robust expression of I_f channels and reduced expression of I_{Na} channels. The compact atrioventricular node shows low Cx43 expression, but it has high Cx40 and Cx45 expression, similarly to the inferior nodal extension and retroaortic node. The transitional zone is composed of atrionodal myocytes, while the His bundle is made up of nodo–His myocytes. These two areas have a more intermediate nature, with more negative diastolic potential values and a faster upstroke. The transitional zone has few I_f channels, while the nodo–His region possesses a larger amount of them.[15]

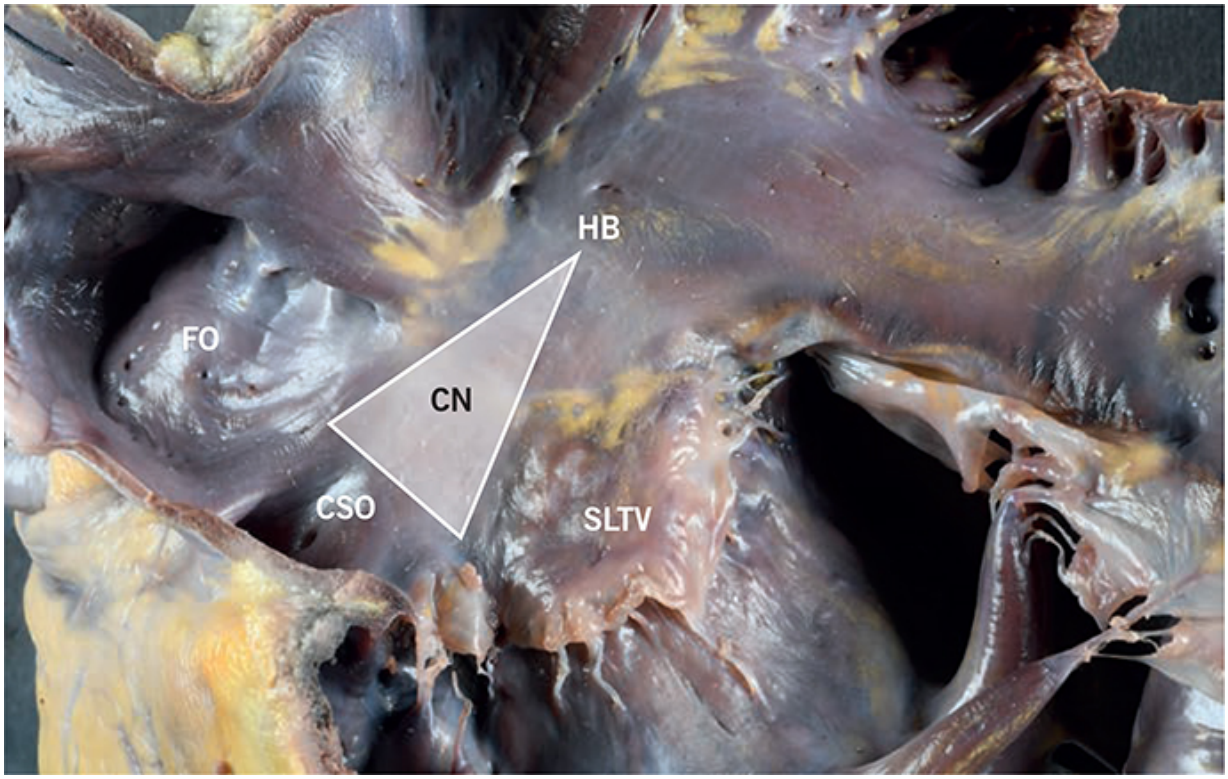


FIGURE 22.3. Gross anatomy of the area of Koch's triangle, site of the compact atrioventricular node (CN). FO, fossa ovalis; HB, His bundle; CSO, coronary sinus ostium; SLTV, septal leaflet of tricuspid valve. Picture courtesy of Dr. Massimiliano Tursi, University of Turin, Italy.

According to electrophysiological observations in rabbits, the atrioventricular region can be also divided into: an atrionodal (AN) (upper) region where the nodal extensions (slow and fast pathways) converge into the atrioventricular node; a nodal (N) (central) region or compact atrioventricular region formed by the interconnection of slender nodal fibers; and a nodal–His (NH) (lower) region where the slender nodal cells connect with the Purkinje-type fibers of the His bundle and where a largest cluster of P cells can be found.[31,35]

All the entry points from the AN to the N region are located before the aggregates of P cells of the area of the distal atrioventricular node. These nodal extensions merge into the outer slender transitional cells, which then connect with other transitional cells within the atrioventricular node, forming compartmentalized layers made up by cords separated by connective tissue, interstitial fluid, and some P cells. The transitional cells of the proximal atrioventricular node are larger, with a very brief intercellular conduction delay.[31] The atrioventricular node has a reverse

source–sink situation since electrical impulses from the atria (source) need to fuse into a diminishing area (sink). In this area, the propagation of the impulse to the ventricles is controlled thanks to the presence of transitional tissue, of different merging pathways, of slowing of conduction, and presence of cells with longer refractory period.[36]

The atrionodal area, and particularly the inferior nodal extension, is the region where *decremental conduction* occurs in dogs.[37] Decremental conduction corresponds to a progressive delay in conduction secondary to increased heart rate or in response to an extrastimulus. The basis for this behavior of the atrioventricular junction is related to the presence of a decreasing gradient of excitability along the extensions, while no effect of the anatomical arrangement of the transitional cells has been found.[37]

The NH area is where atrioventricular nodal automaticity takes place. In dogs, abundant clusters of P cells are present in the NH area. This region is the site of origin of fast junctional rhythms (66% rate relation with the sinus node). Slower junctional rhythms (2:9 rate relation with the sinus node) only arise when the fastest P cells are depressed; these rhythms very likely originate from the few P cells nearest to the His bundle.[35] In the author's experience, however, focal junctional tachycardia can arise from the inferior nodal area extension close to the coronary sinus ostium (see p. 199).

Based on its anatomical and histological features, the most important electrophysiological functions of the atrioventricular junction are to:[31,35]

1. Slow the conduction velocity through the atrioventricular node, thus allowing atrioventricular synchronization and normal ventricular filling.
2. Filter fast supraventricular rhythms.
3. Couple the electrical impulse to the ventricular working myocardium, facilitating contraction.
4. Be the heart's main stable subsidiary pacemaker in case of sinus node failure.

The atrioventricular node can also conduct retrogradely in less than 40% of large breed dogs and frequently in small breed dogs with sinus node dysfunction (see p. 271).

There are several mechanisms by which the delay in the atrioventricular node may occur:

a. The slender cells that form most of the atrioventricular node are much smaller in diameter than the atrial cells to which they are connected and from which their impulse comes. This could account for the decrease in conduction velocity from 500 mm/sec in the atria to about 50–60 mm/sec in the proximal part of the atrioventricular node.[31,35]
b. The histological organization of the fibers in the atrioventricular node—which form a meshwork of cords that induces the action potential to pursue a multidirectional, three-dimensional course through them—and the gradient of decreasing excitability along the nodal extensions result in a decreased velocity of conduction.[31,35,37]
c. Conduction in the sarcolemma membrane of the transitional cells is intrinsically slow due to a slow inward current.[35]
d. The presence of P cells interspersed between transitional cells also may lead to slowing of conduction. These P cells are strategically located at the intersections and meeting points of transitional cells in the body of the atrioventricular node and are also present in big clusters in the distal part of the atrioventricular node.[31,35]
e. Differences in connexin expression also play a major role in slowing of conduction: Cx43 expression is increased in the slow pathway and His–Purkinje system compared with Cx43 expression within the compact atrioventricular node, where conduction is therefore slower.[38]

A significant dominance of the atrioventricular node over the His–Purkinje system in determining the atrioventricular conduction time has been reported, with the ratio of dependence of the atrioventricular interval on the atrial–His interval and on the His–ventricular interval being 13:1. The conduction velocity in the atrioventricular node is around 0.02–0.05 m/sec vs. 1–3 m/sec in the His–Purkinje system.[38]

The compact atrioventricular node continues as the *nonpenetrating bundle* and then as the *penetrating bundle* or *His bundle*, without a histological boundary and with a transition from the compact atrioventricular node of 2 mm, where the cells present a plateau-type action potential.[31] In a medium-sized dog, the His bundle measures 5–10 mm; its cells are organized in a linear fashion and covered by a well-developed insulating fibrous sheath and the central fibrous body. After leaving the compact atrioventricular node, the His bundle crosses the right fibrous

trigone at the level of the noncoronary aortic leaflet (apex of Koch's triangle), and due to the absence of an inferoseptal recess, which supports, in human hearts, the inferior part of the atrial septum, it follows a nonbranching course of variable length before dividing into the posterior fascicles of the left bundle branch, while still sitting in the central fibrous body.[29,33,36]

The *branching part of the His bundle* gives off the two left bundle branch fascicles and the right bundle in the interleaflet region between the noncoronary and right coronary leaflets of the aortic valve. All the intraventricular bundles are insulated by a fibrous sheath and the initial parts also by the central fibrous body.

The *left bundle branch* starts with a truncular subendocardial portion, which in dogs is 6–8 mm long and 5 mm wide. The left bundle branch then courses on the left ventricular aspect of the septal surface and branches into anterosuperior, posteroinferior, and septal divisions. The fascicles of the left bundle branch run towards the posteromedial and anterolateral papillary muscles. The *anterosuperior fascicle* is the direct continuation of the truncular portion of the left bundle branch and is oriented superoinferiorly and posteroanteriorly. It is thin and measures 35–50 mm in dogs. Its relationship with the attachment of the right coronary aortic valve leaflet varies. The *posteroinferior fascicle* emerges perpendicularly from the trunk of the left bundle; it is thick and measures around 35 mm in dogs.[26,33]

The *right bundle branch* is typically cord-like, with a length ranging from 35 to 40 mm in dogs. It can arise directly on the right surface of the interventricular septum or course intramyocardially before surfacing at the level of the medial papillary muscle. It then divides into several branches before merging into the subendocardial Purkinje fibers.[26,33] The penetrating bundle and bundle branches have high Cx40 and Cx45 expression, which contributes to facilitating fast conduction.[39]

The final components of the atrioventricular conduction axis are the *cardiac conduction fibers* or *Purkinje fibers*, which connect the conduction system to the working myocardium and transmit the electrical impulse, thus facilitating the rapid activation of the ventricles and their contraction (in 70 ms in dogs and 40 ms in cats).[40] Depending on their cell size and ultrastructure, cardiac conduction fiber networks in animals can be divided into three groups; dogs and cats are included in group II together with

humans, monkeys, and seals.[40] Along with cell-to-cell junctions, Cxs 40, 43, and 45 couple the conduction system with the ventricular working cardiomyocytes and propagation of the electrical excitation. Three types of junctions between the conduction fibers and the ventricular myocardium have been described: through cell bodies, through cell propagations, and through transitional cardiomyocytes.[40] In dogs, the cardiac conduction fibers are mainly located in the endocardium and are more abundant and thicker in the septal region close to the area where the troncular region of the left bundle emerges, while the conduction fiber–myocardium junctions are mostly distributed in the apical and lateral areas due to the great electrical activity and contraction of this region.[40]

The canine Purkinje fibers have a longer action potential than that of the ventricular myocytes (236 ± 10.6 vs. 204 ± 5.6 ms); vagal activation decreases their discharge rate through the activation of I_{KAch} channels. Their action potentials depend on I_{Na}, while the resting potential is maintained by the strong inward rectifier K^+ currents (I_{K1}, I_{KATP}, and I_{KAch}). Both L-type and T-type calcium channels have also been described in the canine Purkinje fibers, and I_{CaT} could play a more important role in membrane activity in these structures than $I_{CaL,}$ which predominates in the ventricular myocardium. The transient outward current (I_{to}) recovers more slowly in the Purkinje fibers than in the ventricular myocardium, while I_{Ks} and I_{Kr} are significantly larger in canine cardiac conduction fibers and play the predominant role in their repolarization.[41] Purkinje fiber automaticity is overdrive suppressed by the sinus node through enhanced Na^+/K^+ ATPase activity; its nondriven electrical activity depends on the I_f and I_{Kdd} channels, although spontaneous Ca^{2+} waves appear to originate at the cell borders.[41]

The Purkinje fiber–ventricular myocyte junction is the final part where the electrical impulse must cross a high degree of current-to-load mismatch. How the small amount of depolarizing current (source) along the thin cardiac conduction fibers can depolarize a much larger ventricular mass is still unknown. A possible explanation is diminished electrical coupling at this site due to the difference in connexin expression, with greater Cx43

expression in the cardiomyocytes and greater Cx40 and Cx45 expression in the Purkinje fibers.[42]

ELECTROPHYSIOLOGICAL MECHANISM

The occurrence of conduction blocks depends on the anatomy of the region of interest, the channels and connexins involved in the process, and their interaction with the autonomic nervous system, aging, drugs, and pathological disorders.

SINUS NODE EXIT BLOCK

The sinus node exit pathways, due to their size and branching myofibers, slow conduction from the compact sinus node to the atrial myocardium from 25 to 350 ms on average, depending on the autonomic balance. This allows sufficient time to provide the charge necessary to depolarize the larger atrial mass.[10] Aging and cardiac diseases causing an increase in fibrous tissue within the sinus node exit pathways can further decrease the conduction velocity of impulses from the sinus node, leading to conduction abnormalities and sinus node dysfunction (see p. 279). The inferoseptal sinus node exit pathway functions as a backup when the major conduction pathways are blocked. During disease states and heart failure, this function is abolished, thus promoting acquired sinus node dysfunction.[10]

Acquired sinus node dysfunction with or without cardiovascular disease is primarily due to conduction impairment along the sinus node exit pathways, with failure of electrical activation (i.e., exit block) other than depressed automaticity of the pacemaker cells.[10,14] Exit blocks induce a prolongation of the sinus node recovery time, sinus pauses, and in severe cases syncopal episodes.[10,14]

The sinus node exit pathways also serve as a filter creating an entrance block during fast supraventricular tachycardia, atrial fibrillation, or rapid atrial pacing. During atrial flutter, the sinus node complex participates to the circuit due to the barriers that surround it.[12] The mechanism of entrance block is mainly related to differences in refractoriness and conduction times between the surrounding atrial and transitional nodal tissue, to the release of neurotransmitters such as acetylcholine or norepinephrine, and to

disruptions in the ionic mechanisms for P cell automaticity.[13,14] Vagal stimulation depresses electrical conduction along the sinus node exit pathways, allowing the P cells to maintain their own automaticity, while adrenergic stimulation increases conduction along these pathways, allowing the ectopic atrial wave to enter the sinus node and overdrive it.[13] These autonomic influences on the sinus node also play a role in perpetuating or interrupting atrial flutter. During this type of arrhythmia, a vagal input induces a unidirectional block in the sinus node exit pathways and therefore impedes the suppression of sinus node automaticity, which in turn can interact with the reentrant tachycardia, converting it in either sinus rhythm or atrial fibrillation.[13]

INTERATRIAL BLOCK

The pathophysiology of interatrial atrial block mainly depends on conduction abnormalities along Bachmann's bundle, although other areas of the atria can be involved. It can be the substrate for atrial fibrillation in both structurally normal and diseased hearts.[17,22,43]

Atrial structure disruption induced by age-related or pathological myocardial fibrosis is considered the most frequent cause of interatrial block. Fibrosis involves mainly the atrial myocardium and partially the interatrial pathways. Atrial fibrosis increases axial resistance through the gap junctions and reduces sodium channel density, with a secondary decrease in the maximum upstroke velocity of the action potential.[22,43]

Interatrial conduction delay and block are defined, respectively, as a prolongation or block of conduction from the right atrium to the left atrium. Bachmann's bundle is the preferential pathway for interatrial conduction, and the degree of delay or block depends on its conduction characteristics. Interatrial block can occur independently from atrial enlargement, even if increased atrial strain can favor a conduction delay or block along Bachmann's bundle. Increased P wave duration and altered morphology are actually related to a reduction in the resting membrane potential, the presence of fractionated endocardial electrograms, signs of fibrosis or changes in connexin concentrations, and secondary nonuniform anisotropic conduction, but not directly to atrial enlargement.[44] Different studies in

dogs have also shown that P wave duration is not strictly correlated with atrial size.[45,46]

In humans, interatrial conduction disturbances have been found to be associated with hemodynamic changes suggestive of left atrial dysfunction (e.g., a decreased left atrial ejection fraction, left atrial stroke volume, and left atrial kinetic energy) and to be a potent predictor of atrial fibrillation.[17,20,22,43]

Interatrial preferential pathways represent crucial connections from the left to the right atrium during focal and reentrant atrial tachycardias, which act as a trigger for initiation and perpetuation of atrial fibrillation, particularly in the presence of myocardial fibrotic strands, which are a substrate for nonuniform anisotropic conduction and unidirectional block.[17,20,22,43] Longitudinal dissociation of conduction within Bachmann's bundle has also been reported, which further predisposes to reentry.[22]

Other rare types of atrial conduction disturbances are aberrant atrial conduction and atrial dissociation.

Aberrant atrial conduction is a functional block that can be suspected in cases of alterations in the P wave morphology, polarity, and/or duration after an atrial ectopic beat, a junctional ectopic beat, a ventricular ectopic beat, or a parasystolic beat.[47] It occurs after a long postectopic pause, particularly when the ectopic atrial depolarization is not conducted to the ventricle. Aberrant atrial conduction is not related to variations in the atrial rate, but rather to variations in the atrial refractory period promoted by the ectopic depolarization (concealed atrial conduction).

Atrial dissociation or *unilateral atrial rhythm* is an arrhythmia rarely described in dogs and characterized by the presence of an ectopic rhythm confined to one part of the atria, which depolarizes independently from the concomitant sinus rhythm due to the presence of entrance and exit blocks. The differential diagnosis of atrial dissociation includes electrical and motion artifacts (muscle tremor, diaphragmatic contractions, animal holder heartbeat or respiratory motion) and atrial parasystole.[48,49]

ATRIOVENTRICULAR AND INTRAVENTRICULAR BLOCKS

A reduced membrane potential is the most common cause of conduction disturbances. Partial depolarization of conduction cells can occur anywhere, and depending on the location, it can induce atrioventricular or intraventricular block. A reduction in membrane potential can be due to incomplete repolarization, which affects refractoriness and conduction, or to decreased or spontaneous slow diastolic depolarization during phase 4 of the action potential in pacemaker cells induced by factors such as ischemia, hypoxia, stretch, changes in connexin concentrations, and alterations in pH and electrolytes, or antiarrhythmic drugs.[5]

Atrioventricular and intraventricular blocks can be classified as anatomical when they are caused by acquired or genetic disorders involving the conduction system,[15,50–65] or as functional when they are induced by changes in the transfer of the electrical impulse to the atrioventricular node due to a rapid atrial rate or to premature ectopic beats arising from the atria, the ventricles, or the atrioventricular junction.[31,35]

Anatomical atrioventricular and intraventricular blocks

Progressive and *permanent* atrioventricular and intraventricular blocks are usually caused, in dogs and cats, by degeneration of the conduction system, infiltrative or endocrine neoplasia, trauma, intracardiac procedures, or heart failure, while *transient conduction block* is caused by acute myocardial inflammation, drug-related toxicity, hyperkaliemia, or inappropriate vagal reflex or vagal hyperreactivity (see p. 20).[15,50–65]

Genetic diseases identified in humans that can cause atrioventricular or intraventricular blocks have not been found in dogs or cats. These diseases include progressive cardiac conduction defect (Lev-Lenègre disease) caused by loss-of-function mutations of the *SCN5A* gene, heart block secondary to *SCN1B* and *KCNJ2* mutations, and Cx40 deficiency inducing right and left bundle branch block.[15,66]

Age can induce morphological changes of the atrioventricular conduction axis; these include: fibrosis; chondroid metaplasia; mineralization and ossification of the basal interventricular septum, central fibrous body, and left fibrous cardiac skeleton at the level of the aortic root; and focal fibrosis and fatty tissue infiltration of the atrioventricular conduction axis with loss of conduction fibers (51–76%).[50–67] These changes appear to be more severe in case of concomitant chronic mitral valve degeneration, in which

the penetrating and branching portion of the distal atrioventricular bundle is encased within the central fibrous body. In this pathological condition, the fibrotic lesions also involve the upper portions of the left and right bundle branches, with a mild to moderate loss of conduction fibers (25–50%) inducing permanent complete atrioventricular block. The excessive mechanical stress created by the motion of the prolapsed mitral valve leaflet and the long-term volume overload have been suggested as possible explanations for this process.[68] In cats with chronic progressive and permanent high-grade atrioventricular block, the atrioventricular conduction axis presents a moderate (25–50% of the cases) or severe (50% of the cases) loss of conduction fibers in association with replacement fibrosis of the branching distal atrioventricular bundle and the upper portion of the left bundle branch. Cats with complete atrioventricular block appear more severely affected.[51] Infiltrative neoplastic disorders such as cardiac leiomyoma and hemangiosarcoma have been reported as possible causes of permanent complete atrioventricular block in dogs.[54,58] Pheochromocytoma can lead to atrioventricular or intraventricular blocks due to the direct toxic effects of catecholamines on the heart, which induce vasoconstrictive-ischemic myocarditis.[56]

Traumatic lesions creating acquired left ventricular–to–right atrial communication (Gerbode defect) and an atrial septal defect have very occasionally been reported as causes of complete atrioventricular block.[53] Interventional procedures such as ventricular septal defect closure, aortic and pulmonic valvuloplasty, and ablation of anteroseptal accessory pathways carry a potential risk of iatrogenic damage at different levels of the atrioventricular conduction axis (e.g., right bundle branch block).[69] Permanent atrioventricular block can also be caused by heart failure due to the increased fibrosis, apoptosis, hypertrophy, and downregulation of HCN4 of the atrioventricular node in failing hearts.[15] Finally, different cardiomyopathies involving the left ventricle can promote anatomical and electrophysiological changes in the myocardium and induce left bundle branch block, interventricular dyssynchrony, and abnormal conduction-induced cardiomyopathy (see p. 401).

Viral and bacterial myocarditis are the most common causes of transient myocardial thickening and transient atrioventricular and intraventricular block in cats and of inflammatory cardiomyopathy and transient conduction

disorders in dogs.[55,57,59–63] A detailed description of these myocardial disorders can be found in Chapter 27. Incorrect ingestion of drugs such as β-blockers, sotalol, calcium-channel blockers, digoxin, and opioids can induce transient atrioventricular block. Although it is very rare either in dogs or cats, hyperkalemia can induce transient atrioventricular block. Hyperkalemia usually induces a reduction in the slope of phase 4 of the action potential in pacemaker cells; major effects are therefore observed on the sinus node, but in rare cases, it can also alter atrioventricular conduction.[70]

A very common cause of transient paroxysmal atrioventricular block reported in dogs is inappropriate vagal reflex or sleep apnea inducing cardioinhibitory type 1B reflex syncope (see p. 428).[64] In the author's experience, another potential cause of transient paroxysmal atrioventricular block reported in humans and very likely present but not yet proven in dogs is vagal hyperreactivity due to overexpression of muscarinic receptors.[65]

Functional atrioventricular and intraventricular blocks

By definition, a functional block is usually rate dependent. When it occurs at the atrioventricular node, it is defined as a rate-related atrioventricular block, while when it occurs at the level of the bundle branches, it is termed aberrancy or, if sustained, linking.

Rate-related atrioventricular block induces changes in the atrioventricular conduction ratio, which varies according to the type of supraventricular tachycardia. A 1:1 atrioventricular conduction ratio is seen in reciprocating tachycardia and sinus tachycardia as well as in 97% of cases of focal atrial tachycardia and 41% of cases of atrial flutter, while a 2:1 ratio is seen in 41% of cases of atrial flutter and 3% of cases of focal atrial tachycardia. The atrioventricular conduction ratio is variable in atrial fibrillation and in 18% of cases of atrial flutter.[71]

The ventricular activation frequency and pattern depend upon the atrial impulse rate and site of origin, amount of concealed conduction, autonomic influence, timing, and inherent atrioventricular nodal function. Different complex electrophysiological mechanisms have been proposed to explain the different conduction ratios observed during atrial flutter and atrial fibrillation. These include decremental conduction, concealed conduction, gap phenomenon, electrotonic conduction, fatigue, and facilitation.[72,73]

The term *concealed conduction* refers to the slowing of atrioventricular conduction induced by a previous atrial impulse that fails to conduct to the ventricle. *Gap phenomenon* refers to the difference in conduction along the atrioventricular node due to atrial beats with variable coupling intervals. The distal atrioventricular node has a longer refractory period than its proximal part; an early atrial beat can therefore be conducted to the ventricle while a later one is blocked.[72,74]

Electrotonic conduction and modulation occur in a tissue area distal to the impulse blocked within the conduction system. The depolarization caused by this beat induces a subthreshold event in the cells distal to the block, with an electrotonic current spreading from depolarized to nondepolarized cells. Electrotonic depolarizations have profound electrophysiological effects on the area distal to the block; they can delay or even block the following impulse (electrotonic inhibition).[73]

The term *atrioventricular node fatigue* is a time-dependent prolongation of conduction time that develops in dogs in the first 2 to 5 minutes of fast rate and then dissipates with a similar time course. When the nodal conduction time of a premature beat is shorter than expected from the level of fatigue and recovery time, *facilitation* occurs. [73]

Repetitive concealed conduction is the main mechanism behind the various degrees of impulse penetration (atrioventricular conduction ratio) in the atrioventricular node with secondary slowing of the ventricular rate. The atrioventricular conduction ratio is a fraction with the number of conducted P waves as the numerator and the number of QRS complexes as the denominator. In atrial flutter, even conduction ratios (i.e., 2:1 or 4:1) are more common than odd conduction ratios (i.e., 3:1 or 5:1). Multilevel atrioventricular conduction block theory postulates the presence of at least two sites of block: the upper part of the atrioventricular junction for the dominant 2:1 conduction block and the distal part for the Wenckebach block. The atrioventricular conduction ratio can be progressive (from high to low grade block) or regressive (from low to high grade block).[72]

The atrioventricular conduction ratio during atrial fibrillation also depends on the amount of concealed conduction, autonomic balance, and atrioventricular node anatomy and function. During atrial fibrillation, the atrioventricular node is bombarded with impulses from different atrial regions, with various directions and varying degrees of penetration.

Propagation depends on the timing of the inputs traveling along the atrial septum, the crista terminalis, and the inferior nodal extension (site of the slow pathway), through which closely coupled atrial activations are conducted.[73] The constant bombardment of atrial wavefronts with the constant variations in cycle length and strength induces different degrees of concealed conduction, which reduces ventricular penetrance. Fluctuations in the autonomic tone play a major role in ventricular response during atrial fibrillation; vagal tone exerts a negative dromotropic effect on the atrioventricular node, thus enhancing the negative chronotropic effect of concealed conduction.[73]

Aberrancy is a rate-dependent alteration in the configuration of the QRS complex of supraventricular ectopic beats. It is part of the group of conduction alterations that includes concealed conduction, supernormal conduction, and rate-related atrioventricular block. Aberrancy occurs due to altered impulse propagation along the His–Purkinje system resulting from reduced membrane potential during excitation, which can be caused by incomplete repolarization, a low resting potential, or phase 4 depolarization in pacemaker cells. Alterations in impulse propagation may also be attributed to conduction abnormalities, reduced responsiveness of excitable tissues, or a combination of these factors. Aberrancy is facilitated when conduction occurs along partially depolarized cells, with sequential increases in the action potential duration from the initial portion of the His bundle to the terminal portions of the cardiac conduction fibers.[5]

Aberrancy can be classified into three types:

1. Aberrancy following a reduction in cycle length and increased heart rate (phase 3 block)
2. Aberrancy following an increase in cycle length and reduced heart rate (phase 4 block)
3. Aberrancy in the absence of relevant changes in cycle length and/or heart rate

Type 1 aberrancy is the most common form of aberrancy in patients with a normal or abnormal heart. The aberrant beat follows a reduced RR interval and assumes a right bundle branch block morphology in up to 85% of cases since the right bundle has a slightly longer refractory period than the left bundle. A disease of the left ventricle should be suspected if a left

bundle branch block aberrancy is observed. Type 1 aberrancy is very common in premature atrial ectopic beats, atrial fibrillation, and in the first beats of reciprocating tachycardia. In case of premature atrial ectopic beats, aberrancy is caused by an alteration of the conduction time along the His–Purkinje system due to a slow upstroke and low amplitude potentials resulting from incomplete cell repolarization. The duration of the coupling interval and preceding cycle determine the degree of aberrancy: the shorter the coupling interval, the greater the chances the impulse will travel along a partially repolarized tissue and the more likely the aberrancy is to occur. An increased heart rate shortens the time for repolarization and action potential duration, while a reduced heart rate has the opposite effect. Therefore, the longer the RR interval of the preceding cycle, the greater the likelihood to encounter partially depolarized tissue and the aberrancy to occur. The combination of long–short cycle aberrancy is also known as *Ashman's phenomenon*.[5,75] The use of antiarrhythmic drugs that slow repolarization such as class I antiarrhythmics favor the occurrence of type 1 aberrancy. Type 1 aberrancy occurring during supraventricular tachycardias is similar to aberrancy caused by supraventricular ectopic beats and the resulting reduction in cycle length. Sustained increases in atrial rate impair the ability of the His–Purkinje fibers to have a shorter action potential duration and thus compensate for the decreased duration of diastole; as a result, the cells are still partially depolarized when they receive the next impulse and aberrancy occurs. The degree of atrial rate increase and aberrancy also depend, however, on the geometry of the impulse propagation, the electrophysiological characteristics of the conduction system, and the possible prolongation of phase 3 of the action potential in cases of myocardial disease. If changes in the atrial rate are sudden, the setting of a new steady state for repolarization and reduction of the action potential duration does not occur immediately, which is why aberrancy can be seen in the first beats (see p. 211).[5]

Type 2 aberrancy results from a combination of prolonged cycle length and decreased heart rate. This type of aberrancy can be explained by the presence of numerous latent P cells along the His–Purkinje system, which undergo phase 4 depolarization and contribute to the slowing of conduction. Diastolic depolarization of these cells can be the result of an increased diastolic time, which allows more time for depolarization and conduction abnormalities, or of an increased intrinsic rate of the latent P cells. The

increase in the discharge rate of latent P cells can be due to changes in pH or pCO_2, increased stretch secondary to chamber dilation, ischemia, hypoxia, electrolytes imbalances, and use of drugs that enhance automaticity of these subsidiary pacemaker regions. The latter mechanism in association with reduced responsiveness of the latent P cells can be suspected if aberrancy occurs after a mild increase in the previous cycle length.[5] Diastolic depolarizations in latent pacemaker cells also explain *supernormal conduction and excitability* (*supernormality)* of the intraventricular system. Supernormality is defined as faster conduction than expected or conduction that occurs without an anticipated block.[75] P cells start to depolarize just after repolarization is complete at a specific membrane potential range; as a result, the membrane potential is maximal early in the cycle with a more rapid conduction and then declines progressively. In case of enhanced phase 4 depolarization impairing conduction along the His–Purkinje system, an early premature beat can present a normal conduction pattern since it travels along the affected bundle in the early phase of the cycle, when the cells are completely repolarized and conduction is more rapid (timed after the inscription of the T wave, which reflects recovery of the ventricular myocardium).[5,75] Most authors believe that supernormality exists just in the His–Purkinje fibers, but not in the rest of the conduction system or atrial or ventricular myocardium.[75] However, other electrophysiological mechanisms can mimic supernormality of the atrioventricular node, such as the peeling back effect, Wedensky phenomenon, and gap phenomenon. *Peeling back* of a refractory barrier within the atrioventricular node by an atrial or ventricular ectopic beat, or by summation of these two beats, can facilitate conduction along the atrioventricular node.[75]

The *Wedensky phenomenon* shares similar characteristics with supernormal conduction along the His bundle and its branches, with QRS complexes after shorter RR intervals with a lesser degree of block. This phenomenon can be divided into the Wedensky effect and Wedensky facilitation. The former refers to how a subthreshold stimulus may induce a response if preceded by a suitable strong electrical, chemical, or mechanical impulse, while the latter explains how an impulse reaching a blocked area may enhance conduction and excitability beyond the block. The Wedensky effect and Wedensky facilitation are related; the effect regulates impulse

propagation within the same tissue, while facilitation occurs distal to block. The mechanism behind the Wedensky phenomenon is an enhancement of excitability through the spread of electrotonic impulses in depressed areas.[76]

Type 3 aberrancy occurs without changes in the previous cycle length and heart rate. The mechanism behind this rarer type of aberration is a combination of the factors responsible for the previous types of aberrancies, such as a reduction in responsiveness of the fibers due to changes in their resistance and capacitance, a low membrane potential with incomplete repolarization, or a low resting potential or phase 4 P cell depolarizations. Fiber responsiveness is considered the critical factor as impulse conduction along a partially depolarized fiber is determined by factors other than the cycle length.[5]

The term *linking* is generally used to describe a sustained aberrancy and the mechanism for perpetuating the functional bundle branch block. Linking is common during reentrant supraventricular tachycardia, since it is an electrophysiological consequence of a beat that defines the pathway of propagation of the following beat due to concealed conduction.[77]

Two mechanisms have been proposed to explain linking (Fig. 22.4):

- Each new antegrade beat (A_n) finds an area of antegrade functional block in one limb of the circuit that presents a longer refractory period induced by concealed retrograde conduction of the previous beat (R_{n-1}). When the impulse traveling along the excitable limb of the circuit turns back (R_n), it is also blocked due to the residual refractoriness induced by the concealed antegrade impulse. Once this type of linking is established, it can persist despite variations in the tachycardia cycle length. This mechanism is also termed *linking by interference*, and it is attributed to repetitive concealed conduction. This linking is relatively common in orthodromic atrioventricular reciprocating tachycardia, or in abrupt changes in QRS morphology during monomorphic ventricular tachycardia without changes in the ventricular cycle length.
- The block is maintained by the continuous collisions between every new antegrade beat (A_n) and the previous returning one (R_{n-1}). This second mechanism is also termed *linking by collision* and can be observed when ventricular pacing entrains macroreentrant supraventricular tachycardia

or monomorphic ventricular tachycardia.[77] When the external input ceases, the last returning beat (R_{n+1}) does not encounter the antegrade beat and can progress.[77]

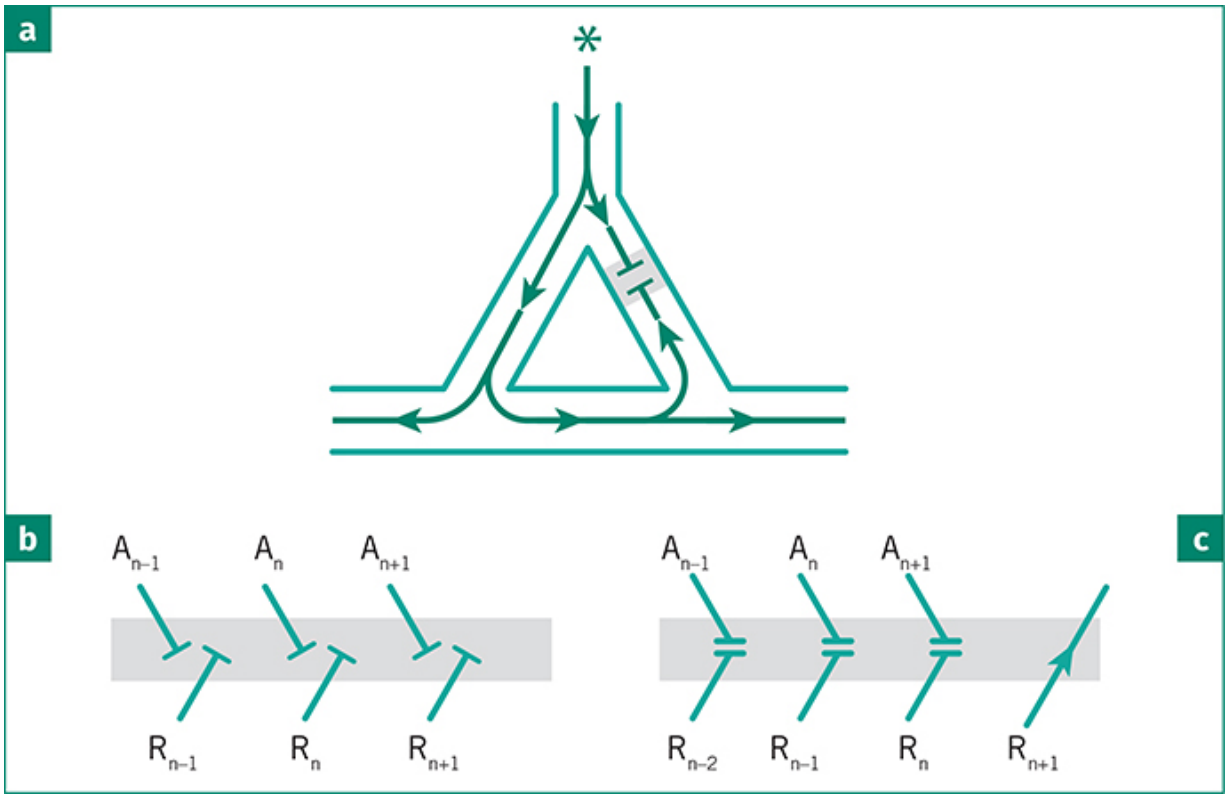


FIGURE 22.4. Schematic representation of an anatomical circuit (a) and electrophysiological theories (b, c) behind linking. Source: Modified from Lehmann M. H. et al.[77] See text for explanations.

ELECTROCARDIOGRAPHIC FINDINGS

Depending on the affected anatomical structure, electrocardiographic findings of conduction disturbances can include: sinus arrest; alterations in P wave morphology, polarity and duration; prolongation of the atrioventricular conduction time; intermittent or complete atrioventricular block; and QRS complex alteration of morphology, polarity, and duration.

SINOATRIAL BLOCKS

Sinoatrial block is frequently associated with sinus node dysfunction, and it is characterized by the presence of sinus pauses with a different duration preceded by either sinus rhythm or supraventricular tachycardias and followed by escape junctional or ventricular beats. Electrocardiographic findings of sinus node dysfunction are treated in Chapter 20.

INTERATRIAL BLOCKS

Interatrial blocks are classified, based on the degree of conduction impairment in Bachmann's bundle, into first-degree or partial block, second-degree or intermittent block, and third-degree or advanced block. Waldo et al. described the variations in the appearance of P waves after surgical lesions were produced on specialized atrial pathways in dogs,[78] providing the basis for the definition of electrocardiographic criteria for diagnosing interatrial blocks.[43]

- *First-degree or partial interatrial block*: In this case, interatrial conduction is delayed; the sinus impulse still travels across the septum along Bachmann's bundle. As a result, P waves become prolonged (range, 62–76 ms), positive in the inferior leads (II, III, aVF) and negative in lead V1, and they appear notched or bimodal (the wrongly called P mitrale), with a clear separation between the first peak representing right atrial depolarization and the second peak representing left atrial depolarization (Fig. 22.5).
- *Third-degree or advanced block*: In this case, conduction in the superior part of the atria along Bachmann's bundle is completely blocked, and therefore the activation moves in an inferior-to-superior direction starting from the coronary sinus musculature. Conduction in this area is slower, resulting in further prolongation of the P wave duration (range, 72–84 ms). The P wave assumes a biphasic morphology: positive/negative in the inferior leads (II, III, and aVF) and negative/positive in lead V1 (Fig. 22.6). Some atypical patterns have been described in humans, with a P wave that is positive/negative/positive in lead II but positive/negative in III and aVF. On other occasions, the initial positive part of the P wave in the inferior lead may be less prominent, mimicking a junctional beat.
- *Second degree or intermittent interatrial block*: In this case, interatrial block is transient with variations in the degree of block depending on the heart rate (Fig. 22.7).

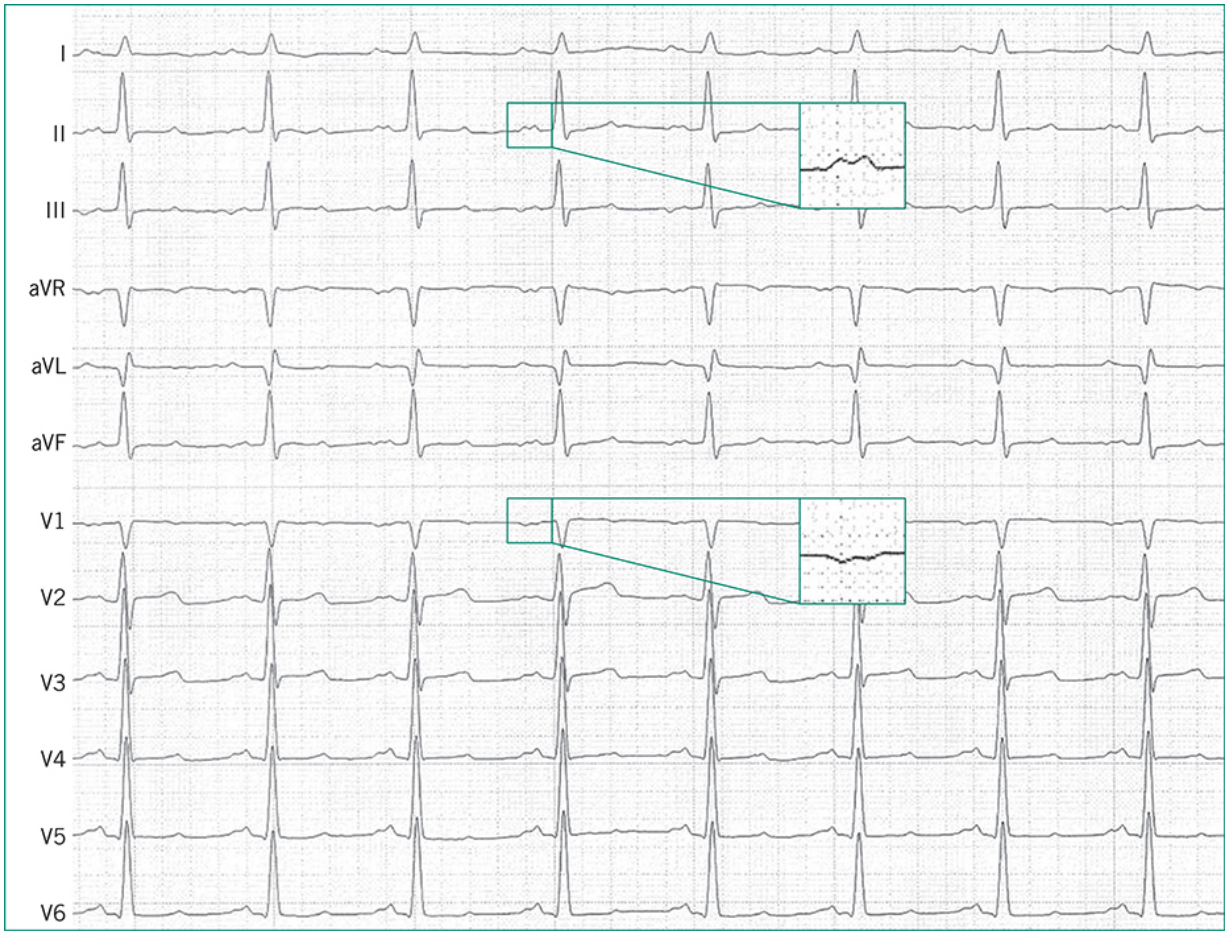


FIGURE 22.5. First-degree or partial interatrial block in an 8-year-old male English Bulldog. Note the presence of bimodal P waves in lead II and V1 (close-ups), with the first peak representing right atrial depolarization and the second peak delayed left atrial depolarization. The PQ interval is isoelectric. Twelve leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6); speed, 50 mm/s; calibration, 10 mm/1 mV.

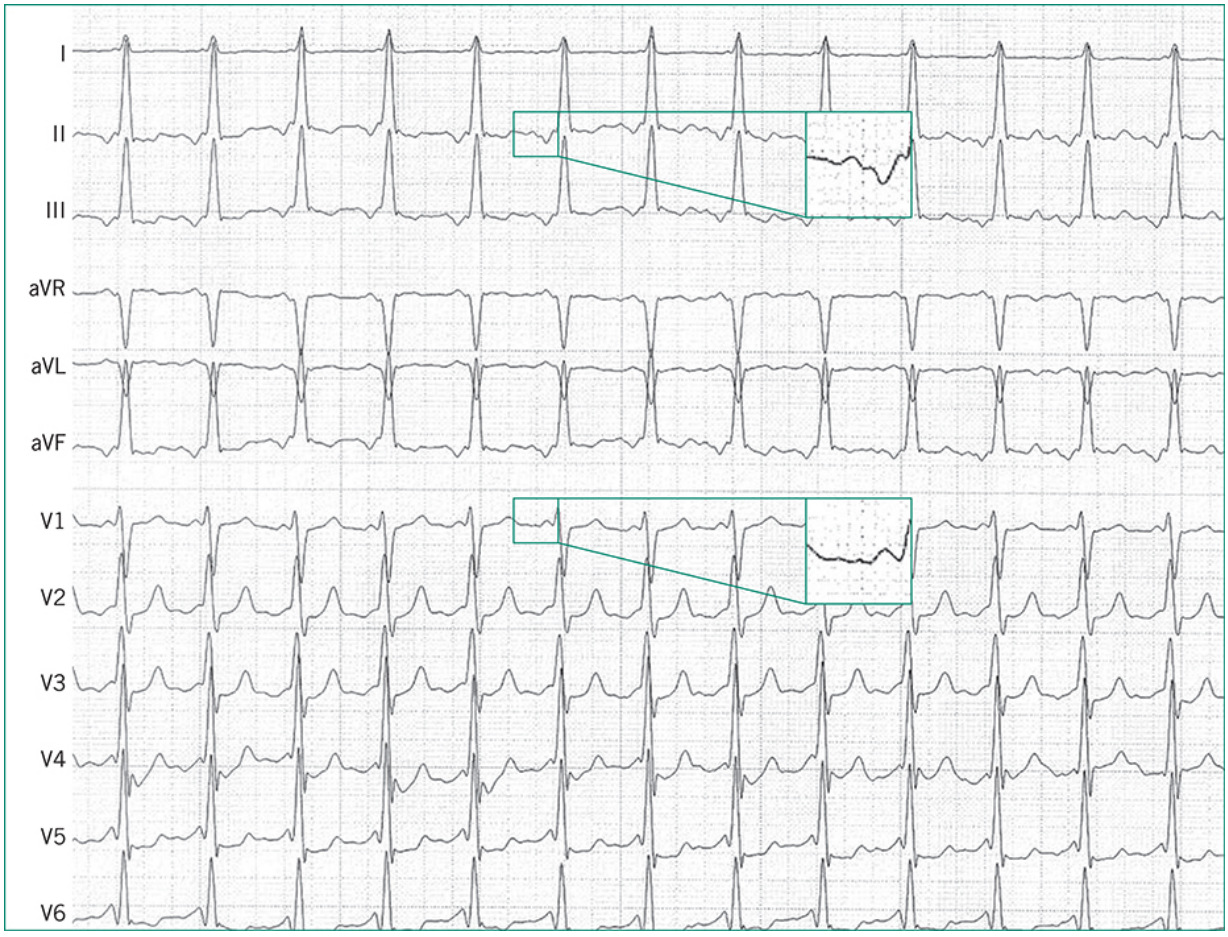


FIGURE 22.6. Third-degree or advanced interatrial block in a 13-year-old female Rottweiler with a lesion involving the whole Bachmann's bundle. Note how the P wave is positive/negative in lead II and negative/positive in lead V1, with the second portion lasting throughout the PQ segment. The first peak represents right atrial depolarization, and the markedly delayed second peak corresponds to left atrial depolarization starting from the coronary sinus musculature with an inferior-to-superior direction. Twelve leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6); speed, 50 mm/s; calibration, 5 mm/1 mV.

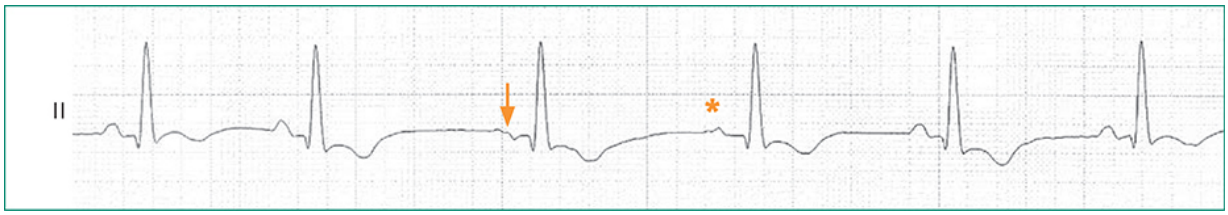


FIGURE 22.7. Second-degree or intermittent interatrial block in a 5-year-old female Doberman. Note the presence of a third-degree interatrial block (arrow) alternating with a first-degree interatrial block (*) and of slightly delayed P waves (1st, 2nd, 5th, and 6th beats). Lead II; speed, 50 mm/s; calibration, 5 mm/1 mV.

Aberrant atrial conduction appears on the electrocardiogram as P waves with different polarity, morphology, and duration after long postectopic pauses due to atrial, junctional or ventricular ectopic beats, or to parasystolic beats particularly when atrial ectopic beats are not conducted. The differential diagnosis for aberrant atrial conduction includes wandering pacemaker, atrial fusion beats, junctional escape beats, and multiform atrial ectopic beats (Fig. 22.8a).[47]

Atrial dissociation is characterized by the presence of P' waves with different duration, morphology, polarity, and rate depending on the site of origin. These P' waves appear dissociated from the QRS complexes, which are normally conducted by sinus beats. Very often atrial fusion beats can be present (Fig. 22.8b).[48,49]

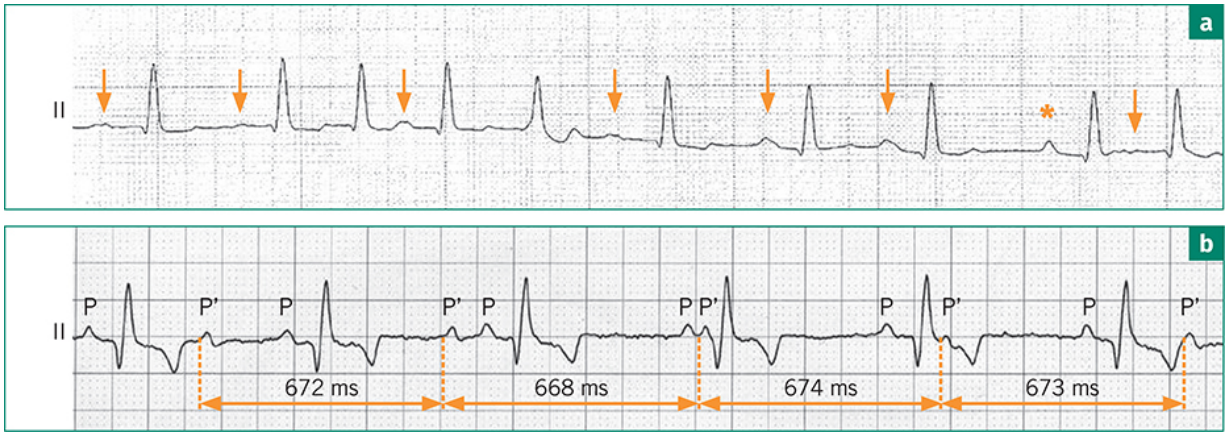


FIGURE 22.8. a) Aberrant atrial conduction in a 12-year-old male American Staffordshire with a dilated cardiomyopathy phenotype. Note the presence of a rate-dependent aberrant first-degree interatrial block alternating with bimodal P waves during sinus rhythm and atrial couplets with shorter PP intervals (arrows), and a normally conducted sinus P wave with a longer RR interval (*). The fifth beat is a ventricular ectopic beat. b) Atrial dissociation or ectopic unilateral atrial rhythm in a 11-year-old male Afghan Greyhound. Note the coexistence of normally conducted P waves and P' ectopic waves with a regular cycle length that are not conducted to the ventricles. The P' waves do not disrupt the PP and RR intervals. Lead II; speed, 50 mm/s; calibration, 5 mm/1 mV.

ATRIOVENTRICULAR BLOCKS

Atrioventricular block can occur at different levels of the atrioventricular conduction axis (atrioventricular nodal, intra-Hisian, or infra-Hisian); multilevel atrioventricular block can also occur. It can be anatomical or functional, permanent, transient, or paroxysmal, and it can be manifest as a delay in conduction (first-degree atrioventricular block), an intermittent

block (second-degree atrioventricular block), or a complete interruption of atrioventricular conduction (third-degree atrioventricular block).

Atrioventricular nodal block occurs at an intranodal level, and it is usually characterized by Wenckebach periodicity and a normal ventricular depolarization sequence. *Intra- and infra-Hisian blocks* occur respectively at the His bundle region or in the distal part of the conduction axis; they do not show Wenckebach periodicity and often present alterations in the ventricular depolarization sequence.[79] Determining the site of block is an important prognostic aspect, since more distal blocks and wide QRS complexes are linked to a worse prognosis.[80]

Atrioventricular conduction is evaluated through the analysis of the relationship between the P waves and the QRS complexes, the atrial and ventricular rates, and the duration and axis of the QRS complexes.

First-degree atrioventricular block or atrioventricular delay

In this type of conduction disorder, a P wave precedes each QRS complex with 1:1 atrioventricular conduction, and the PQ interval is >130 ms in the dog and >90 ms in the cat. Since no P waves are blocked, this conduction abnormality should be defined as atrioventricular conduction delay.[79]

First-degree atrioventricular block can occur at different levels of the atria and atrioventricular conduction axis. The presence of first-degree atrioventricular block with narrow QRS complexes (≤70 ms in the dog and ≤40 ms in the cat) is more common in interatrial and intranodal blocks, while the location of the block is more distal or multilevel when it is associated with wide QRS complexes (>70 ms in the dog and >40 ms in the cat).[79]

The duration of the PQ interval is crucial, since a prolongation of this interval causes atrial contraction to occur too early in diastole (superimposed on the early diastolic filling phase), with a shortening of the diastolic filling time and a decreased atrial contribution to the stroke volume and cardiac output. Programming the atrioventricular delay is particularly important during pacemaker programming and resynchronization therapy, as atrioventricular dyssynchrony and the occurrence of diastolic mitral regurgitation with a longer PQ interval can produce hemodynamic sequelae (Fig. 22.9).[81]

There is no cutoff value in veterinary medicine to define the optimal atrioventricular delay to maximize cardiac output. However, in the author's experience, a PQ interval >160–170 ms is usually associated with early atrial contraction observed using Doppler echocardiography as a fusion of the E and A waves.

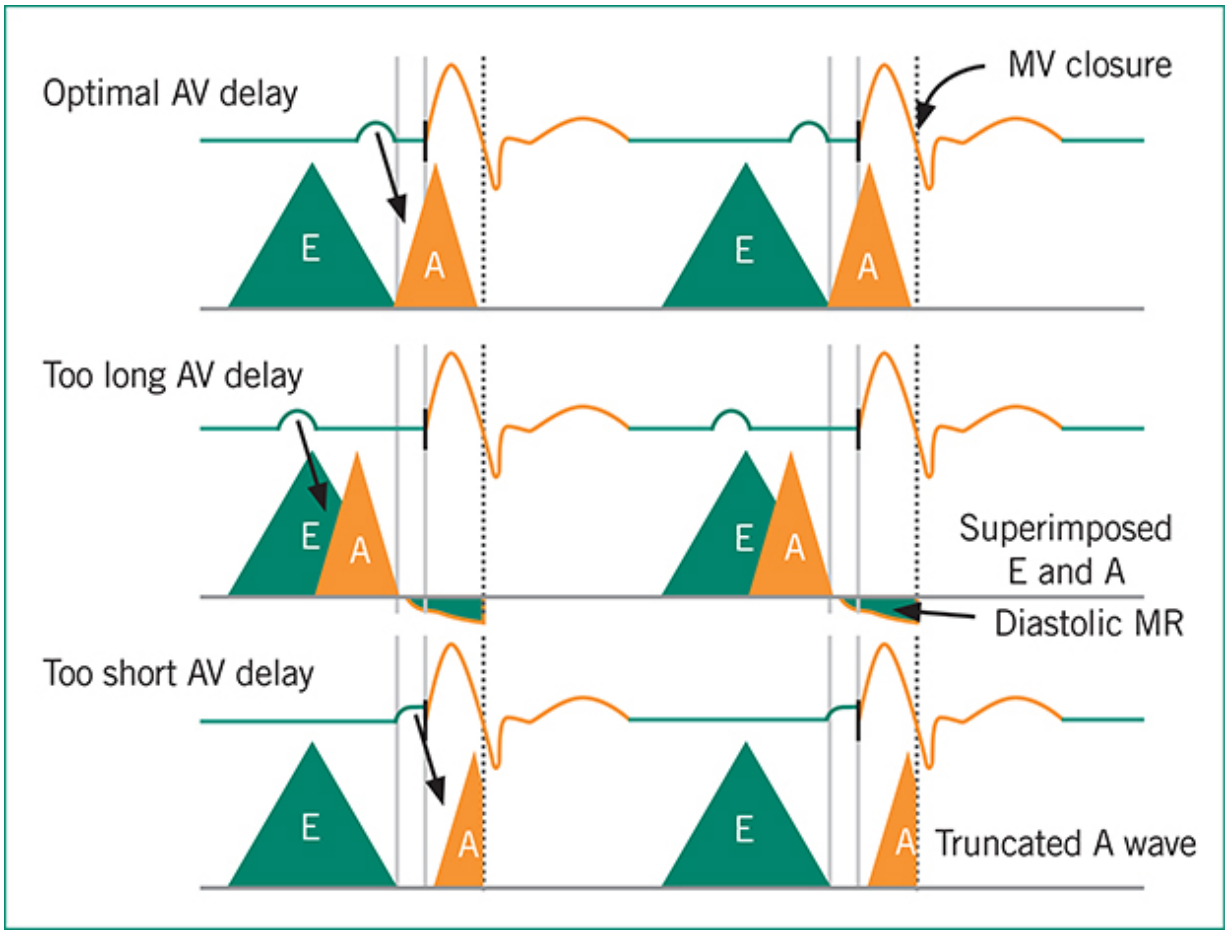


FIGURE 22.9. Schematic representation of the effect of atrioventricular delay duration on left ventricular filling. With an optimal atrioventricular interval, the mitral valve closes at the end of the A wave (upper image). In case of a prolonged atrioventricular delay (middle image), the E and A waves become fused with a decreased diastolic filling time. In this case, late diastolic mitral regurgitation (MR) may occur. Conversely, when the atrioventricular delay is too short (bottom image), the E and A waves become widely separated and the A wave is truncated by early mitral valve (MV) closure. Source: Modified from Barold S. S. et al.[81]

Second-degree atrioventricular block

Second-degree atrioventricular block is an intermittent interruption of atrioventricular conduction, characterized by the presence of P waves with a rate ≤180 bpm in the dog and ≤220 bpm in the cat, with an atrioventricular

conduction ratio that is not 1:1. The evaluation of the atrial rate is essential to distinguish supraventricular tachycardias (e.g., atrial flutter) with different atrioventricular conduction ratios from second-degree atrioventricular block in cases of intrinsic conduction system disorders.[79]

Second-degree atrioventricular block is classified into:

- Mobitz type I
- Mobitz type II
- 2:1 atrioventricular block
- Advanced or high-grade atrioventricular block

Mobitz type I second-degree atrioventricular block is characterized by P waves with a rate ≤180 bpm in the dog and ≤220 bpm in the cat, intermittent nonconduction of a single P wave, and an inconstant PQ interval duration before and after the block (Fig. 22.10a). The typical form of this conduction disturbance, which is very rare in dogs, shows Wenckebach periodicity (with progressive slowing of the atrioventricular delay before the blocked P wave due to the increase in the relative refractory period of the atrioventricular node), maximal prolongation of the PQ interval at the second beat after the blocked P wave, a progressive reduction in the RR interval before the block, and when normal conduction resumes, a shorter PQ interval than the PQ interval before the block. The atypical form occurs when the atrioventricular conduction ratio is greater than 7:6, the PQ interval does not show maximal prolongation at the second beat after the blocked P wave, and there is no shortening of the RR interval before the block. This type of block is usually intranodal, and in most cases the QRS complexes are therefore normal in duration and morphology.[79]

Mobiz type II second-degree atrioventricular block is characterized by P waves with a rate ≤180 bpm in the dog and ≤220 bpm in the cat, intermittent nonconduction of a single P wave, and a constant PQ interval duration before and after the block (Fig. 22.10b). In humans, this block is usually intra- or infra-Hisian, and it is therefore often associated with wide QRS complexes.[79] In the author's experience, Mobitz type II atrioventricular block is often present in dogs with respiratory sinus arrhythmia and in brachycephalic dogs.

2:1 Second-degree atrioventricular block is characterized by P waves with a rate ≤180 bpm in the dog and ≤220 bpm in the cat, with conduction

of every other P wave to the ventricle. The atrial rate can be irregular due the presence of sinus arrhythmia or ventriculophasic sinus arrhythmia. The latter is characterized by variations in the PP interval duration induced by ventricular systole. Mechanical systole activates the aortic and carotid baroreceptors, with a vagal surge 600 ms later; the PP interval with no QRS complex therefore has a longer duration. Conversely, the P wave after the QRS complex occurs just prior to the increase in parasympathetic tone, which induces a shortening of the PP interval including the QRS complex (Fig. 22.10c).[79] Depending on the site of block, 2:1 second-degree atrioventricular block can be observed with narrow or wide QRS complexes. In dogs, this block is commonly anatomical and intra- or infra-Hisian; consequently, it becomes permanent and progresses into third-degree atrioventricular block in 57.1% of cases, while it is transient and regresses to sinus rhythm within 1 month of diagnosis in only 28.5% of cases.[82] 2:1 Second-degree functional atrioventricular block is commonly observed in dogs during atrial flutter and rarely in case of focal atrial tachycardia.[71]

Advanced or high-grade second-degree atrioventricular block is characterized by at least ≥2 consecutive P waves that are not conducted to the ventricles, but with evidence of some atrioventricular conduction (Fig. 22.10d).[79] Depending on the site of block, high-grade atrioventricular block can be observed with narrow or wide QRS complexes. In dogs, it is usually anatomical and intra- or infra-Hisian; consequently, it becomes permanent and progresses into third-degree atrioventricular block in 61.5% of cases, while it is transient and regresses to sinus rhythm within 1 month of diagnosis in 23% of cases.[82] Dogs with high-grade atrioventricular block have the same prognosis as dogs with complete atrioventricular block, with a high risk of sudden cardiac death within the first 30 days of diagnosis in 24% of cases and within the first 6 months in 40% of cases.[80] Functional advanced or high-grade atrioventricular block is frequently observed during atrial flutter with progressive atrioventricular block caused by alternating Wenckebach mode. This phenomenon is characterized by the presence of a 2:1 conduction ratio with a progressive lengthening of the FQ interval until a greater degree of block appears (Fig. 22.11). Two forms of regressive atrioventricular block during atrial flutter can also be observed; the most common is characterized by an initial number of nonconducted F waves

followed by a sudden change to a lower-grade block. The F wave responsible for the regression to lower-grade atrioventricular block has a longer FQ interval than the preceding ones. In the second form of regressive atrioventricular block, termed reverse alternating Wenckebach mode, the switch from a high- to a low-grade block is preceded by gradually decreasing FQ and RR intervals in a nonconstant manner.[72]

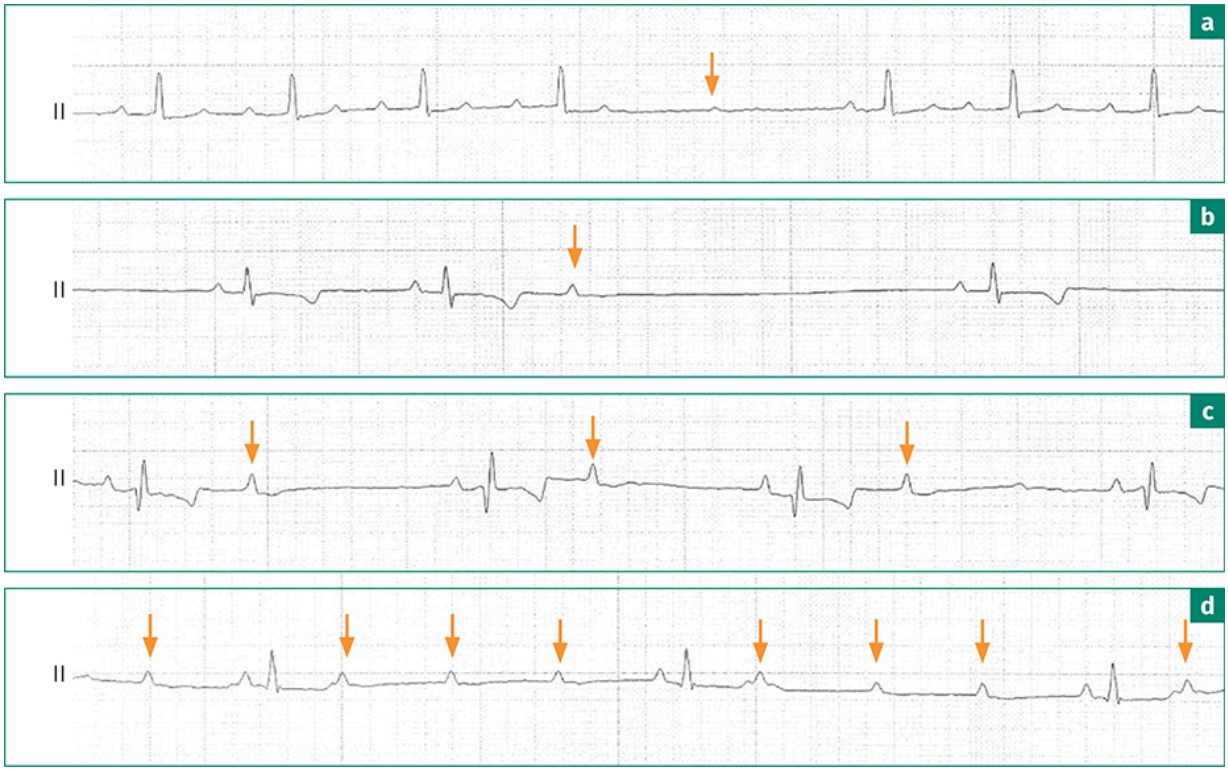


FIGURE 22.10. a) Mobitz type I second-degree atrioventricular block in a 4-year-old female mixed-breed dog. Note the progressive lengthening of the first four PQ intervals (from 120 ms to 160 ms), with a concurrent progressive increase in the sinus rate, followed by a blocked P wave (arrow). The first PQ interval after the dropped P wave is shorter (120 ms) than the one before the block. The PQ interval then starts to prolong again with the maximal prolongation at the second beat. Lead II; speed, 50 mm/s; calibration, 5 mm/1 mV. b) Mobitz type II second-degree atrioventricular block in a 11-year-old male West Highland White Terrier. Note the presence of a fixed PQ interval (100 ms) before and after the blocked P wave (arrow). Lead II, speed, 50 mm/s; calibration, 5 mm/1 mV. c) 2:1 Second-degree atrioventricular block in a 7-year-old female mixed-breed dog. Note the presence of blocked sinus P waves every other beat (arrows) with ventriculophasic sinus arrhythmia. The PP intervals that include QRS complexes are shorter than those that do not include them. Lead II; speed, 50 mm/s; calibration, 10 mm/1 mV. d) Advanced or high-grade second-degree atrioventricular block in a 15-year-old female Pinscher. Note the presence of more than two consecutively blocked sinus P waves (arrows), while those preceding QRS complexes are conducted. Lead II; speed, 50 mm/s; calibration, 5 mm/1 mV.

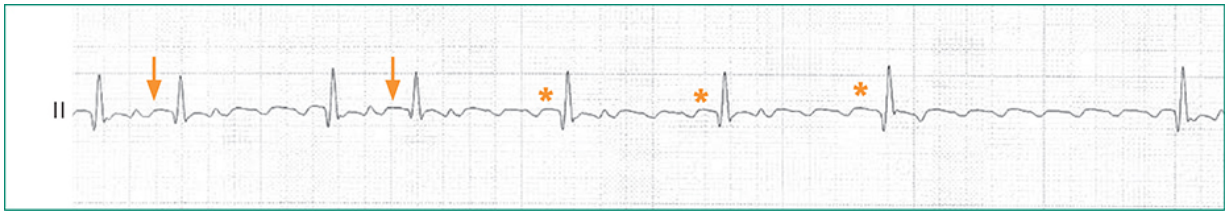


FIGURE 22.11. Functional advanced or high-grade atrioventricular block in a 12-year-old male mixed-breed dog with cavotricuspid isthmus–dependent typical atrial flutter and alternating Wenckebach mode. The FQ intervals preceding the regression to a lower-grade block are longer (arrows). The FQ intervals become progressively longer (from 120 to 160 ms) before the progression to a higher-grade block (*). Lead II; speed, 50 mm/s; calibration, 5 mm/1 mV.

Paroxysmal atrioventricular block

Paroxysmal atrioventricular block is defined as an abrupt and unexpected complete atrioventricular block in a patient with otherwise 1:1 atrioventricular conduction, with a usually prolonged ventricular asystole and delayed ventricular escape.[83] During ventricular asystole, several nonconducted P waves can be observed with different rates depending on the underlying cause, in the absence or with a very delayed ventricular escape beat interrupting the pause. Depending on its duration, paroxysmal atrioventricular block causes syncope and in some cases sudden cardiac death.[64]

Three major etiologies for paroxysmal atrioventricular block have been identified: vagally mediated block, intrinsic or phase 4 atrioventricular block, and idiopathic block.[83] Vagally mediated paroxysmal atrioventricular block is usually associated with reflex syncope due to vagally induced cardioinhibition or vagal hyperreactivity.[64,65] This type of block is characterized by sudden ventricular arrest preceded by a slowing of the ventricular rate, often with an increased PQ interval, and a P wave rate that slows down during the asystole and then progressively accelerates with an improvement of atrioventricular conduction right after the pause (Fig. 22.12a).[64]

Intrinsic or phase 4 atrioventricular block is associated with intrinsic disease of the His–Purkinje system (e.g., myocarditis). After a supraventricular or ventricular ectopic beat followed by a pause (if the beat does not completely traverse the His–Purkinje system), this area is partially depolarized, with inactivation of the sodium channels in late phase 4 of the action potential. The system is therefore unavailable for conduction until

the membrane potential is excitable again thanks to another premature depolarization (Fig. 22.12b). During ventricular arrest induced by intrinsic paroxysmal atrioventricular block, the P wave rate gradually increases during ventricular asystole in response to the positive baroreceptor reflex activated by the drop in cardiac output. Bundle branch block is commonly observed during this type of paroxysmal atrioventricular block.[83]

Idiopathic atrioventricular block is a relatively novel entity, with features that do not fit the description of the other two types of paroxysmal atrioventricular blocks.[83]

In dogs, intrinsic paroxysmal atrioventricular block is anatomical and thus often becomes permanent, with progression into third-degree atrioventricular block in 72.7% of cases.[82]

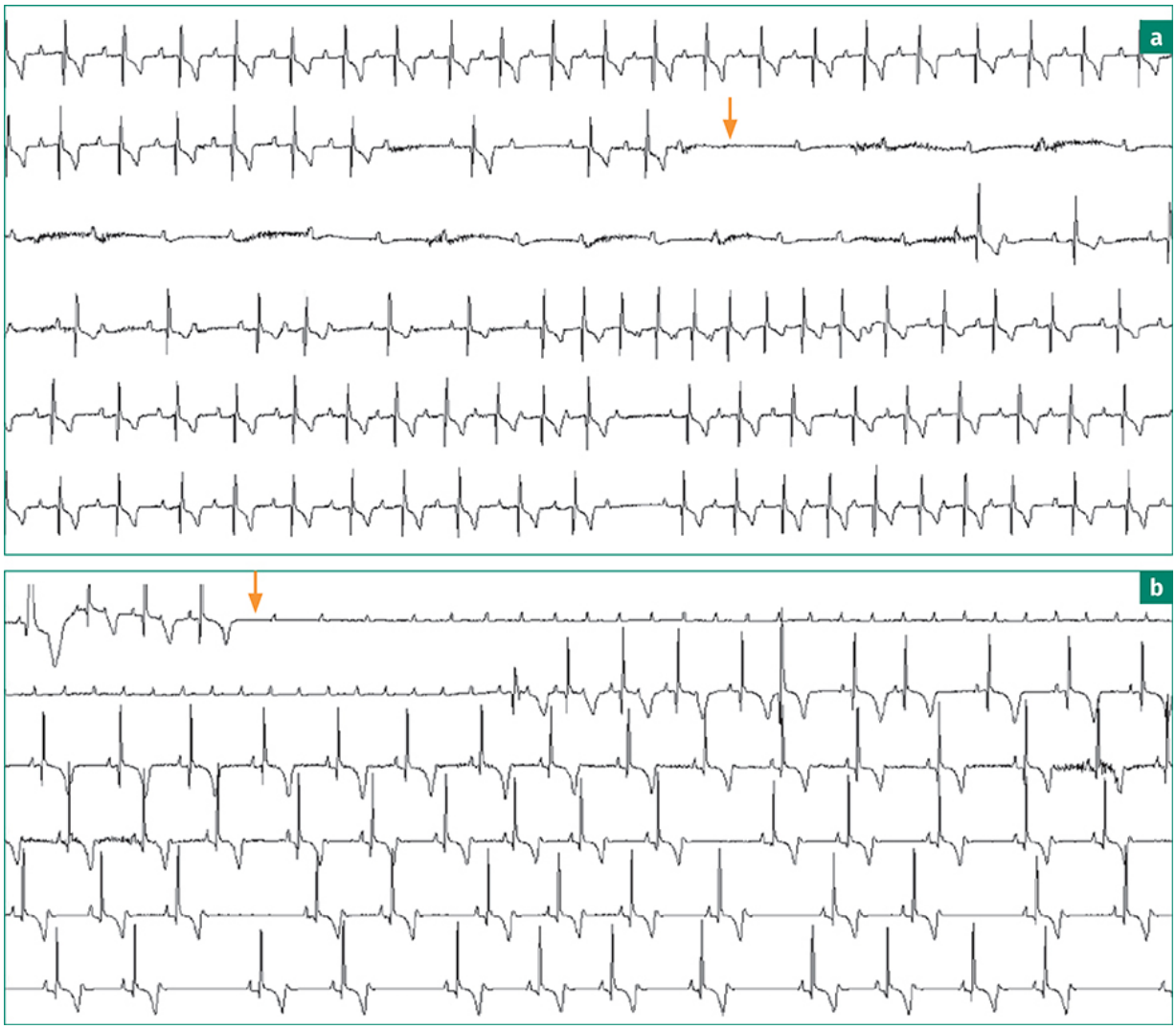


FIGURE 22.12. a) Ambulatory electrocardiographic recording from a 9-year-old male mixed-breed dog with type 1B paroxysmal atrioventricular block.[64] Note the sudden onset of atrioventricular block (arrow) with a concomitant sinus bradycardia (58 bpm) characteristic of an inappropriate vagal reflex. Lead Y; each line corresponds to 10 seconds. Speed, 12.7 mm/s; calibration, 5 mm/mV. b) Ambulatory electrocardiographic recording from a 12-year-old male Cocker Spaniel with type 1E paroxysmal atrioventricular block.[64] Note the sudden onset of atrioventricular block (arrow) with a concomitant sinus tachycardia (from 140 to 217 bpm) characteristic of an intrinsic conduction disorder with a positive baroreceptor response induced by the drop in cardiac output. Lead Y; each line corresponds to 10 seconds. Speed, 28 mm/s; calibration, 5 mm/mV.

Third-degree atrioventricular block

Third-degree atrioventricular block or complete atrioventricular block is characterized by the absence of atrioventricular conduction. The P waves are independent from the QRS complexes (*atrioventricular dissociation*) and a junctional or ventricular subsidiary pacemaker focus takes control of the heart as no P waves reach the ventricles (Fig. 22.13). If the site of block is intranodal, a narrow QRS complex (≤70 ms in dogs and ≤40 ms in cats) junctional escape rhythm is evident. Conversely, if the site of block is intra- or infra-Hisian, a wide QRS complex (>70 ms in dogs and >40 ms in cats) ventricular escape rhythm or idioventricular rhythm controls the heart.[79] Most dogs with third-degree atrioventricular block have a wide QRS complex escape rhythm, while 90% of cats with this rhythm disorder have a narrow QRS complex escape rhythm.[52,80] During third-degree atrioventricular block, the atrial rate ranges from 80 bpm to 150 bpm in dogs and from 140 bpm to 260 bpm in cats. The atrial rate is faster than the ventricular rate, which is 40–60 bpm in dogs and 100–140 bpm in cats.[52,80] The extent of the increase in the atrial rate depends on the ventricular rate: the slower the ventricular rate, the faster the atrial rate due to the positive baroreceptor response to compensate for the decrease in diastolic pressure.

Long-standing third-degree atrioventricular block with a ventricular rate below 30–40 bpm in dogs and 100 bpm in cats induces congestive heart failure and right- and left-sided volume overload with biatrial and biventricular dilation (see p. 326). This leads to persistent atrial fibrillation in old dogs, and this condition should therefore be distinguished from persistent atrial standstill to establish the prognosis (see p. 294).

In most cases, third-degree atrioventricular block is progressive and permanent (87.2%, which rises to 100% in case of third-degree atrioventricular block and atrial fibrillation). Only a minority of cases are

the result of acute myocarditis and are thus transient and regress into sinus rhythm within 1 month of the diagnosis (12.7% in dogs and 5.8% in cats).[52,82]

In dogs, given the presence in most cases of sequelae such as severe bradycardia, prolongation of the QT interval, repolarization dispersion, early afterdepolarizations, torsades de pointes, and ventricular fibrillation, correction of the ventricular rate with a permanent pacemaker should be performed as soon as possible to avoid sudden cardiac death. Terminal events are very common in dogs with third-degree atrioventricular block (42.7%); 24% of them experience sudden cardiac death within the first 30 days of diagnosis and 40% within the first 6 months, with a poorer prognosis in cases with narrower and faster QRS complex escape rhythms.[80,84]

In cats, third-degree atrioventricular block portends a better prognosis, with a median survival time ranging from 25 to 2,013 days.[52]

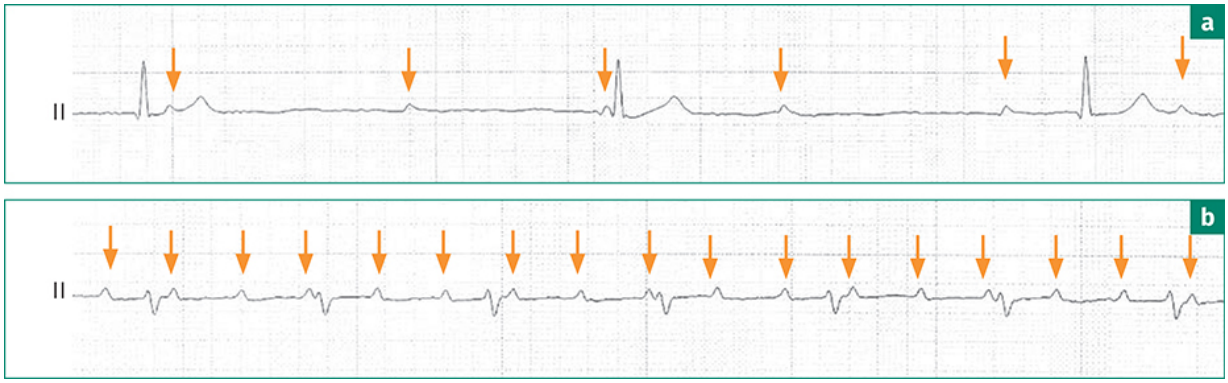


FIGURE 22.13. a) Third-degree or complete atrioventricular block in a 1-year-old male Dogue de Bordeaux with suspected vagal hyperreactivity. Note the presence of blocked sinus P waves (arrows) dissociated from the QRS complexes. The sinus rate appears to be very low (61 bpm). Lead II; speed, 50 mm/s; calibration, 5 mm/1 mV. b) Third-degree or complete atrioventricular block in a 14-year-old male domestic shorthair cat with an intrinsic conduction disorder. Note the presence of blocked sinus P waves (arrows) dissociated from the QRS complexes. The sinus rate appears to be very fast (250 bpm). Lead II; speed, 50 mm/s; calibration, 10 mm/1 mV.

Intraventricular blocks

Despite the presence of several interconnections between the left bundle branch fascicles, the intraventricular system can be considered trifascicular and is composed of the right bundle branch, left anterior fascicle, and left posterior fascicle. Anatomical data on the septal fascicle reported in humans

have not yet been defined in dogs and cats. Intraventricular blocks, depending on the underlying cause, are classified as anatomical or functional and transient or permanent. Depending on the number of branches involved, they can also be classified into monofascicular, bifascicular, and trifascicular blocks. The segments of the intraventricular system have variable anatomical and electrophysiological vulnerability: the distal right bundle is the most vulnerable, followed by the left anterior fascicle, the proximal right bundle, the left posterior fascicle, and finally, the troncular or predivisional portion of the left bundle.[85]

Depending on the site of bundle block, intraventricular conduction blocks should be analyzed to define any possible primary or secondary disorder of the conduction system (e.g., myocarditis, degeneration, surgical damage) and to assess interventricular dyssynchrony and development of abnormal conduction–induced cardiomyopathy (e.g., secondary to left bundle block).[86]

Distal right bundle branch block is very common in right ventricular myocardial disorders (e.g., arrhythmogenic cardiomyopathy) or in cases of right ventricular pressure or volume overload, while proximal right bundle branch block is common in cases of damage induced by valvuloplasty of the pulmonic valve and of inflammatory or degenerative disorders of the conduction system. Right bundle branch block induces interventricular dyssynchrony with no hemodynamic sequelae. Left anterior fascicular block is very common in cats with any disorder of the left ventricular myocardium, while complete left bundle branch block is often a sign of inflammatory or degenerative conduction system disorders or primary or secondary myocardial diseases. Left bundle branch block induces interventricular dyssynchrony with a great impact on left ventricular performance.[86,87] Bifascicular and trifascicular blocks are always associated with inflammation or degeneration of the conduction system.[59,60,62,63]

Bundle branch blocks induce alterations in the duration, morphology, and axis of QRS complexes in both the frontal and horizontal planes. These alterations depend on the site of block, the number of bundles involved, and the amount of ventricular myocardium that is slowly depolarized. Proximal blocks and blocks involving more than one bundle have wider QRS complexes than distal or monofascicular blocks.[85]

Monofascicular blocks

In monofascicular blocks, only one fascicle is affected, while the remaining fascicles conduct properly. Monofascicular blocks include right bundle branch block, left anterior fascicular block, and left posterior fascicular block.

Right bundle branch blocks can be further classified as complete or proximal and incomplete or distal blocks. The same changes in vector direction and in QRS complex morphology and axis are similar in both types of blocks. The only difference between complete and incomplete right bundle branch block is the duration of the QRS complex, which is wide (>80 ms in dogs and >40 ms in cats) in the former type, while in the latter type the QRS complex is ≤80 ms in dogs and ≤40 ms in cats.[85,87]

In right bundle branch block, the first septal vector and third left ventricular vector have a normal direction and sequence of ventricular activation: left-to-right, inferior-to-superior, and posterior-to-anterior for the former and right-to-left, superior-to-inferior, and anterior-to-posterior for the latter. The second right ventricular vector is delayed with a normal sequence of activation (left-to-right, inferior-to-superior, and posterior-to-anterior).

The electrocardiogram in case of right bundle branch block shows: small R waves in lead II with a median amplitude of 0.28 mV (range, 0.14–0.39 mV); deep S waves in lead I and the inferior leads (II, III, and aVF) with a median amplitude in lead II of 1.59 mV (range, 1.18–2.51 mV); deep S waves in the left precordial leads (V2–V6); a rR', Rr', or rr' morphology in lead V1; and a transition zone between V1 and V2. The median electrical axis in the frontal plane is –111° (range, 120° to –100°) (Fig. 22.14a). Complete right bundle branch block has a median QRS complex duration of 105 ms (range, 99–111 ms). The repolarization phase (QT interval) is prolonged (233 ± 24 ms). The R-peak time in dogs with right bundle branch block is longer in V1 (61 ms; range, 55–72 ms) than in the left precordial leads (V2, 25 ms [22–30 ms]; V3, 25 ms [22–29 ms]; V4, 24 ms [21–29 ms]; V5, 25 ms [22–29 ms]; V6, 25 ms [22–29 ms]) and than the R-peak time in V1 in normal brachymorphic, mesomorphic, and dolichomorphic dogs (median of 10.5 ms, 16 ms, and 15 ms, respectively). A prolongation of the R-peak time in V1 greater than 28 ms is a predictor of right bundle branch block with a sensitivity of 100% and specificity of 99.4%. The median interventricular dyssynchrony index is 33 % (range, 30–38%) in

dogs with right bundle branch block, compared to 23% (range, 16–29%) in normal dogs.[86,87]

The electrocardiographic findings in cats with right bundle branch block are: deep S waves in lead I and the inferior leads (II, III, aVF); deep S waves in the left precordial leads (V2–V6); a rR', Rr' or rr' morphology in lead V1; and a transition zone between V1 and V2. The mean electrical axis in the frontal plane has a range included between +80° and –105°, and the QRS complex duration is ≤40 ms in case of incomplete block and >40 ms in case of complete block (Fig. 22.15a).[59]

In dogs and cats with no underlying left heart diseases, type I or tachycardia-dependent aberrancy is commonly associated with right bundle branch block.[5]

The electrocardiographic findings of right bundle branch block should be differentiated from those of right ventricular hypertrophy, since up to 93% of dogs with concentric right ventricular hypertrophy present a right axis shift from +103° clockwise to 0°; deep S waves in lead I (>0.05 mV), II (>0.35 mV) and in the left precordial leads (>0.80 mV in V2 and >0.70 mV in V4); and an R/S ratio in V4 <0.87 (Figs. 22.14b and 22.15b).[87]

Left anterior fascicular block is an alteration of conduction in the anterosuperior portion of the left bundle that alters normal activation of this area and the interventricular septal region. In normal conditions, the first septal vector arises from the anterior and posterior fascicles. In left anterior fascicular block, the first vector is deviated with a superior-to-inferior direction (+ 80° to + 90°), the second right ventricular vector is normal and follows a normal sequence of activation, and the anterosuperior part of the left ventricle is activated with a small delay through the interconnections between the posterior and anterior fascicles. As a result, the final part of left ventricular activation (3a) has an inferior-to-superior and right-to-left direction.

The electrocardiographic findings of left anterior fascicular block are similar in dogs and cats, and include: narrow QRS complexes (≤70 ms in dogs and ≤40 ms in cats), although a mild increase in their duration can be observed either due to different degrees of block or to concomitant myocardial disease; left axis shift (–30° to –60°); loss of Q waves in lead II and a qR morphology in aVL as a result of the change in direction of the first vector arising from the posterior left ventricular wall; and deep S

waves in the inferior leads (II, III, and aVF) (Figs. 22.14c and 22.15c).[59,85,87]

Old cats can have a change in the orientation of the heart within the thoracic cavity, with a counterclockwise shift of the apex when viewed from the front, which induces a left-axis shift in the frontal plane (horizontal heart). This leads to electrocardiographic features of left anterior fascicular block; however, there is no alteration in the first vector direction, so that Q waves are often present in lead II and a qR morphology is not observed in aVL (Fig. 22.15d).

Left posterior fascicular block is rarely diagnosed in veterinary medicine. Although it alters the direction of the first septal vector and the 3b component of the third left ventricular vector and thus induces a change in wavefront direction with a delayed anterior-to-posterior activation, the electrocardiographic alterations are minimal (slight right-axis shift between +100° and +120°) and easily confused with right ventricular hypertrophy.

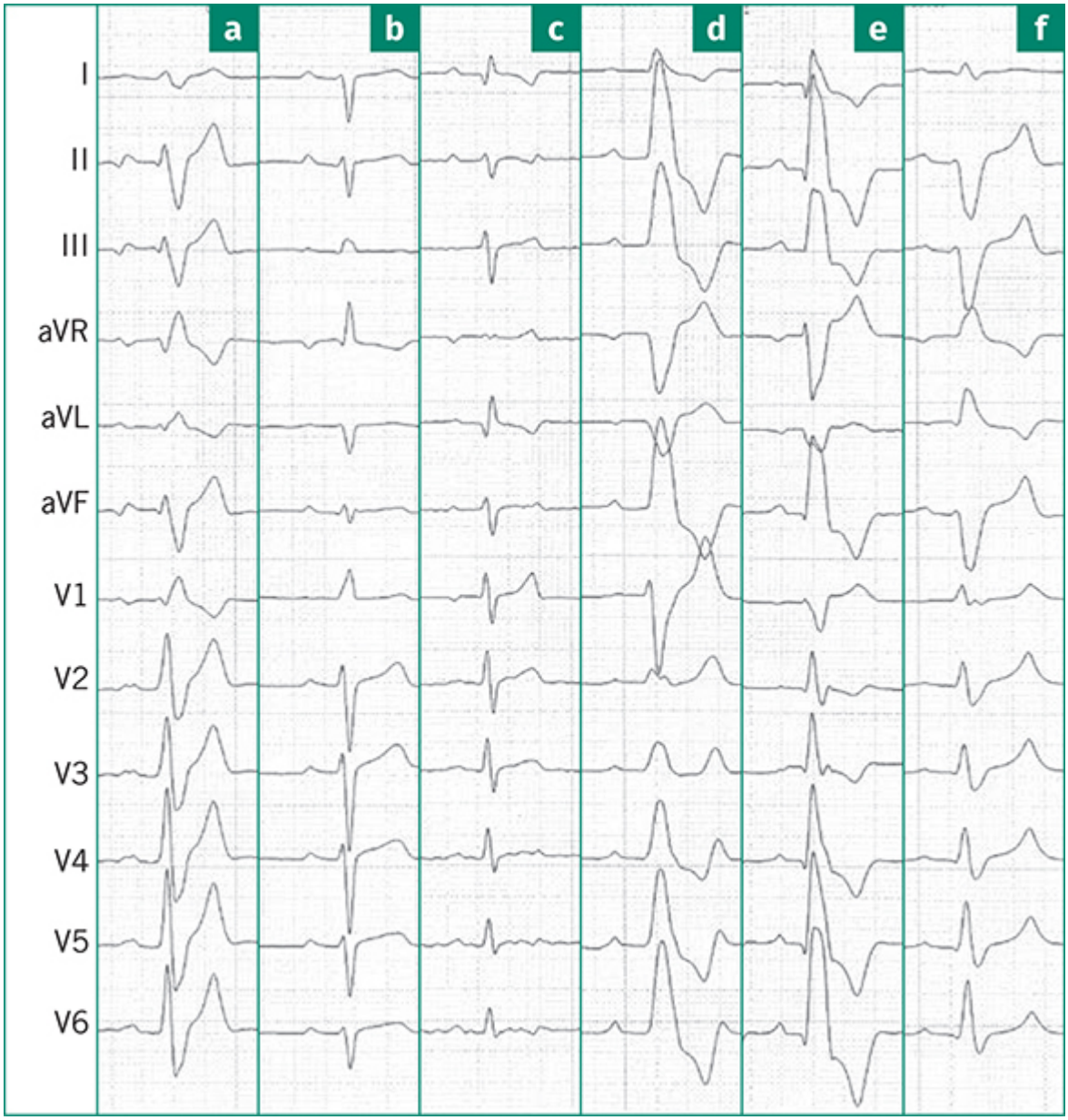


FIGURE 22.14. Electrocardiographic appearance in dogs of complete right bundle branch block (a), right ventricular hypertrophy (b), left anterior fascicular block (c), truncular or predivisional left bundle branch block (d), postdivisional left bundle branch block (e), and complete right bundle branch block plus left anterior fascicular block (f). Note the different QRS complex duration, electrical axis, and appearance in the six-limb lead system compared with the precordial lead system depending on the site of block and differential diagnosis with ventricular hypertrophy. See text for explanation. Twelve leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6); speed, 50 mm/s; calibration, 5 mm/1 mV.

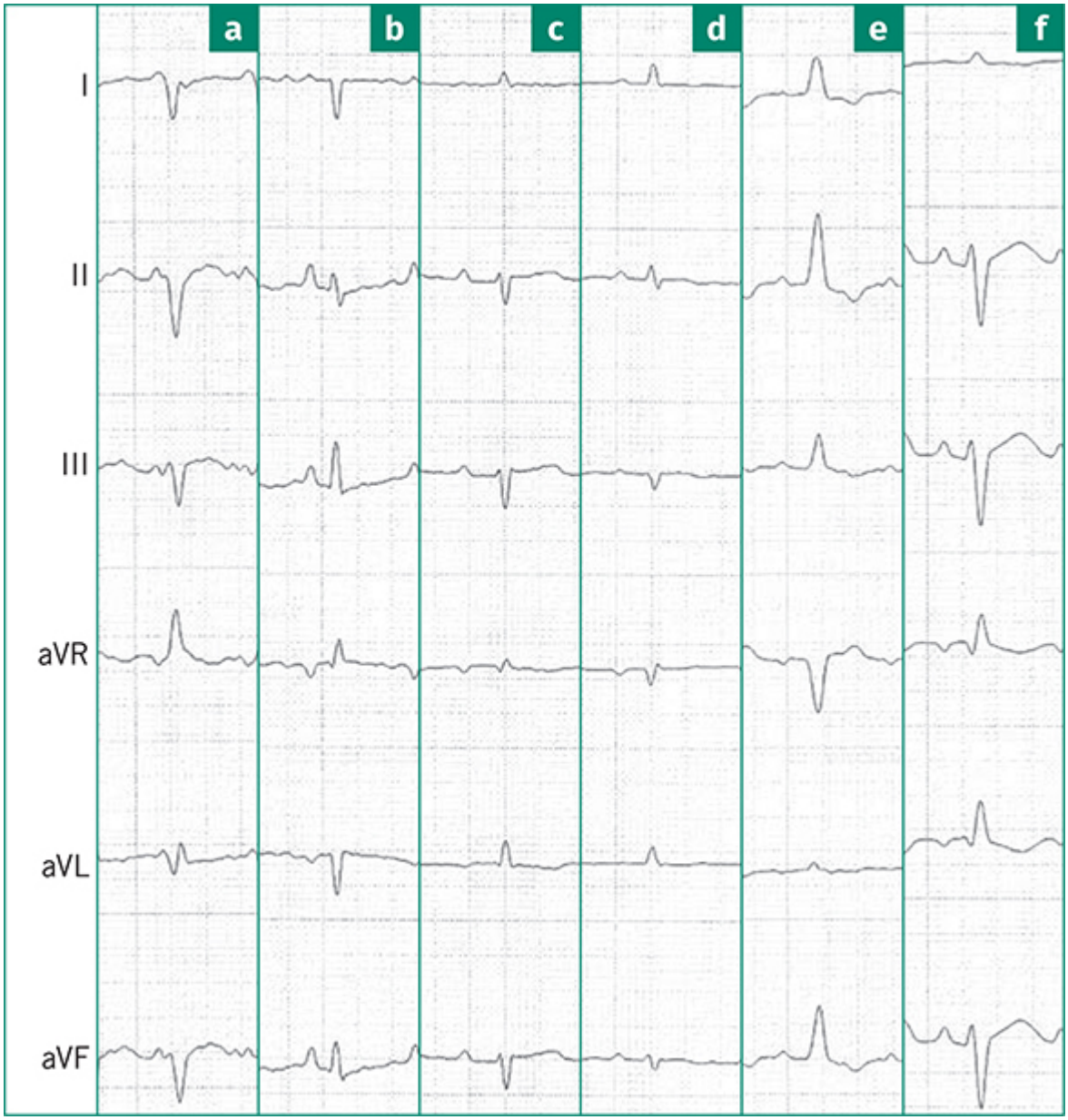


FIGURE 22.15. Electrocardiographic appearance in cats of complete right bundle branch block (a), right ventricular hypertrophy (b), left anterior fascicular block (c), left-axis shift due to horizontal heart (d), truncular or predivisional left bundle branch block (e), and complete right bundle branch block plus left anterior fascicular block (f). Note the different QRS complex duration, electrical axis, and appearance in the six-limb lead system between the different types of block, ventricular hypertrophy, and a change in the position of the heart within the chest cavity. See text for explanation. Six limb leads (I, II, III, aVR, aVL, aVF); speed 50 mm/s; calibration, 10 mm/1 mV.

Bifascicular blocks

In bifascicular blocks, two fascicles are simultaneously affected, while the remaining one conducts properly. Bifascicular blocks include: 1) left bundle

branch block; 2) right bundle branch block with left anterior fascicular block; 3) right bundle branch block with left posterior fascicular block.

Left bundle branch blocks can be further classified as complete, predivisional or truncular, and incomplete postdivisional. Both types of blocks have the same of QRS complex morphology and axis. The only differences between complete and incomplete left bundle branch blocks are the duration of the QRS complex, which is wide (>80 ms in dogs and >40 ms in cats) in the former and ≤80 ms in dogs and ≤40 ms in cats in the latter, and the alteration of the first septal vector.[85,87] In predivisional left bundle branch block, the first septal vector disappears since conduction through the fascicle is blocked, and the Q waves in lead II are therefore not visible anymore. In some cases, however, the second vector, which has the same direction (inferior-to-superior, left-to-right, and posterior-to-anterior) as the first vector and is usually masked by the concomitant third left ventricular vector, can be seen because of the delayed left ventricular activation secondary to predivisional block. As a result, in some cases, a tiny Q wave appears in lead II, and it is induced by normal activation of the second right ventricular vector (Fig. 22.16). The third left ventricular vector is markedly delayed, since the left ventricular myocardium is activated starting from the right ventricle along the working myocardium.

In case of postdivisional left bundle branch block, the first septal vector is unaffected and Q waves can therefore be seen in the inferior leads (II, III, and aVF).[85–87]

The electrocardiographic findings of left bundle branch block in dogs include: widest component of the QRS complex positive in lead I, II (median R wave amplitude, 2.32 mV; range, 1.08–3.28 mV), III, aVF and from V2 to V6, negative in V1 and aVR, with a transition zone between V1 and V2; a normal mean electrical axis in the frontal plane (median, 76°; range, 70°–81°); wide QRS complexes (median, 107 ms; range, 97–122 ms); and a prolonged median QT interval (233 ± 24 ms). In the author's experience, the presence or absence of Q waves in lead II and their measurement can define the site of block: the absence of Q waves in lead II or their presence with an amplitude ≤ 0.2 mV is suggestive of a predivisional block (Figs. 22.14d and 22.16), while the presence of Q waves in lead II with an amplitude >0.2 mV suggests the existence of a postdivisional block (Fig. 22.14e).



FIGURE 22.16. Intermittent truncular or predivisional left bundle branch block in a 10-year-old male Cavalier King Charles Spaniel with intrinsic conduction disorders. The first four beats present wide QRS complexes (80 ms) with a normal mean electrical axis and small Q waves (0.1 mV). From the 5th beat, normal intraventricular conduction resumes, the QRS complexes are narrow (60 ms) and the Q waves increase in amplitude (0.25 mV). The first part of the tracing shows a complete left bundle branch block, and the Q wave is the second right ventricular vector that can be seen due to the delay in the third left ventricular vector. When normal conduction resumes, the Q wave increases in amplitude since it represents the first septal vector. Lead II; speed, 50 mm/s; calibration, 5 mm/1 mV.

The R-peak time in dogs with left bundle branch block in the left precordial leads (V2–V6) is longer (V2, 49 ms [range, 34–58 ms]; V3, 49 ms [range, 43–57 ms]; V4, 52 ms [range, 45–62 ms], V5, 53 ms [range, 45–63 ms]; and V6, 55 ms [range, 45–63 ms]) than in V1 (17 ms; range, 15–20 ms) and than the R-peak time in the left precordial leads in normal brachymorphic, mesomorphic and dolichomorphic dogs (median around 20 ms, 23 ms, 29 ms respectively). A prolongation of the R-peak time in V5 greater than 36 ms is a predictor of left bundle branch block with a sensitivity of 96.7% and a specificity of 99.5%. The median interventricular dyssynchrony index is 32 % (range, 23–41%) in dogs with left bundle branch block, compared to 23% (range, 16–29%) in normal dogs.[85–87] The electrocardiographic findings of left bundle branch block in cats include: widest component of the QRS complex positive in lead I, II, III, aVF and from V2 to V6, negative in V1 and aVR, with a transition zone between V1 and V2; a normal mean electrical axis in the frontal plane (between 0° and +160°); wide QRS complexes (>60 ms); and a prolonged median QT interval (Fig. 22.15e).

A functional left bundle branch block (type 1 aberrancy) can develop in case of underlying left ventricular myocardial disorder (Fig. 22.17).

The electrocardiogram of right bundle branch block and left anterior fascicular block shows a combination of findings resulting from the change in the activation pattern of the first septal vector. This vector, which contributes to the first part of the QRS complex, has a superior-to-inferior direction due to left anterior fascicular block, while the rest of the QRS complex is the result of delayed activation of the right ventricle secondary

to right bundle branch block. The main electrocardiographic changes determined by the presence of left anterior fascicular block are seen in the frontal plane, while the precordial leads reveal a right bundle branch block pattern.[59,85,88]

The electrocardiographic findings of right bundle branch block and left anterior fascicular block are similar in dogs and cats and include: largest negative deflections in the inferior leads (II, III, and aVF) and left precordial leads (V2 to V6); rR', Rr' or rr' morphology in lead V1; transition zone between V1 and V2; R waves in aVL taller than R waves in aVR; presence of Q waves in aVL; a left superior mean electrical axis deviation (–60° to –90°); and wide QRS complexes (>80 ms in dogs and >60 ms in cats) (Figs. 22.14f and 22.15f).[59,85,88]

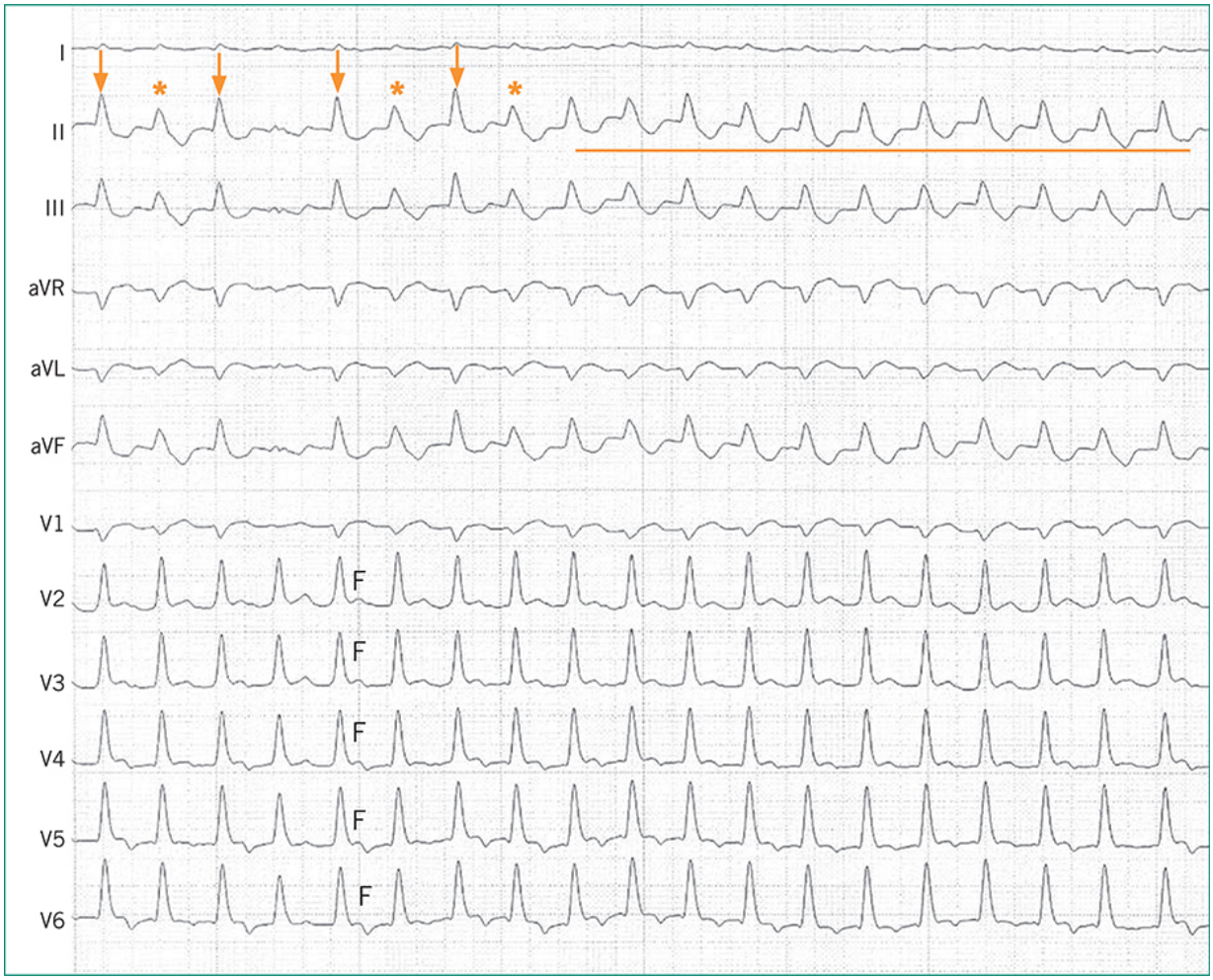


FIGURE 22.17. Functional complete left bundle branch block (sustained aberrancy or linking) alternating with supernormal conduction in a 12-year-old male Corso dog with atypical atrial flutter. The 1st, 2nd, 3rd, 5th, 6th, 7th and 8th beats show alternans of QRS complexes with different

durations and slight changes in morphology. The widest (60 ms, asterisks) are aberrant, while the narrowest (40 ms, arrows) fall in the supernormal conduction zone. QRS complex alternans then ceases, and linking starts (horizontal line). The 4th beat is a ventricular ectopic beat. Atrial flutter waves (F) are visible in the left precordial leads (V2 to V6) in the ST segment of previous beat. Twelve leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6); speed, 50 mm/s; calibration, 10 mm/1 mV.

The electrocardiogram of right bundle branch block and left posterior fascicular block shows a combination of findings resulting from the change in the activation pattern of the first septal vector. This vector, which contributes to the first part of the QRS complex, has an inferior-to-superior and right-to-left direction due to left posterior fascicular block, while the rest of QRS complex is the result of delayed activation of the right ventricle secondary to right bundle branch block.

The association of right bundle branch block and left posterior fascicular block can be suspected if the electrocardiogram shows findings of right bundle branch block with a right inferior shift of the mean electrical axis in the frontal plane, Q waves in the inferior leads (II, III, aVF) but not in leads I and aVL, and wide QRS complexes (>80 ms in dogs and >60 ms in cats).[85,88]

Figure 22.18 shows the range of mean electrical axis with the relative shifts in the frontal plane in case of right bundle branch block, left bundle branch block, left anterior and left posterior fascicular block, and the association of right bundle branch block and left anterior fascicular block.

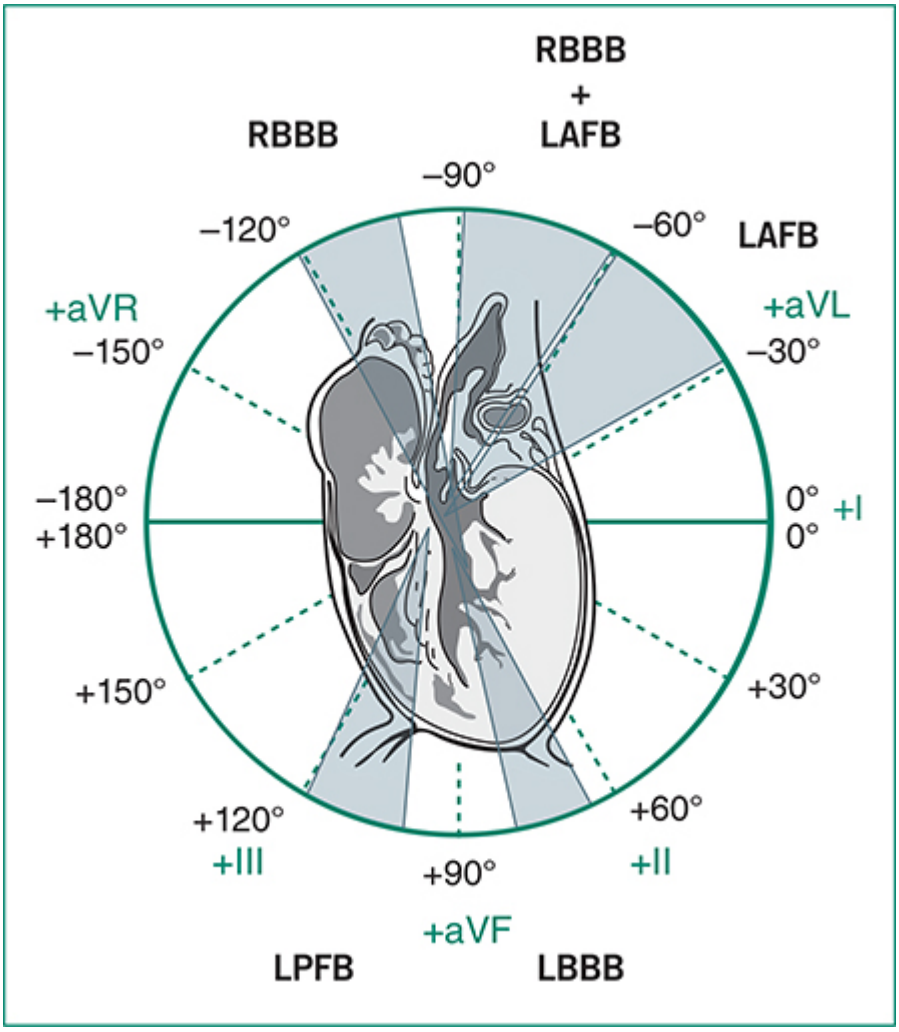


FIGURE 22.18. Mean electrical axis in the frontal plane in case of left bundle branch block (LBBB; range, +70° to +81°), right bundle branch block (RBBB; range, –120° to –100°), left anterior fascicular block (LAFB; range, –30° to –60°), left posterior fascicular block (LPFB; range, +100° to +120°), and right bundle branch block plus left anterior fascicular block (RBBB + LAFB; range, –60° to –90°).

Trifascicular blocks

Trifascicular block is diagnosed when an interruption in conduction occurs alternately in any one of the three fascicles in the same or consecutive tracings, or when a bifascicular block is associated with Mobitz type II second-degree atrioventricular block.[59,85,86,88]

The most common electrocardiographic features of trifascicular block in dogs and cats include an alternation between complete right bundle branch block and complete left bundle branch block or the presence of right bundle branch block associated with left anterior fascicular block together with

episodes of Mobitz type II second-degree atrioventricular block (Fig. 22.19).

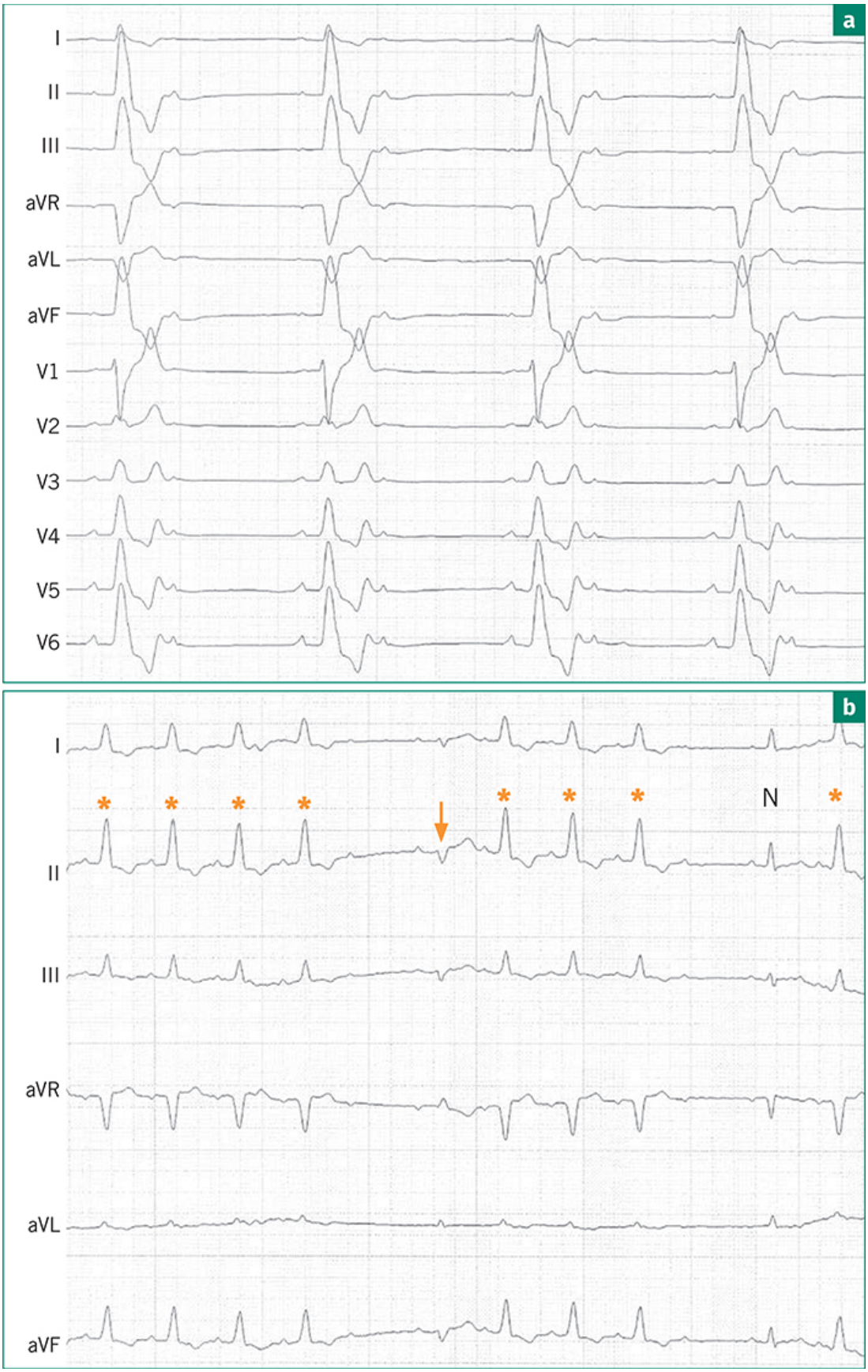

a
I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6
b
I
II
III
aVR
aVL
aVF
N

FIGURE 22.19. a) Trifascicular block in a 9-year-old female Irish Setter with an intrinsic conduction system disorder. The presence of a bifascicular bundle branch block (predivisional left bundle branch block) with 2:1 second-degree atrioventricular block confirms the diagnosis of trifascicular block. Twelve leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6); speed, 50 mm/s; calibration, 5 mm/1 mV. b) Trifascicular block in a 7-year-old male domestic shorthair cat with an intrinsic conduction system disorder. The presence of a bifascicular bundle branch block (predivisional left bundle branch block) with Mobitz type II second-degree atrioventricular block confirms the diagnosis of trifascicular block. In this case, an alternation between complete left bundle branch block (*), complete right bundle branch block (arrow), and a normally conducted beat (N) is also visible. Six limb leads (I, II, III, aVR, aVL, aVF); speed, 50 mm/s; calibration, 10 mm/1 mV.

Supernormal conduction

The classic manifestation of supernormal conduction on the electrocardiogram is characterized by an improvement in bundle branch conduction or its normalization after a RR interval that is shorter than that responsible for the aberrancy. The QRS complex duration and the amount of slurring is less evident or completely disappears in supernormal beats, while it remains evident in aberrant beats (Fig. 22.17). Supernormal excitability can be seen in patients with a malfunctioning pacemaker when there is unexpected ventricular capture with a subthreshold stimulus. Supernormal excitability can occur in a brief period comprised between the end of the T wave and the beginning of the isoelectric line.[75]

CLINICAL PRESENTATION

Demographic data on dogs with sinus node dysfunction and information on their clinical signs have been provided in Chapter 20. Interatrial conduction delays are common in large breed dogs and are not linked to a specific clinical signs other than those secondary to the underlying cardiovascular disease.

ATRIOVENTRICULAR BLOCKS

Dog breeds predisposed to atrioventricular blocks include the Labrador Retriever, the German Wirehaired Pointer, the Cocker Spaniel, the Dachshund, the Chow Chow, and the Afghan; female, geriatric, and heavier dogs are overrepresented. Dogs with high-grade atrioventricular block have fewer clinical signs than dogs with third-degree atrioventricular block

(64.7% vs. 93.1%). The prevalence of clinical signs for these two populations are shown in Table 22.1.[80]

Clinical signs are attributable to the decrease in cardiac output secondary to the low ventricular rate, atrioventricular dyssynchrony, and paroxysmal ventricular arrests. During third-degree atrioventricular block, the stroke volume is increased due to the elevated number of atrial systoles, but the cardiac output drops due to the prolonged diastolic time (Fig. 22.20). The presence or absence of clinical signs is not associated with survival. At presentation, dogs are bradycardic, weak, with a strong pulse and in some cases jugular pulsation (cannon A waves due to atrioventricular dyssynchrony); ascites are also present.[80]

TABLE 22.1. Prevalence of clinical signs in dogs with high-grade atrioventricular (AV) block and dogs with third-degree AV block.

	High-grade AV block	Third-degree AV block
Lethargy	26.5%	44.8%
Weakness and exercise intolerance	23.5%	53.4%
Dyspnea	8.8%	19%
Coughing	17.6%	17.2%
Syncope	20.6%	39.7%
Vomiting, diarrhea, and anorexia	5.9%	19%
Ascites	0%	5.2%

Cats with third-degree atrioventricular block are mainly domestic shorthair cats, with an age ranging from 7 to 19 years, with no gender predisposition. The presenting complaints include dyspnea (41.6%), syncope (12.5%), pleural effusion (9.5%), and nonspecific signs (9.5%).[52] At presentation, cats are bradycardic (80–140 bpm), with an audible murmur in 61.9% of cases, respiratory effort (28.5%), gallop rhythm (14.2%), and palpable thyroid nodules (14.2%).

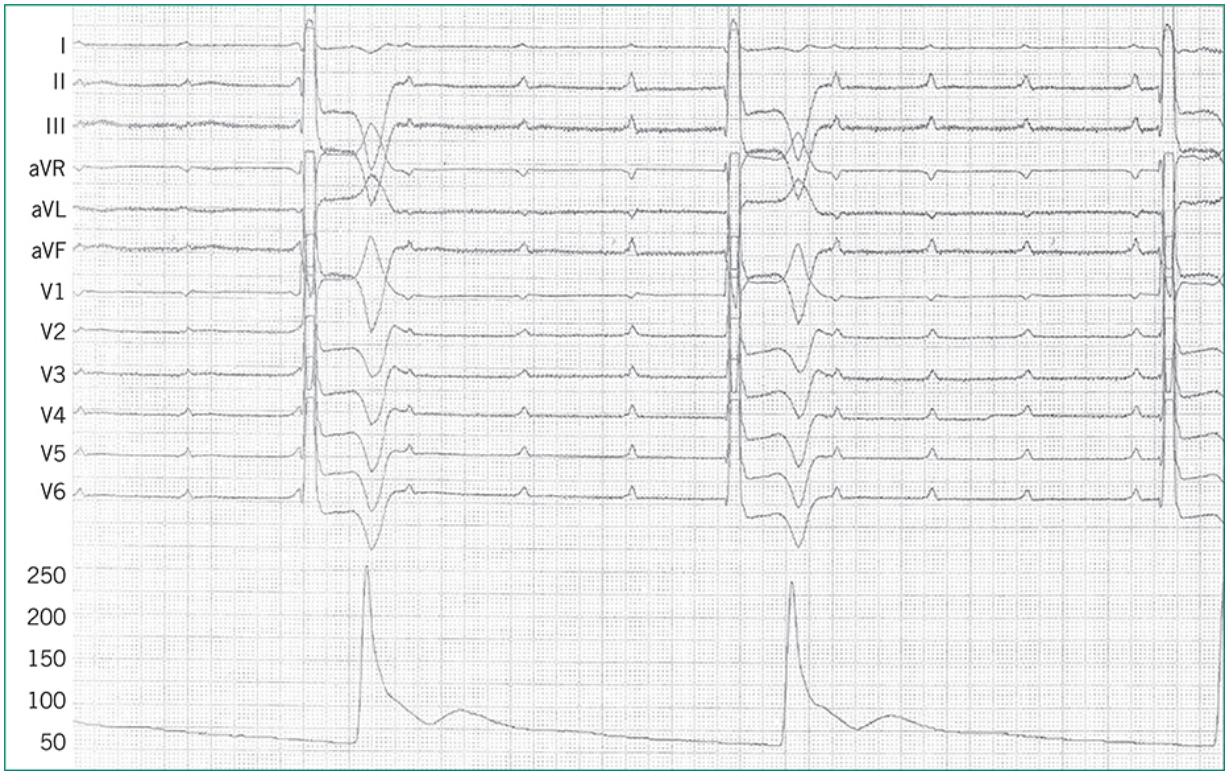


FIGURE 22.20. Peripheral arterial systemic pressure tracing in a 13-year-old male German Shepherd with third-degree or complete atrioventricular block. Note the rise in systolic pressure during ventricular systole and the drop in diastolic pressure during the ventricular pause. In third-degree atrioventricular block, the presence of nonconducted P waves induces prolonged ventricular filling, which, due to the Frank–Starling law, causes a more potent ventricular systole. As result, an increase in stroke volume and a decrease in cardiac output can be seen. Twelve leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6); speed, 50 mm/s; calibration, 10 mm/1 mV; pressure tracing scale, 50–250 mmHg.

Cats with transient atrioventricular and intraventricular block and transient myocardial thickening are younger (0.4–11.4 years), and they are usually presented for acute onset congestive heart failure, that rarely recurs.[59–61,89]

OTHER METHODS OF EVALUATION

ECHOCARDIOGRAPHY

Dogs with sinus node dysfunction usually have no echocardiographic abnormalities unless it is associated with myxomatous mitral valve disease. Dogs with interatrial conduction block usually present underlying myocardial disorders with left and/or right atrial dilation, although no

relationships between P wave duration and atrial dimension have been found in the dog.[45,46] In the author's experience, different degrees of interatrial block with no atrial dilation can be found in large breed dogs predisposed to atrial fibrillation.

Dogs with long-standing third-degree atrioventricular block may show biatrial and biventricular dilation with left and right ventricular hyperdynamic state depending on the severity of the bradycardia (Fig. 22.21). In the author's experience, long-standing bradycardia induces *bradycardia-induced cardiomyopathy* with right-sided congestive heart failure, caval plethora, ascites, and rarely pleural effusion. The mechanism behind bradycardia-induced cardiomyopathy is still unclear, but possibly related to the prolonged diastolic filling time, volume overload, atrioventricular dyssynchrony, myocardial hypoperfusion, diastolic mitral regurgitation, and neuroendocrine activation.[90]

Several cats with third-degree atrioventricular block have an underlying myocardial disorder (38.8%), such as hypertrophic, dilated, restrictive, or unclassified cardiomyopathy. The echocardiographic signs depend on the associated structural myocardial disorder, but a combination of right- and left-sided chamber dilation and wall thickening are usually detectable.[52] Cats with transient myocardial thickening and atrioventricular and intraventricular block show severe left ventricular thickening and an increased left atrium/aortic ratio, which regress within 1 month.[59–61,89]

Dogs with left bundle branch block as the primary conduction disorder can develop abnormal conduction–induced cardiomyopathy. When left bundle branch block complicates an underlying myocardial disorder, it can worsen systolic function adding interventricular dyssynchrony.

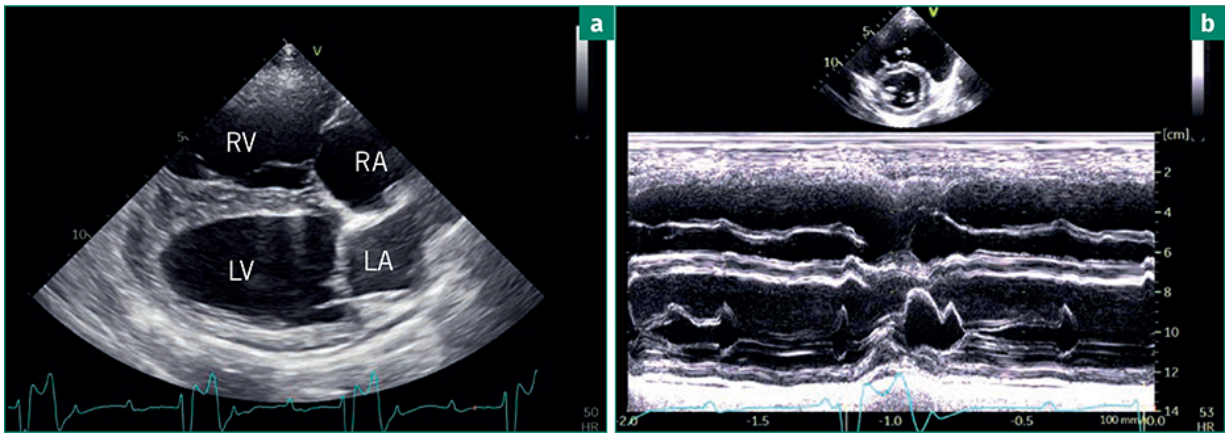


FIGURE 22.21. Right parasternal four-chamber view (a) and M-mode scan (b) at the level of the mitral valve annulus in an 8-year-old male Labrador with third-degree atrioventricular block secondary to an intrinsic conduction system disorder. Note the presence of biatrial and biventricular dilation secondary to bradycardia with an increased end-diastolic diameter and decreased end-systolic diameter, characteristic of the hyperdynamic state of bradycardia-induced cardiomyopathy.

AMBULATORY ELECTROCARDIOGRAPHIC RECORDING

In dogs and cats with syncope, Holter monitoring is the method of choice to correlate the clinical signs to the rhythm disturbance. Holter monitoring should be performed in dogs or cats if vagally mediated paroxysmal atrioventricular block (types 1B and 1C), ventricular asystole during complete third-degree atrioventricular block (1E), or paroxysmal atrioventricular block in case of preexisting trifascicular block is suspected as a possible etiology for transient loss of consciousness or transient loss of posture; it can also confirm these etiologies are the reason for sudden cardiac death.[59,60,64,84]

ELECTROPHYSIOLOGICAL STUDY

An electrophysiological study is rarely performed in dogs with sinus node dysfunction, atrioventricular block, or intraventricular block.

Electrophysiological studies allow the localization of the site of atrioventricular block, as they can differentiate between intranodal, intra-Hisian, and infra-Hisian blocks. Although no data on electrophysiological findings in dogs with atrioventricular block have been reported, recordings during endocardial mapping for the ablation of supraventricular or ventricular tachycardias can define the site of block. When analyzing the antegrade Wenckebach point of the atrioventricular node with the His electrode during incremental atrial pacing, an intranodal block will be characterized by A electrograms that are not followed by H and V electrograms. In patients with intra- or infra-Hisian atrioventricular block (e.g., iatrogenic atrioventricular block), intracardiac electrograms show A and H electrograms that are not followed by V electrograms (Fig. 22.22).

In patients with a regular, slow, narrow or, more frequently, wide QRS complex rhythm with no atrial depolarization, endocardial mapping while implanting a permanent pacemaker is crucial to better define the long-term prognosis. The differential diagnosis between persistent atrial standstill,

sinus standstill, and permanent atrial fibrillation with third-degree atrioventricular block can only be done by observing the presence or absence of atrial electrograms and the response to atrial pacing. In persistent atrial standstill, no atrial electrograms can be found, and atrial capture cannot be achieved even with high-output stimuli (up to 25 mA). In sinus standstill, no atrial electrograms can be found, but different sites of the atria can be captured with even low-output stimuli. Finally, in permanent atrial fibrillation with third-degree atrioventricular block, high frequency fibrillatory waves can be observed during atrial mapping (Fig. 22.23). In the author's experience, most cases of permanent atrial fibrillation with coarse fibrillatory waves and third-degree atrioventricular block can be confused with persistent atrial standstill, which portends a guarded prognosis.



FIGURE 22.22. Iatrogenic transient advanced or high-grade second-degree atrioventricular block in an 8-month-old male German Shepherd during radiofrequency catheter ablation of an anteroseptal accessory pathway. Five lead-surface electrocardiogram (I, II, III, V1, V6) and four intracardiac electrocardiograms recorded at the distal coronary sinus (CSd), proximal coronary sinus (CSp), proximal and distal His bundle area (HBEd, HBEp). Note, after every atrial electrogram (A), the presence of a His potential (H), which confirms the existence of an intra- or infra-Hisian block. Only two atrial deflections are normally conducted to the ventricle (V). Speed, 50 mm/s; calibration, 10 mm/13.2 mV.



FIGURE 22.23. Surface electrogram (II), atrial markers, and atrial electrogram (EGM) in a 12-year-old male mixed-breed dog with third-degree atrioventricular block and persistent atrial fibrillation. Note the presence of rapid nonconducted fibrillatory atrial activity in the EGM tracing, and of idioventricular rhythm on the surface electrocardiogram. Lead II; speed, 50 mm/s; calibration, 10 mm/1 mV.

THERAPY

SINUS EXIT BLOCKS

Sinus exit blocks, when associated with syncope or exercise intolerance (sick sinus syndrome), should be treated with pacemaker implantation. Pharmacological therapy is usually inefficacious, although an emerging drug named cilostazol, a phosphodiesterase III inhibitor, at 5–10 mg/kg per os (PO) every 12 hours, increases the heart rate in healthy dogs and seems to be promising as an alternative treatment if pacemaker therapy is not affordable.[91,92]

INTERATRIAL BLOCKS

In humans, treatment of interatrial blocks is aimed at preventing paroxysmal atrial fibrillation, changing the refractory period of Bachmann's bundle, and unloading the overstretched atria with angiotensin-converting enzyme inhibitors or with synchronous biatrial pacing acting on the right atrium and Bachmann's bundle.[20]

ATRIOVENTRICULAR BLOCKS

Due to the presence of clinical signs, the high risk of sudden cardiac death and the likely progression into a permanent form of third-degree atrioventricular block, 2:1 second-degree atrioventricular block, high-grade atrioventricular block, and paroxysmal atrioventricular block should be treated with permanent pacemaker implantation. The same treatment approach is used in patients with third-degree atrioventricular block. Permanent pacemaker is in fact the treatment of choice, and atrioventricular blocks are the reason for device implantation in 53–64% of cases.[80,93] Dogs with high-grade or third-degree atrioventricular block in which a pacemaker was implanted had a better survival time at 900 days than those left untreated, while dogs treated with vagolytic medications or methylxanthines had a similar survival time to that of those dogs left untreated.[80] Cilostazol has been suggested as an alternative pharmacological treatment in dogs with high-grade and third-degree atrioventricular block.[92] A dose of 10 mg/kg PO twice a day improved clinical signs in most cases, with an increased ventricular escape rhythm rate and reduced risk of cardiac-related death (hazard ratio from 2.98 to 0.38).

How this drug increases the ventricular rate in dogs with third-degree atrioventricular block is still unknown. Its action may involve increasing cAMP and promoting dilation of the coronary vessels.[92]

Transient atrioventricular block likely due to acute myocarditis can regress to sinus rhythm within 1 month in up to 13% of dogs.[82] However, these acute onset atrioventricular blocks are very often unstable, with a high risk of death. Implantation of a permanent pacemaker should therefore also be considered in this subgroup of dogs.

Given the better long-term prognosis reported in cats with high-grade and third-degree atrioventricular blocks, permanent pacemaker treatment with an epicardial electrode is rarely performed. Cilostazol at 0.8 mg/kg PO every 12 hours has also been used in a cat with this rhythm disorder, obtaining a survival time of 650 days.[94] In the author's experience, another pharmacological alternative are methylxanthines (e.g., aminophylline 5 mg/kg PO every 8–12 hours), which delays the appearance of and improve clinical signs and prolongs the patient's survival time. In the author's experience, transient acute onset paroxysmal atrioventricular block in cats should be treated with methylxantines or cilostazol, as is done in dogs.

INTRAVENTRICULAR BLOCKS

Resynchronization therapy is the gold standard treatment for human beings with left bundle branch block and interventricular dyssynchrony; this technique increases survival and improves left ventricular systolic function.[95] Unfortunately, resynchronization therapy has not yet been included in the therapeutic algorithms for dogs with this conduction disorder complicating left ventricular myocardial disease.

If complete monofascicular, bifascicular, or trifascicular bundle branch blocks are diagnosed on a routine electrocardiogram, a prolonged ambulatory recording is needed to assess the presence of ventricular asystole or the progression to paroxysmal or permanent atrioventricular block, which will require pacemaker therapy.[64]

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CHAPTER 23

Agonal rhythms

Roberto Santilli

DEFINITION

An agonal rhythm is a ventricular rhythm often recognized as a terminal rhythm of a dying patient. There is usually no pulse associated with an agonal rhythm due to significant underlying myocardial damage and metabolic alterations.[1]

The most common agonal rhythms reported in dogs experiencing sudden cardiac death or cardiopulmonary resuscitation are asystole (37–60%), pulseless electrical activity (18–42%), ventricular fibrillation (21–63%), and pulseless ventricular tachycardia (2%).[2–4] The agonal rhythms documented in cats are asystole (44%), pulseless electrical activity (35%), and ventricular fibrillation (21%).[3] Pulseless electrical activity can be the terminal rhythm or can follow asystole, ventricular fibrillation, or occur postdefibrillation.[2,3,5,6]

The classification of these rhythm disturbances plays a major role during cardiopulmonary resuscitation maneuvers, since different advanced life support measures should be taken: asystole and pulseless electrical activity are nonshockable, while ventricular fibrillation or pulseless ventricular tachycardia are shockable.[7,8]

ASYSTOLE

Asystole is characterized by the cessation of ventricular electrical or mechanical activity, and depending on its duration, it can cause transient loss of consciousness or be a lethal rhythm.[2,6–9]

Transient asystole is secondary to intrinsic rhythm disturbances, such as sinus node dysfunction and third-degree or paroxysmal atrioventricular block (31.5%), or due to an inappropriate vagal reflex (46.7%) or sleep apnea.[9,10]

The duration of transient asystole ranges from 4 to 180 seconds, with neurally mediated asystole lasting longer.[9]

ELECTROPHYSIOLOGICAL MECHANISM

Asystole was the underlying cause in 37% of dogs that died suddenly during Holter recording and is often preceded or followed by pulseless electrical activity and induced by malignant inappropriate vagal reflexes.[2]

In case of cardiac arrest, asystole usually occurs as a consequence of nonperfusing arrhythmias such as pulseless ventricular tachycardia, ventricular fibrillation, or pulseless electrical activity.[7,8]

Asystole can be classified as primary or secondary. Primary asystole usually follows intrinsic rhythm disturbances caused by degeneration or inflammation of the conduction system (e.g., high grade atrioventricular block, paroxysmal atrioventricular block, sinus node dysfunction, or atrial standstill) or pacemaker malfunctioning.[2,9] Primary asystole is also a ventricular arrest due to an inappropriate vagal reflex inducing atrial arrest or paroxysmal atrioventricular block or secondary to sleep apnea.[9,10] Secondary asystole usually follows extracardiac disorders inducing hypoxia and acidosis.[7,8]

ELECTROCARDIOGRAPHIC FINDINGS

The electrocardiogram during asystole can display different features depending on the underlying cause. An isoelectric line with no signs of atrial or ventricular activation can be seen in case of sinus arrest or standstill or atrial standstill (Fig. 23.1a). An isoelectric line with no ventricular activation but with sinus P waves can be seen in case of advanced second-degree, third-degree, or paroxysmal atrioventricular block (Fig. 23.1b), with F waves in case of atrial flutter with paroxysmal

atrioventricular block and f waves in case of atrial fibrillation with paroxysmal atrioventricular block (Fig. 23.2).[2,9]

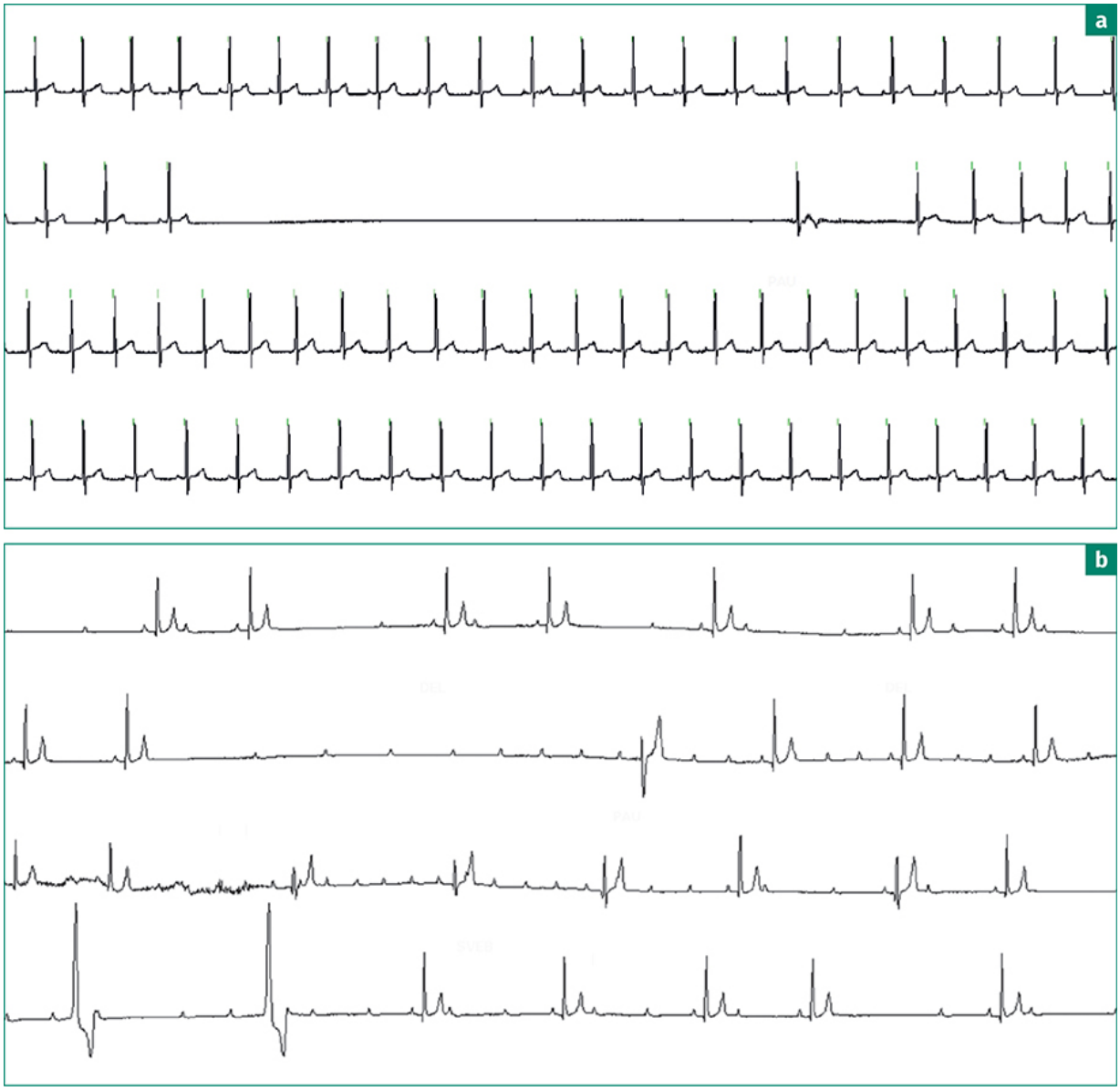


FIGURE 23.1. a) Ambulatory electrocardiographic recording of a type 1D syncope in a 12-year-old female West Highland White Terrier with sick sinus syndrome. Before the ventricular arrest, the dominant rhythm is a sinus rhythm with an average heart rate of 88 bpm, followed by a ventricular arrest lasting 8.4 seconds due to a sudden sinus arrest, and then normal reoccurrence of sinus rhythm. Y lead; each line corresponds to 15 seconds. Speed, 8.5 mm/s; calibration, 5 mm/1 mV. b) Holter tracing during a type 1E syncope in a 5-year-old female Boxer with paroxysmal atrioventricular block. Before the ventricular arrest, the dominant rhythm is a sinus rhythm conducted with 2:1 and then advanced atrioventricular block with an average heart rate of 42 bpm, followed by a ventricular arrest lasting 6.9 seconds due to a paroxysmal atrioventricular block, and then progressive recovery

of atrioventricular conduction from third-degree to advanced second-degree atrioventricular block. Y lead; each line corresponds to 15 seconds. Speed, 13.7 mm/s; calibration, 5 mm/1 mV.

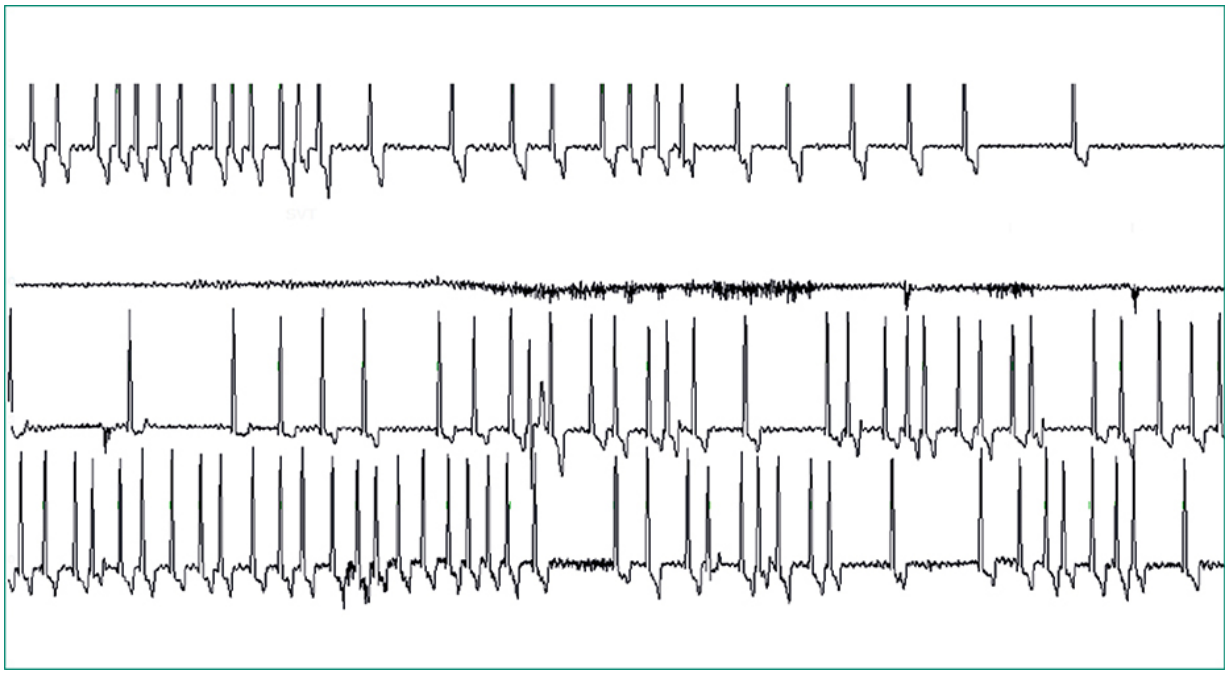


FIGURE 23.2. Ambulatory electrocardiographic recording of a type 1C syncope in an 11-year-old male Cavalier King Charles Spaniel with advanced mitral valve disease and long-standing atrial fibrillation. Before the syncopal episode, the dominant rhythm is atrial fibrillation with an average ventricular rate of 70 bpm, followed by a ventricular arrest lasting 16.9 seconds due to a sudden paroxysmal atrioventricular block, and then slow recovery of normal atrioventricular conduction. Y lead; each line corresponds to 15 seconds. Speed, 8.5 mm/s; calibration, 5 mm/1 mV.

THERAPY

Transient asystole, either due to intrinsic rhythm disturbances or to an inappropriate vagal reflex or vagal overreactivity, requires a pacemaker implantation.[11–13] Asystole during cardiopulmonary arrest should be treated starting with basic life support maneuvers: chest compressions in lateral recumbency (100–120 per minute regardless of species or size); ventilation (10 breaths per minute simultaneously with compressions with approximately 10 mL/kg tidal volume). Continuous monitoring of the animal in cardiopulmonary arrest during basic life support maneuvers is mandatory to evaluate the necessity of administering reversals in case asystole is drug-induced (naloxone for opioids, atipamezole for α-2 agonists, or flumazenil for benzodiazepines) or any other drugs.[7,8] In case of asystole, administration of low-dose epinephrine (0.01 mg/kg

intravenously [IV]) and/or vasopressin (0.8 U/kg IV) every 3–5 minutes early during cardiopulmonary resuscitation is recommended. Although not strongly supported, the use of atropine (0.04 mg/kg IV) in animals with asystole due to high vagal tone can be considered. When prolonged cardiopulmonary arrest lasts for more than 10 minutes, high-dose epinephrine (0.1 mg/kg IV) and bicarbonate therapy (sodium bicarbonate, 1 mEq/kg IV) should be administered.[7,8]

VENTRICULAR FIBRILLATION

Ventricular fibrillation is a frequent cause of cardiac arrest and/or sudden cardiac death in both dogs and cats.[2–4] Ventricular fibrillation should be considered a lethal malignant arrhythmia leading to rapid and uncoordinated electrical activity, inability of the heart to pump blood, circulatory collapse, and clinical and eventually biological death if left untreated.[14] In the dog, ventricular fibrillation is most commonly triggered by monomorphic ventricular tachycardia (42%) or polymorphic ventricular tachycardia (21%) secondary to channelopathies or third-degree atrioventricular block.[2,15–18]

ELECTROPHYSIOLOGICAL MECHANISM

Two main electrogenic mechanisms have been postulated to explain ventricular fibrillation:

1. The arrhythmia is the result of several reentrant wavelets in the ventricular myocardium promoting a spatially extended chaotic system, the dynamics of which cannot be explained by a single, meandering spiral wave (type 1 ventricular fibrillation).
2. A single, rapidly firing focal source due to reentry or abnormal automaticity leads to ventricular fibrillation (type 2 ventricular fibrillation). This is called the focal source hypothesis.[19,20]

Type 1 ventricular fibrillation is associated with normal excitability and can self-defibrillate. It can convert into type 2 ventricular fibrillation in conditions of low excitability due to acute global ischemia.[19]

Different studies evaluated the sequence of activation, endocardial-epicardial gradients, and the role of Purkinje fibers in maintaining the arrhythmia during long-duration ventricular fibrillation (lasting more than 1 minute).[21–23]

In dogs, 2 minutes after starting, ventricular fibrillation can show three different types of activation patterns: one type is highly chaotic, and two are highly organized (types II and III). Type II arises from the apex, is highly regular and repeatable, and may be driven by an intramural mother rotor. Type III arises focally in the endocardium and Purkinje fibers, which are more resistant to ischemia, and may be caused by early afterdepolarizations.[24]

The first 10 minutes of ventricular fibrillation in dogs are characterized by organized myocardial activity with the following electrocardiographic frequency structure: for the first 2 minutes, low-frequency oscillations (4–7 Hz) predominate; from 3 to 10 minutes after onset, low- and medium-frequency oscillations (4–12 Hz) are predominant; and after 10 minutes, low-frequency oscillations become nondominant.[25] There are indeed three time-sensitive phases during cardiac arrest induced by ventricular fibrillation that should be considered: the electrical phase (0–4 minutes), the circulatory phase (4–10 minutes), and the metabolic phase (>10 minutes).[19] During the electrical phase, type 1 ventricular fibrillation predominates, and defibrillation is highly effective. As ischemia progresses, type 2 ventricular fibrillation occurs due to reduced myocardial excitability caused by the accumulation of ischemic metabolites.[19]

ELECTROCARDIOGRAPHIC FINDINGS

During ventricular fibrillation, the electrocardiogram shows rapid oscillations of the isoelectric lines and the absence of P waves, QRS complexes, and T waves. The amplitude and cycle length of oscillations vary according to the time of onset of the arrhythmia (from 35 to 150 ms). Ventricular fibrillation evolves throughout four different temporal stages:

1. A tachysystolic phase, which lasts around 1 second and is characterized by wide and rapid contractions that appear on the surface electrocardiogram as 3–10 fluctuations of the isoelectric lines.
2. A convulsive incoordination phase, which lasts from 1 to 40 seconds after the onset of ventricular fibrillation and appears on the surface

electrocardiogram as rapid waves with a more irregular cycle length and a rate exceeding 600/minute.

3. A tremulous incoordination phase, which lasts from 40 seconds to 3 minutes and is characterized on the surface electrocardiogram by an oscillation rate between 1100 and 1700/minute.
4. An atonic incoordination phase, during which oscillations have less amplitude and the rate drops to 400/min (Fig. 23.3).[26]

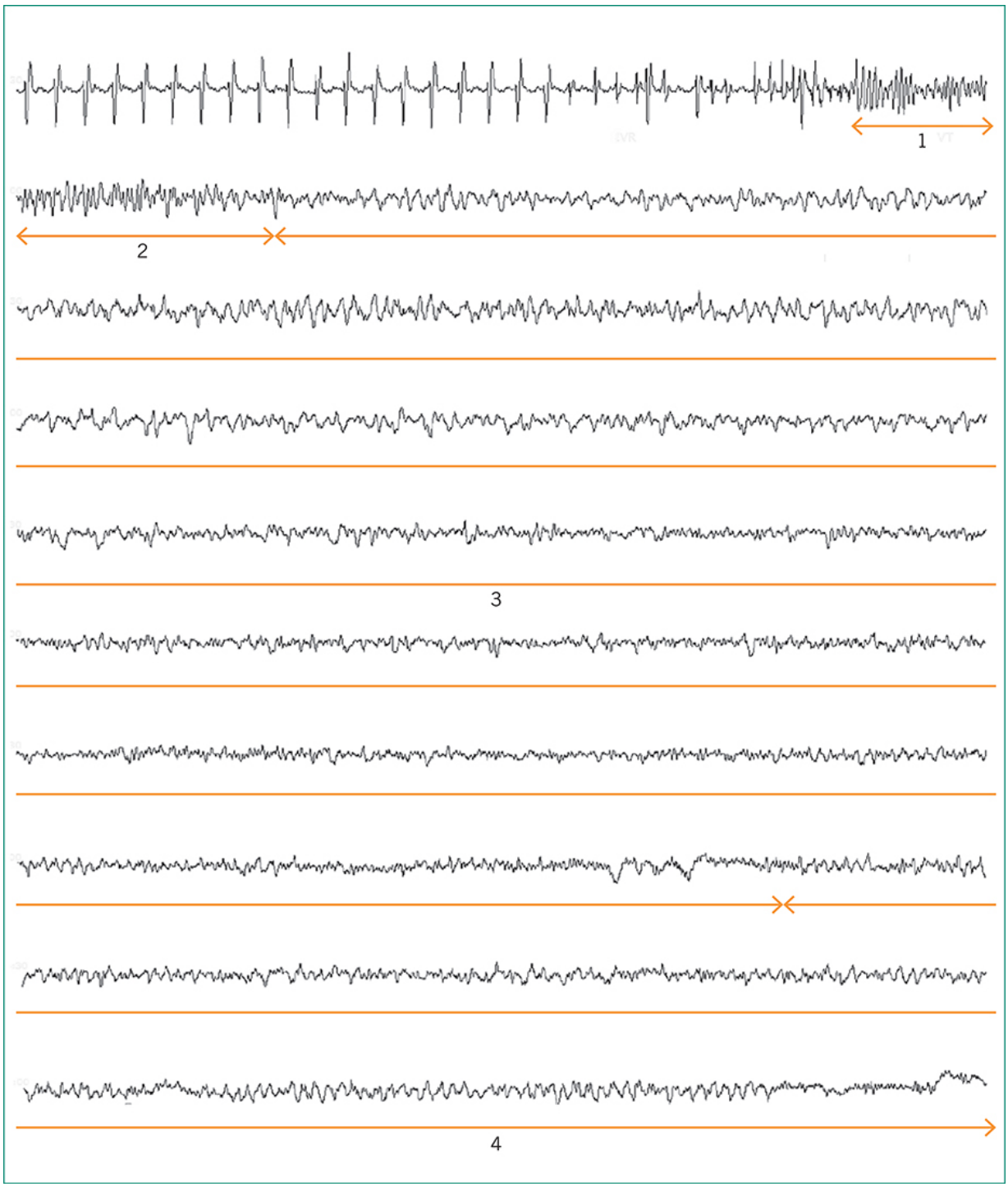


FIGURE 23.3. Ambulatory electrocardiographic recording showing sudden cardiac death in a 5-year-old male Pit Bull Terrier with dilated cardiomyopathy and congestive heart failure. Note the different phases of ventricular fibrillation that occurred after an episode of accelerated idioventricular rhythm: 1) a tachysystolic phase, which lasts around 1 second and is characterized by wide and rapid contractions that appear on the surface electrocardiogram as 3 to 10 fluctuations of the isoelectric lines; 2) a convulsive incoordination phase, from 1 to 40 seconds after the onset of ventricular fibrillation, which appears on the surface electrocardiogram as rapid waves with a more irregular

cycle length and a rate exceeding 600/minute; 3) a tremulous incoordination phase, which lasts from 40 seconds to 3 minutes and appears on the surface electrocardiogram with a rate from 1100 and 1700/minute; 4) an atonic incoordination phase, during which oscillations have less amplitude and the rate drops to 400/min. Y lead; each line corresponds to 30 seconds. Speed, 9.3 mm/s; calibration, 5 mm/1 mV.

THERAPY

Asynchronous ventricular defibrillation is the treatment of choice for ventricular fibrillation and should be applied during the electrical phase (first 4 minutes), when type 1 ventricular fibrillation is observed. As soon as ischemia progresses and type 2 ventricular fibrillation occurs, the success rate of electrical cardioversion drops.[7,8,19] Biphasic defibrillation (2–4 J/kg) has been proven to be more efficacious than monophasic defibrillation (4–6 J/kg) both for ventricular fibrillation and pulseless ventricular tachycardia. Asynchronous defibrillation is applied after basic life support maneuvers (see above), and if the first shock is not efficacious, a 50% increase in the energy delivered should be considered.[7,8] Prolonged ventricular fibrillation or pulseless ventricular tachycardia should also be treated with amiodarone (5 mg/kg IV) or lidocaine (2 mg/kg IV), and low-dose epinephrine (0.01 mg/kg IV) and/or vasopressin (0.8 U/kg IV) every 3–5 minutes early during cardiopulmonary resuscitation. On rare occasions, a chest thump may be efficacious.[7,8]

PULSELESS ELECTRICAL ACTIVITY

Different definitions have been proposed to characterize pulseless electrical activity in humans; most of them have been summarized as the presence of organized electrical activations with no synchronous myocardial fiber shortening and therefore a subsequent loss of cardiac output.[27] Pulseless electrical activity occurs very frequently after defibrillation of long-duration ventricular fibrillation not previously treated with cardiopulmonary resuscitation.[27] Pulseless electrical activity is the terminal rhythm in 37% of dogs that died suddenly during Holter monitoring, and it is present in 18–42% of dogs and 35% of cats during cardiopulmonary resuscitation maneuvers.[2–4]

Pseudo-pulseless electrical activity is a condition that occurs when cardiac electrical activity is present without a palpable pulse, but myocardial contraction can be seen by echocardiography, or a carotid artery flow is documented by Doppler ultrasound.[28] In human medicine, pseudo-pulseless activity represents 42–86% of cases of pulseless activity, and its recognition has a profound impact on resuscitation maneuvers, since the former, if left untreated, can progress into the real form.[28]

ELECTROPHYSIOLOGICAL MECHANISM

Pulseless electrical activity results from inadequate coronary perfusion pressure and secondary diffuse myocardial ischemia from different causes: myocardial injury, infarct, systemic shock, sepsis, pulmonary embolism, and pneumothorax.[27,29] The incidence of postdefibrillation pulseless electrical activity when defibrillation is performed 5–8 minutes after the occurrence of ventricular fibrillation is around 50%.[5] Other than ventricular fibrillation duration, a drop in the mean arterial pressure and arterial oxygen concentration and a rise in arterial potassium and carbon dioxide concentrations are strictly correlated to the onset of pulseless electrical activity.[5] Cardiac sympathetic efferent stimulation can also promote pulseless electrical activity by increasing the heart rate, cardiac work, and oxygen consumption.[30]

Pseudo-pulseless activity is secondary to a significant pathophysiological event, such as profound hypovolemia, cardiac infarction, pulmonary embolism, tension pneumothorax, cardiac tamponade, tachydysrhythmias, or hypocontractile states with profound vasodilation that impairs the cardiovascular ability to perfuse tissues. It can be considered a state of cardiogenic shock, with a low perfusion pressure resulting in a nondetectable pulse.[28]

ELECTROCARDIOGRAPHIC FINDINGS

Pulseless electrical activity is usually a bradycardic rhythm with different electrocardiographic appearances:[26]

- 1) Normal QRS complexes, isoelectric ST segments, and normal T waves (29%).

- 2A) Atrial activity, wide QRS complexes, and abnormal ST segments and T waves (39%).
- 2B) Same appearance as group 2A, but with no atrial activity (12%).
- 3) Monophasic slurred RST complexes (10%).[26]

Another study showed that 90% of cases of pulseless electrical activity had wide QRS complexes, 63% had wide and slow QRS complexes, and only 6% had normal P-QRS-T complexes. No unique cause-specific electrocardiographic pattern can be identified.[31] In the dog, the most documented appearance is that of group 3, a wide and slow pattern (Fig. 23.4).[2]

Electrocardiographic findings in cases of pseudo-pulseless activity are very similar to those in patients with the real form, and only the presence of weak ventricular contractions detected with echocardiography or arterial doppler flow can differentiate the two entities.[28]

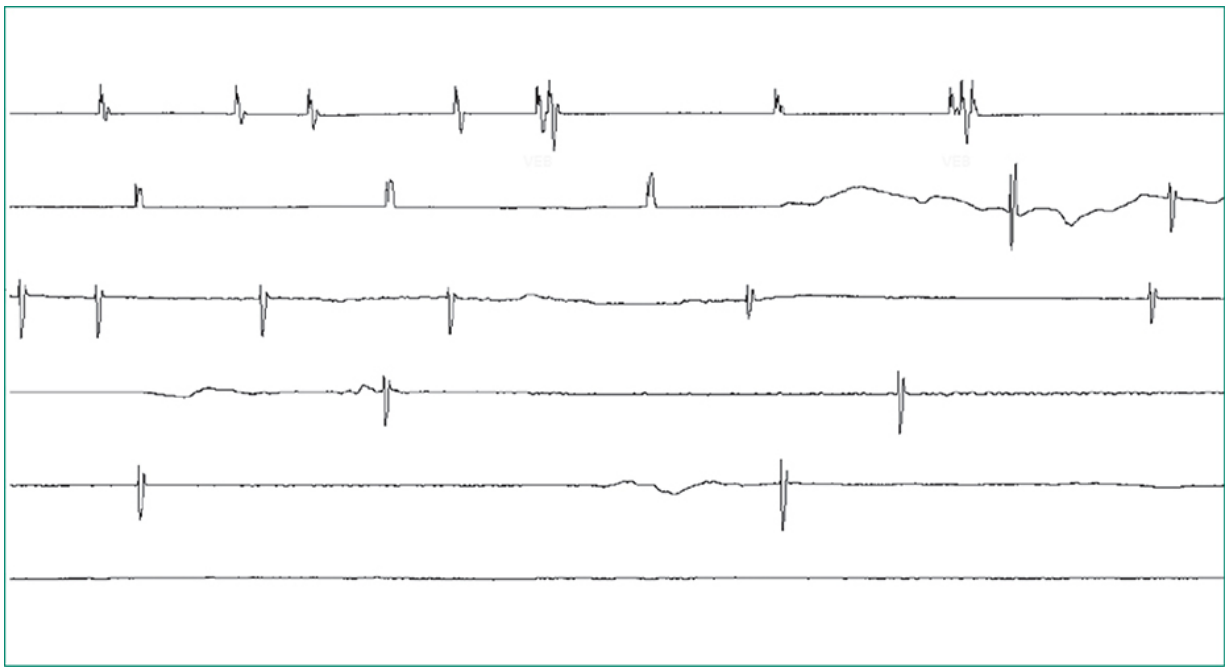


FIGURE 23.4. Ambulatory electrocardiographic recording showing sudden cardiac death in a 16-year-old female Poodle with malignant vasovagal syncope. The dog experienced several consecutive type 1A ventricular arrests of variable duration, followed by a wide QRS complex rhythm with no palpable pulse and a progressively slower rate and final asystole suggestive of pulseless electrical activity. Y lead; each line corresponds to 10 seconds. Speed, 3.6 mm/s; calibration, 5 mm/1 mV.

THERAPY

Both real and pseudo-pulseless electrical activity are nonshockable rhythms that require aggressive resuscitation maneuvers and compressions synchronized with ventricular systole to increase coronary perfusion and blood flow throughout the body.[7,8,28] After basic life support starts, administration of low-dose epinephrine (0.01 mg/kg IV) and/or vasopressin (0.8 U/kg IV) every 3–5 minutes early during cardiopulmonary resuscitation is recommended to improve survival and neurological outcome.[28,32] When prolonged cardiopulmonary arrest has occurred for more than 10 minutes, high-dose epinephrine (0.1 mg/kg IV) and bicarbonate therapy (sodium bicarbonate, 1 mEq/kg IV) should be administered.[7,8] Chronotropic drugs such as atropine are usually not effective, unless very high doses are considered.[33]

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SECTION VI

SPECIFIC DISEASES

CHAPTER 24

Familial ventricular arrhythmias

Romain Pariaut

DEFINITION

Familial ventricular arrhythmias affect young animals. They are characterized by the absence of obvious structural heart disease, periods of polymorphic ventricular arrhythmias, and a risk of sudden cardiac death. In some cases, they can be associated with the presence of a long QT interval during sinus rhythm.

VENTRICULAR ARRHYTHMIA IN GERMAN SHEPHERD DOGS

German Shepherd inherited ventricular arrhythmia is the best studied and recognized form of familial ventricular arrhythmias. Puppies usually develop the arrhythmia after 12 weeks of age.[1] The arrhythmia worsens in frequency and complexity until approximately 28 weeks and starts declining afterwards.[2] Dogs between 4 months and 1 year of age are considered to have the highest risk of sudden cardiac death. In animals that

survive beyond 2 years, the arrhythmia progressively dissipates. There are, however, rare reports of dogs dying suddenly beyond that age limit.[3] Overall, it is estimated that 15% to 20% of affected dogs experience sudden cardiac death.[3] The disease remains asymptomatic throughout its course, and the clinical diagnosis is only based on the detection of an arrhythmia on physical examination, an electrocardiogram, or Holter recording. Because the arrhythmia is more prevalent during periods of slow heart rate (bradycardia-dependent), it might not be present on physical examination or on an electrocardiogram in a clinical setting when the animal is stressed and tachycardic (Fig. 24.1). Therefore, a 24-hour Holter is the best method to detect affected animals. The arrhythmia is often first detected when young dogs are anesthetized to be neutered, as the slowing of the heart rate associated with sedatives and anesthesia promotes the arrhythmia. There are no significant abnormalities on bloodwork, thoracic radiographs, and the echocardiogram, and no lesions on gross examination of the heart.[1,3,4] The arrhythmia is characterized by rapid (occasionally over 400 to 450 bpm), nonsustained runs of polymorphic ventricular tachycardia occurring during periods of bradycardia and after pauses, in the absence of a prolongation of the QT segment during sinus rhythm.[2] Episodes of monomorphic ventricular tachycardia and occasional supraventricular ectopies are identified in some dogs.[1] A young German Shepherd is considered to be affected if more than 10 ventricular premature beats per hour are present on a 24-hour Holter recording. On the surface electrocardiogram, these ventricular ectopies typically have a right bundle branch block morphology in the frontal plane (negative QRS complex in leads II, III, and aVF). Dogs are considered to have a 50% risk of sudden death if they have more than 10 runs of rapid polymorphic ventricular tachycardia over a 24-hour period. The terminal event typically occurs during sleep, specifically during the phase of rapid eye movement (REM) sleep, during rest after exercise and during early morning hours. Dogs free of episodes of polymorphic ventricular tachycardia have a very remote risk of dying suddenly.[1,4]

In this breed, the arrhythmia is described as pause-dependent and is known to be triggered by early afterdepolarizations originating in the Purkinje fibers of the left ventricle.[1,5] Affected dogs also have abnormalities in ventricular repolarization in various parts of the left ventricle that have been attributed to alterations in potassium currents (I_{kr}, I_{ks}, I_{to}) and calcium

currents (I_{CaL}).[1,6–8] In addition, abnormal sympathetic innervation has been identified, mainly α-1 adrenergic fibers in the anterior portion of the interventricular septum and apical, anterior, and lateral portions of the left ventricular free wall.[1,9–12] Delayed afterdepolarzations were shown to be responsible for the episodes of monomorphic ventricular tachycardia found in approximately 17% of dogs.[10]

The exact mode of inheritance has not been determined, nor has a mutation been identified. The offspring of two apparently unaffected dogs can still develop the disease.[1,13]

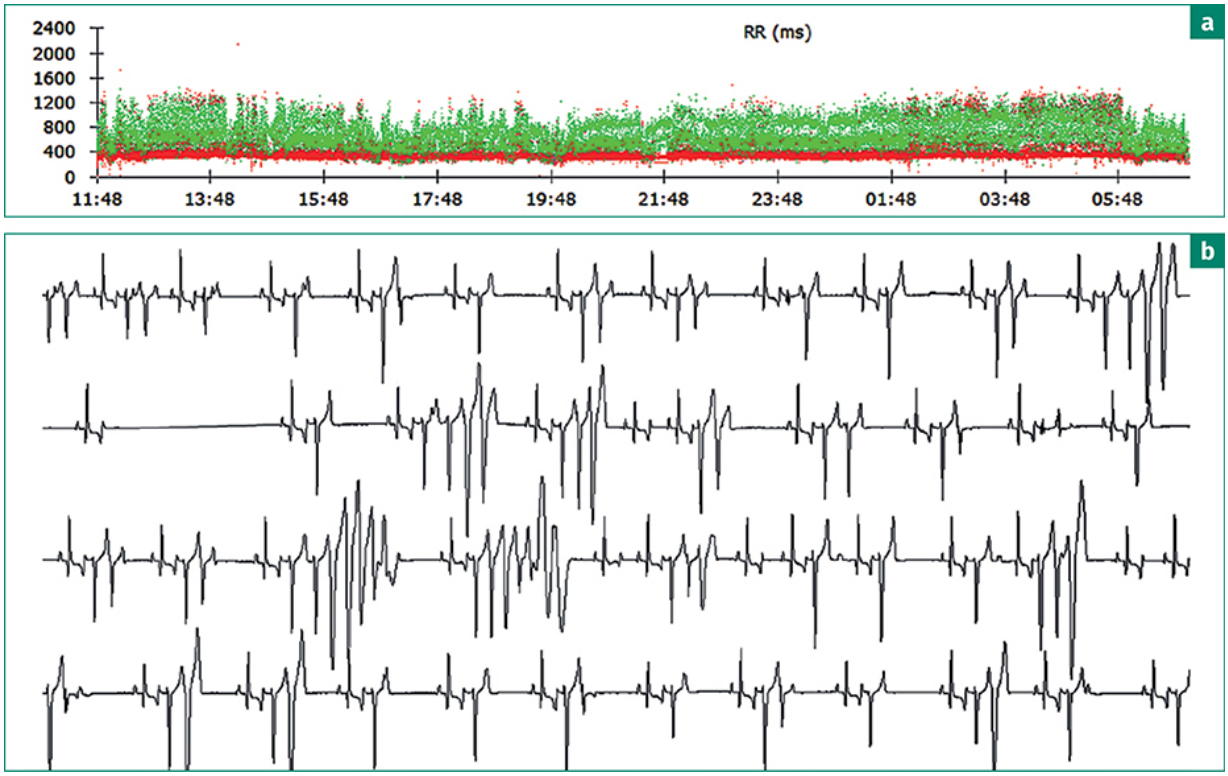


FIGURE 24.1. Holter recording from a 4-month-old male German Shepherd with inherited ventricular arrhythmia. a) Twenty-four-hour tachogram showing the distribution of normal RR intervals (green dots) and ventricular ectopic beats (red dots). Y-axis, RR interval duration; x-axis, hours of the day and night. b) Note the presence of repetitive polymorphic couplets, triplets, and runs of polymorphic ventricular tachycardia always triggered by a pause and a sinus beat. Y lead; each line corresponds to 15 seconds. Speed, 6.1 mm/s; calibration, 5 mm/1 mV.

VENTRICULAR ARRHYTHMIA IN RHODESIAN RIDGEBACKS

Sudden death between the age of 7 and 12 months was reported in 4 related males and females Rhodesian Ridgebacks in the United States.[14] No structural heart disease was identified to explain the death. The animals died during sleep and soon after exercise or excitement. Holter recordings obtained in related dogs showed a moderate ventricular arrhythmia including singles, couplets, triplets, and short runs of ventricular tachycardia (Fig. 24.2). Occasional atrial ectopies and second-degree atrioventricular block were also documented. A DNA variant in the *QIL1* gene was associated with the arrhythmia, and an autosomal recessive mode of inheritance was identified.[14,15] The *QIL1* gene is involved in mitochondrial function. Skeletal muscle biopsy in 1 homozygous affected dog revealed mitochondrial abnormalities consistent with changes previously described in human carriers of a *QIL1* gene mutation.[15] Therefore, this disease has been described as a mitochondrial arrhythmic cardiomyopathy.



FIGURE 24.2. Repetitive polymorphic ventricular tachycardia in an 8-month-old male Rhodesian Ridgeback with juvenile ventricular arrhythmias. Note the presence of wide QRS complexes (90 ms) with variable morphology on a beat-to-beat basis and a ventricular rate of 250–280 bpm. Each run of polymorphic ventricular tachycardia is triggered by a previous sinus beat. Six limb leads (I, II, III, aVR, aVL, aVF); speed, 50 mm/s; calibration, 5 mm/1 mV.

VENTRICULAR ARRHYTHMIA IN LEONBERGERS

Sudden death with no obvious cause and no prodromes has been observed in Finland in Leonbergers between 2 months and 3 years of age.[16] In a small cohort of dogs considered to be affected based on Holter recordings, 2 out of 14 dogs suddenly died 8 and 11 months after the initial diagnosis.[16] The terminal event typically occurs during periods of rest preceded or not by a period of exercise. The postmortem evaluation does not show any macro- or microscopic changes in the heart. In dogs suspected to be affected, Holter recordings reveal a moderate ventricular arrhythmia burden including singles, couplets and triplets of variable morphology, and short runs of rapid monomorphic and polymorphic ventricular tachycardia (Fig. 24.3). The ventricular arrhythmia appears to be more prevalent during periods of slower heart rate, pronounced sinus arrhythmia and during rest after exercise, but it is not always preceded by a long RR interval. This disease is not associated with a prolonged QT interval during sinus rhythm. Because affected dogs may only have a moderate number of ventricular arrhythmias over a 24-hour period, a 3- to 5-min surface electrocardiogram might not be adequate to identify affected dogs. The mode of inheritance of this familial idiopathic ventricular arrhythmia is unknown.[16]



FIGURE 24.3. Repetitive polymorphic ventricular tachycardia in an 11-month-old male Leonberger with juvenile ventricular arrhythmia. Notice the presence of wide QRS complexes (80 ms) with variable morphology on a beat-to-beat basis and a ventricular rate of 270–600 bpm. Each run of polymorphic ventricular tachycardia, single ventricular ectopic beat, or couplet is triggered by a previous sinus beat. Lead II; speed, 50 mm/s; calibration, 5 mm/1 mV.

VENTRICULAR ARRHYTHMIA WITH LONG QT SYNDROME

An inherited long QT syndrome was identified in 3 littermates from a 5-year-old female English Springer Spaniel that died suddenly a few months after delivering her offspring. Two of the puppies subsequently died at 5 and 7 months of age. All dogs died while being active or soon after exercise. None of the dogs experienced clinical signs before they died suddenly. The corrected QT interval of the affected puppies was 304 to 314 ms using Van De Water's formula, compared to 218 to 265 ms in unaffected dogs (Fig. 24.4). The QT/TQ ratio was >1 in all affected dogs. In addition, the affected dogs had a large-amplitude biphasic T wave. A missense mutation in the *KCNQ1* gene, which codes for the alpha subunits of the slow-activating delayed rectifier potassium channel (I_{kr}), was found to be the cause of the QT prolongation in these dogs. It can be compared to long QT syndrome type 1 (LQT1) in people, which is associated with syncope and sudden death from torsade de pointes progressing to ventricular fibrillation. The clinical manifestations of LQT1 are typically triggered by a high sympathetic tone.[17]



FIGURE 24.4. Sinus rhythm with long QT syndrome in a 2-year-old female Springer Spaniel. Note the presence of a prolonged QT interval (300 ms), normal QRS complex duration and axis, and a normal ventricular rate of 120 bpm. Six limb leads (I, II, III, aVR, aVL, aVF); speed, 50 mm/s; calibration, 10 mm/1 mV.

TREATMENT OF FAMILIAL VENTRICULAR ARRHYTHMIAS

Various treatment strategies have been investigated to decrease the risk of sudden cardiac death in German Shepherds with inherited ventricular arrhythmias. Bradycardia should be avoided whenever affected dogs are managed in the clinical setting, for example at the time of an anesthetic event. Increasing the heart rate with atropine, glycopyrrolate, or isoproterenol typically eliminates the arrhythmia if the heart rate is maintained above 130 bpm. Transvenous or transthoracic pacing is another effective method to keep a constant and elevated heart rate. Intravenous lidocaine at 2 mg/kg also suppresses the arrhythmia.[1] Chronic management of those affected dogs considered to be at high risk of sudden cardiac death is frustrating as no antiarrhythmic protocol works very well at decreasing the arrhythmia burden. A mild reduction in the number of ventricular ectopies may be observed with a combination of mexiletine (5 to 8 mg/kg every 8 hours) and sotalol (2 to 3 mg/kg every 12 hours). Sotalol alone worsens the arrhythmia.[18] Commonly, a similar approach is chosen in young dogs from other breeds suspected to have a bradycardia-induced ventricular arrhythmia, although published data is lacking.

In dogs with a ventricular arrhythmia associated with a prolonged QT segment, the use of ß-blockers might be helpful based on the positive response observed in people with LQT1 syndrome.[17]

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CHAPTER 25

Arrhythmias in left ventricular hypertrophy

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DEFINITION

Left ventricular hypertrophy is a condition in which an increase in left ventricular mass occurs secondary to an increase in wall thickness or left ventricular enlargement.[1]

In cats, *hypertrophic cardiomyopathy* is the most common structural heart disease leading to left ventricular hypertrophy. In general terms, hypertrophic cardiomyopathy is a primary myocardial disease that most commonly causes either regional asymmetric or diffused thickening of the left ventricular myocardium in the absence of other cardiovascular causes. This condition is associated with a reduction in left ventricular chamber size and impaired ventricular relaxation, which, together with concentric hypertrophy, impede diastolic filling. The current proposed classification of this disease is based on structural and functional characteristics; therefore, it does not distinguish between specific disease entities but rather between phenotypic categories.[1–5] These phenotypic categories include cardiomyopathies of different causes such as sarcomeric gene mutation, hyperthyroidism, hypertension, neoplastic infiltration, acromegaly, and transient myocardial thickening.[1] In order to describe the clinical impact of hypertrophic cardiomyopathy in cats, a staging system adapted from those of the American Heart Association and American College of Veterinary Internal Medicine has been proposed (Table 25.1).[1]

The estimated prevalence of hypertrophic cardiomyopathy phenotypes is approximately 15% in the general cat population; however, the prevalence increases in older cats, with up to 29% of affected patients. The left ventricular hypertrophy is commonly associated with right ventricular hypertrophy, which depends on the severity of the increase in left ventricular wall thickness and the patient's clinical status.[1–6] Most cats with a hypertrophic cardiomyopathy phenotype present with a subclinical disease, with a 5-year incidence of cardiac mortality of approximately 23%, independently of the age at diagnosis. The most common cause of clinical signs is congestive heart failure, followed by arterial thromboembolism; in a minority of cases, sudden cardiac death occurs with no previous clinical signs. Many cats with hypertrophic cardiomyopathy are identified incidentally when a cardiac murmur is heard on auscultation. Most affected cats are nonpedigree breeds, although some breeds are believed to be at increased risk, such as the Maine Coon, Ragdoll, British Shorthair, Persian, Bengal, Sphynx, Norwegian Forest Cat, and Birman. There is a male predisposition to the disease in both human and veterinary medicine, and clinical signs are similar although more common and more severe in the feline population.[1–5]

TABLE 25.1. Staging system for hypertrophic cardiomyopathy.

Stage	Definition
A	Cats at risk for developing hypertrophic cardiomyopathy in the future
B1	Cats with cardiomyopathy without clinical signs and with normal left atrial dimensions
B2	Cats with cardiomyopathy without clinical signs and with left atrial enlargement, left ventricular systolic dysfunction, extreme left ventricular hypertrophy
C	Cats with clinical signs (past or current) such as congestive heart failure and arterial thromboembolism
D	Cats with clinical signs refractory to the treatment

In dogs, the most common cardiac diseases associated with left ventricular hypertrophy are obstructive diseases of the left ventricle. *Subaortic stenosis* causes an increase in left ventricular afterload that induces left ventricular hypertrophy, the degree of which depends on the severity of the stenosis. The disease is characterized by the presence of nodules, a ridge, or a ring of fibrous tissue located below the aortic valve that obstructs the left ventricular outflow tract. The anatomical obstruction increases the left ventricular pressure, resulting in increased aortic outflow tract velocity.[7–11] Mildly affected dogs tend to have a normal lifespan, but severely affected dogs have an average lifespan of 19 months.[7] Severely affected dogs have an increased risk of developing cardiac complications that include sudden death, congestive heart failure, syncope, and endocarditis. Pyle and Patterson[8] described a wide range of phenotypes in Newfoundland dogs, from more subtle fibrous nodules to severe tunnel-like lesions of the left ventricular outflow tract, but determining the phenotype of affected dogs may be challenging. In Newfoundlands, the severity of the disease could not be predicted based on the breeding pair, meaning that even mildly affected individuals can produce severely affected offspring.[8] The disease has also been described to be progressive in nature, and dogs must reach skeletal maturity before the severity of the disease can fully established.[8] Subaortic stenosis has been described to be more common in some breeds such as Boxers, Newfoundlands, Rottweilers, German Shepherds, and Golden Retrievers.[7–11] Based on the higher incidence of subaortic stenosis in these breeds, an underlying genetic cause has been suggested. The mode of inheritance for subaortic stenosis in dogs is reported to be complex and variable.[7] This finding is similar to what has been observed in human medicine, in which autosomal recessive and autosomal dominant modes of inheritance have been described.[7] In dogs, an autosomal recessive mode of inheritance has been reported for the Bullmastiff, Golden Retriever, and Rottweiler.[7] Pedigree evaluation for the Dogue de Bordeaux has also suggested an autosomal recessive pattern of inheritance.[7] The variety of modes of inheritance described within and among the different breeds might be due to the possibility of multiple genetic variants causing this disease in subpopulations of a breed.[7]

Left ventricular hypertrophy has also been described in dogs in the absence of subaortic stenosis, and hypertrophic cardiomyopathy should be taken into consideration as a differential diagnosis.[12] Hypertrophic cardiomyopathy is a rare disease in dogs, although it has been identified in many breeds. It has been more particularly reported in male dogs of large breeds such as German Shepherds, Rottweilers, Dalmatians, German Shorthaired-Pointers, Weimaraners, Boxers, and Golden Retrievers; however, more recent data suggest that hypertrophic cardiomyopathy is also found in small breed dogs, in particular in terrier breeds.[12] The age at diagnosis of dogs with hypertrophic cardiomyopathy ranges from 3 months to 14 years, with approximately one third of dogs younger than 2 years at diagnosis.[12] The main pathophysiological mechanism is a malformation of the mitral valve anterior leaflet leading to dynamic obstruction of the left ventricular outflow tract, which acts as an underlying or contributing cause of concentric left ventricular wall thickening. Evidence of reverse remodeling has been observed in some patients after ß-blocking agent therapy. In this population of dogs, although left ventricular diastolic dysfunction was frequently recorded, the left atrial dimensions were usually unremarkable, and the disease was not usually correlated with clinical signs of congestive heart failure.[12]

PATHOPHYSIOLOGY

In human medicine, more than 1500 causative mutations are now known to be associated with hypertrophic cardiomyopathy phenotypes, with the vast majority of them identified in one of the 11 sarcomeric genes. Nonetheless, up to 30% of human beings with a hypertrophic cardiomyopathy phenotype have no identified mutation. In these cases, the disease may be attributable to a novel mutation in either noncoding gene sequences or in other genes encoding for proteins closely associated with sarcomere function, such as calcium handling proteins.[4,5] Furthermore, humans with sarcomeric gene mutations express a wide range of phenotypes, from no apparent disease to extreme wall thickening, and a wide range of clinical outcomes, from no disease sequelae to sudden death and heart failure. In cats, only three mutations have been identified, two in the myosin-binding protein C gene

(*MYBPC3*)[13,14] and one in the *ALMS1* gene in Sphynx cats.[15] The A31P mutation in *MYBPC3* has been described in Maine Coon cats with an estimated prevalence of 35–42% and a reported penetrance of 6–8% in A31P heterozygotes and 58–80% in A31P homozygotes, while the R820W mutation in *MYBPC3* has been identified in Ragdoll cats. In both humans and cats, some patients with these mutations have mild cardiac abnormalities, while others with the same mutation and in the same family exhibit severe cardiac changes and clinical signs. These variable genotype–phenotype relationships suggest there are other genetic or epigenetic modifiers of the hypertrophic phenotype.[13–15]

Abnormal genes and their associated gene products (e.g., proteins) result in clinical disease. An abnormal gene can cause disease through two straightforward mechanisms: impaired function of the abnormal proteins and reduction in the amount of protein. While it is intuitive that mutations disrupting sarcomere function could cause a decrease in contractile force, many mutations leading to hypertrophic cardiomyopathy cause an increase in contractile activity. Myocardial hypercontractility may be one trigger for hypertrophy.[14] From the histological point of view, hypertrophic cardiomyopathy is defined by four processes dominated by intense remodeling in association with degenerative changes: myocyte hypertrophy, myocyte and myofibrillar disarray, small vessel disease, and fibrosis. Myocyte and myofibrillar disarray are likely due to a direct effect of the abnormal proteins on the myocyte structure, while the presence of fibrosis and small vessel disease is attributable to indirect factors such as left ventricular mass, sex, and perhaps local autocrine factors.[1–7,16] Fibrosis appears to be the final common pathway in most forms of cardiomyopathies. Hypertrophic cardiomyopathy is also associated with a proinflammatory environment in which the myocardial transcription of cytokines (e.g., IL1ß and TNFα) is upregulated.[17] The remodeling process affects both the interstitium and the cardiomyocytes. The interstitium has been found to contain a significantly increased amount of collagen and an increased number of interstitial cells with a macrophage phenotype. Smooth muscle actin-positive cells are more numerous, which indicates an increase in interstitial vessels. In addition, myocytes have been found to be focally replaced by patchy areas of cell-rich fibrosis with embedded macrophages and neovascularization. These histological changes are associated with the

onset of ventricular tachycardia and the risk of sudden cardiac death.[17] In human medicine, ventricular tachycardia has been shown to be a common arrhythmia in patients affected by hypertrophic cardiomyopathy. Hypertrophic cardiomyopathy in human beings is usually associated with sustained monomorphic ventricular tachycardia, which represents almost 80% of the total ventricular arrhythmia burden. In addition, the occurrence of ventricular tachycardia is associated with a phenotype characterized by a decreased left ventricular ejection fraction and increased left ventricular end-diastolic and end-systolic dimensions. Ventricular tachycardia can trigger sudden cardiac death, which is considered a feared complication in hypertrophic cardiomyopathy patients. In human medicine, sudden cardiac death occurs in less than 1% of the general hypertrophic cardiomyopathy population, although some phenotypes carry a much higher risk.[18] In human beings, a positive family history for sudden cardiac death and a personal history of ventricular tachycardia are two major risk factors.

Transient myocardial thickening is a sporadically identified phenomenon characterized by a hypertrophic cardiomyopathy phenotype that resolves spontaneously within a median time of 2 to 5 months. Transient myocardial thickening is characterized by thickening of the left ventricular walls and left atrial enlargement considered mild to moderate if compared with familial hypertrophic cardiomyopathy complicated by congestive heart failure, even if substantial overlap exists. Even if the etiology remains in most cases unknown, it has been speculated that the thickening is due to myocardial edema secondary to myocarditis[19–21] and the association between transient myocardial thickening and *Bartonella henselae* and *Toxoplasma* infection has been described.[22,23] The suspected myocardial injuries due to diffuse edema are thought to cause transient atrioventricular and intraventricular rhythm disturbances and abnormalities of the repolarization phase in affected cats.[22,23]

Increased left ventricular wall thickening has also been associated with hyperthyroidism, which is considered the most common endocrine diseases in middle-aged and old cats. The increased levels of thyroid hormones affect the function of many organs, including the heart. Hyperthyroid cats show an increased cardiac mass and larger heart dimensions (both height and width). The hypertrophy in these cats is more common at the level of the free wall than at the interventricular septum, with severe histological

abnormalities including nuclear enlargement and hyperchromasia, interstitial fibrosis, endocardial fibroplasia, and marked disorganization of the cardiac muscle cells. These histological changes are present despite the lack of obvious cardiomegaly or gross cardiac hypertrophy.[24]

Subaortic stenosis in dogs is associated with concentric hypertrophy of the left ventricle, which may be associated with dilation of the left ventricle and atrium. On gross examination, irregular, patchy areas have been described in the subendocardial portions of the papillary muscles. These findings represent the macroscopic evidence of recent infarction involving the inner portion of the left ventricular myocardium. On histological examination, numerous irregular and dense collagenous areas have been described in the left ventricle that vary in size but are more common at the level of the anterior papillary muscle. Necrotic and often calcified muscle fibers have also been reported in or adjacent to these fibrous scars. Furthermore, subaortic stenosis is accompanied by extensive alterations of the intramural branches of the coronary arteries within the left ventricle but not within the right ventricle. These intramural coronary lesions consist of fibrous intimal proliferation together with fibrous replacement of the medial smooth muscle, intimal thickening, and fragmentation of the elastic lamina.[25]

All the histological lesions previously described in the different types of left ventricular hypertrophy represent the substrate for the onset of ventricular tachycardia. Scar lesions constitute the anatomical substrate for reentrant circuits within the ventricle, with the scar area serving as the site of slow conduction and unidirectional block among the normal myocytes.[26–28] Unidirectional blocks may also be caused by spatial changes in refractoriness or by a nonuniformly anisotropic substrate leading to reentrant ventricular tachycardia, as shown in some canine experimental models.[26]

CLINICAL PRESENTATION

Auscultatory abnormalities such as a left basal systolic murmur, a gallop heart sound, or an irregular rhythm are the most common findings on physical examination in cats with a hypertrophic cardiomyopathy phenotype. Although these abnormalities are correlated with hypertrophic

cardiomyopathy, none is specific or pathognomonic for the disease, even if gallop and irregular rhythms are major predictors of cardiac mortality. The absence of auscultatory abnormalities does not preclude the presence of a hypertrophic cardiomyopathy phenotype.[1–5]

Advanced structural heart diseases are associated with congestive heart failure and arterial thromboembolism. In a retrospective study in 50 cats with atrial fibrillation,[29] this arrhythmia was shown to be mainly due to severe left atrial enlargement, and it was associated with clinical signs (dyspnea, signs of arterial thromboembolism, or ascites) in 56% of cases. Atrial fibrillation was an incidental finding in 11% of cases, but since atrial fibrillation needs a critical atrial mass to be induced and maintained, it is considered an indicator of underlying structural heart disease even in the absence of clinical signs.[29]

Cats with transient myocardial thickening usually present with severe signs of congestive heart failure (alveolar cardiogenic pulmonary edema). Dogs presenting with atrioventricular and/or intraventricular conduction abnormalities can have a slow heart rate, signs of generalized weakness, and transient loss of posture or transient loss of consciousness.[19–23]

Subaortic stenosis in dogs is associated with a left basal systolic murmur and, in general, the severity of the disease is correlated with the severity of the murmur. None of the dogs with soft murmurs due to subaortic stenosis included in a 2018 study had transvalvular pressure gradients greater than 50 mmHg.[30]

Subaortic stenosis in dogs can also be associated with signs of illness varying from generalized weakness to syncope and respiratory signs. Exercise intolerance has been reported in 23% of affected dogs, syncope in 11.4%, and respiratory signs (cough, dyspnea, tachypnea) due to left-sided congestive heart failure in 9.3%. Sudden cardiac death has been reported in 21.8% of cases.[11]

Dogs with hypertrophic cardiomyopathy usually exhibit a basal left systolic cardiac murmur due to the obstruction of the left ventricular outflow tract. This condition is rarely associated with clinical signs.[12]

ARRHYTHMIAS IN LEFT VENTRICULAR HYPERTROPHY

Familial hypertrophic cardiomyopathy can lead to different rhythm disturbances including atrial and ventricular premature ectopic beats, atrial and ventricular tachycardia, and atrial fibrillation.[1,2,31]

Subaortic stenosis with left ventricular hypertrophy can be associated with ventricular rhythm disturbances as a consequence of left ventricular and coronary vessel remodeling. In humans, a prominent Q wave in the inferior leads has been described as a marker of septal hypertrophy in patients with subaortic stenosis.[32]

No rhythm disturbances are reported in dogs affected by hypertrophic cardiomyopathy.[12]

QRS COMPLEX ABNORMALITIES

Cats with hypertrophic cardiomyopathy have been reported to exhibit a prominent J wave. The J wave is a positive deflection found at the R-ST segment junction. Previous reports have described the J wave as a normal electrocardiographic variant in humans, baboons, and dogs, while other studies have documented J waves in pathological conditions such as hypercalcemia, ischemic heart disease, left ventricular hypertrophy, and malignant arrhythmias.[33] Currently, there is no explanation for the electrophysiological mechanism inducing the presence of J waves in some patients, even if a difference in the action potential values between the ventricular endocardium and epicardium during phase 1 (early repolarization phase) of the action potential has been suggested. According to this theory, a prominent transient outward current in the ventricular epicardium elicits a transmural voltage gradient generating a J wave. A J wave has been reported to be present in 63% of cats affected by the familial form of hypertrophic cardiomyopathy, while it is completely absent in the normal population.[33] The amplitude of the J wave in hypertrophic cats is reported to be 0.06 ± 0.02 mV, with a duration of 0.16 ± 0.05 ms in lead II.[33] The J wave has also been described in human patients with hypertrophic cardiomyopathy, in whom intraventricular conduction delay is

a common observation. Myocardial scarring in this population causes conduction disturbances that can lead to J wave genesis.[33]

PREMATURE ATRIAL ECTOPIC BEATS AND SUPRAVENTRICULAR TACHYCARDIAS

Premature atrial ectopic beats can arise from different areas of the atrial myocardium and from the tributary veins. Premature atrial ectopic beats are characterized by normal QRS complexes preceded by atrial depolarizations with variable polarity in the frontal plane depending on the site of origin. Depending on the degree of prematurity and the atrioventricular conduction time, the atrial depolarization may be fused with the previous T wave (Fig. 25.1). The QRS complex in usually normal in duration, with a normal axis in the frontal plane. Atrial ectopic beats can also be organized in couplets, triplets, and allorhythmias.

A study using 24-hour Holter monitoring has shown that cats with the familial asymptomatic form of hypertrophic cardiomyopathy had more frequent and complex ventricular and supraventricular arrhythmias than normal cats, but they did not have different heart rates.[34] Supraventricular arrhythmias were present in 88% of cats with familial hypertrophic cardiomyopathy, with 23% exhibiting complexity (Fig. 25.2). On the other hand, 60% of normal cats had supraventricular rhythm disturbances, with 13% exhibiting complex forms. Cats with hypertrophic cardiomyopathy had significantly more atrial ectopic beats than normal cats.[34,35]

Atrial fibrillation is a rhythm disturbance associated with increased left atrial dimensions in cats affected by familial hypertrophic cardiomyopathy. Atrial fibrillation is typically characterized by narrow QRS complexes (<40 ms), irregular RR intervals, and absence of obvious signs of atrial depolarization (Fig. 25.3). While supraventricular tachycardias may be found in normal cats, atrial fibrillation is usually observed in cats with advanced structural heart disease, and the left atrial diameter is significantly wider in cats with atrial fibrillation than in those presenting with supraventricular tachycardias. Left atrial enlargement is associated with a poor prognosis in cats with acquired heart disease, and consequently, atrial fibrillation has been considered an end-stage event in cats with myocardial disease.[29,35]

The median heart rate obtained from electrocardiographic tracings was higher in supraventricular tachycardias (300 bpm) than in atrial fibrillation (220 bpm).[29,35]



FIGURE 25.1. Atrial premature ectopic beats in a 12-year-old domestic shorthair cat with familial hypertrophic cardiomyopathy. Notice the presence of positive atrial deflections (P waves) with a normal atrioventricular conduction time (80 ms) and a normal QRS complex (40 ms) and the presence of atrial premature ectopic beats (arrows) characterized by a normal QRS complex and a negative atrial deflection superimposed on the T wave of the previous beats. Speed, 50 mm/s; calibration, 20 mm/1 mV.

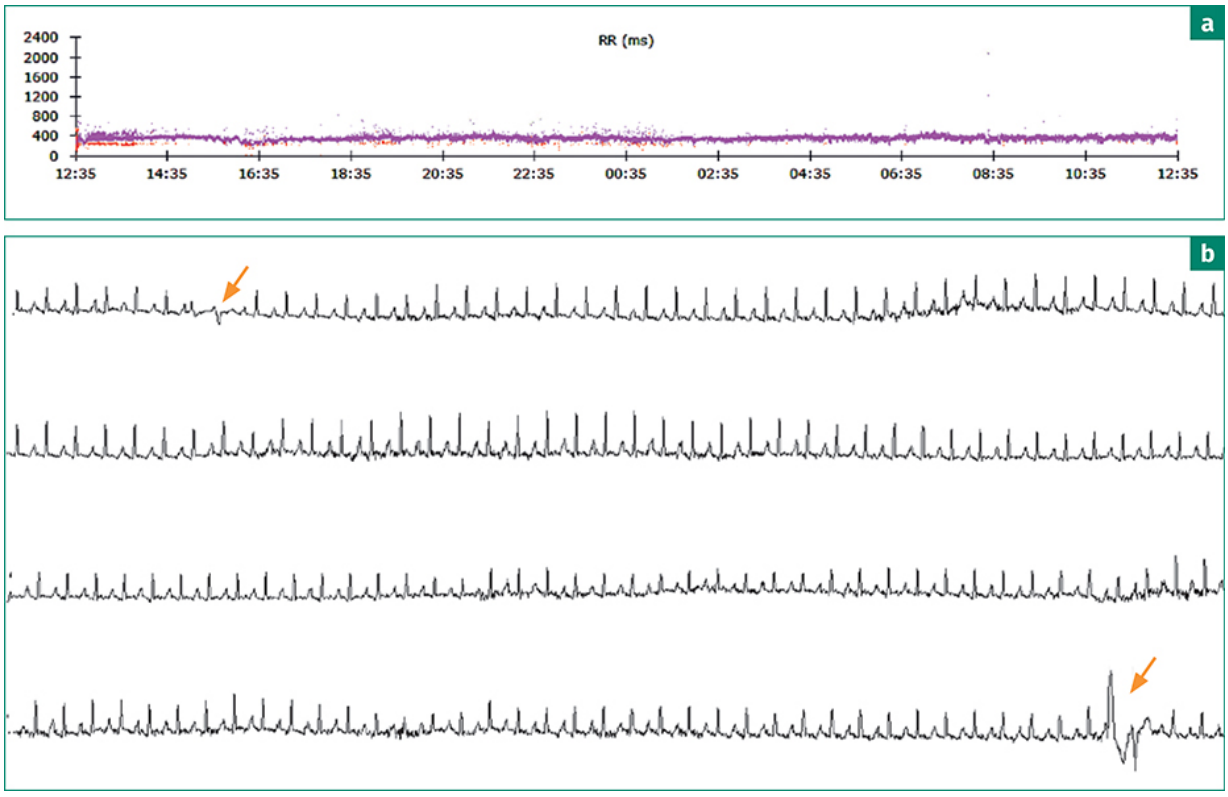


FIGURE 25.2. Holter recording from a 10-year-old Maine Coon cat with familial hypertrophic cardiomyopathy and incessant focal atrial tachycardia. a) Twenty-four-hour tachogram showing the distribution of RR intervals during focal atrial tachycardia (purple dots) and the presence of ventricular ectopic beats in the first part of the monitoring (red dots). Y-axis, RR interval duration; x-axis, hours of the day and night. Note the incessant behavior of the arrhythmia. b) Electrocardiographic recording showing incessant focal atrial tachycardia as the dominant rhythm interrupted by a single premature ventricular ectopic beat and ventricular ectopic beats organized in a

bidirectional couplet (arrows). Each line corresponds to 10 seconds; speed, 2.7 mm/s; calibration, 10 mm/mV.

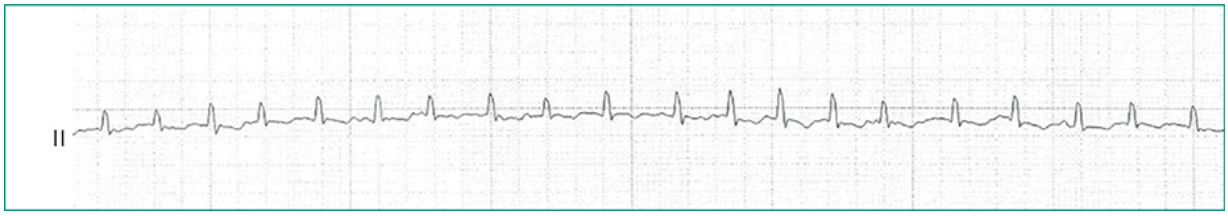


FIGURE 25.3. Atrial fibrillation in a 12-year-old Norwegian Forest Cat with familial hypertrophic cardiomyopathy. Note the presence of a narrow QRS complex (40 ms) tachycardia characterized by irregular RR intervals and the absence of obvious atrial deflections. Lead II; speed, 50 mm/s; calibration, 20 mm/1 mV.

PREMATURE VENTRICULAR ECTOPIC BEATS AND VENTRICULAR TACHYCARDIAS

Familial hypertrophic cardiomyopathy has been reported to be associated with premature ventricular ectopic beats. Cats affected by this disease, either in its subclinical or clinical form, exhibit more ventricular ectopic beats than normal cats. A correlation was found between the number of premature ventricular ectopic beats and cardiac troponin I levels.[34] Premature ventricular ectopic beats usually have a wide QRS complex with bizarre morphology and T wave polarity opposite to that of the QRS complex (Fig. 25.4). Ventricular tachycardias associated with familial hypertrophic cardiomyopathy are usually sustained and monomorphic (Fig. 25.5). In human medicine, 38% of arrhythmias associated with hypertrophic cardiomyopathy are monomorphic ventricular tachycardias in which scar-related reentry is the main mechanism.[36–38] A study in veterinary medicine has shown that all cats affected by familial hypertrophic cardiomyopathy had ventricular arrhythmias on 24-hour Holter monitoring, with 82% of patients exhibiting complex arrhythmias (couplets, triplets, ventricular tachycardia). Most of the normal cats had ventricular arrhythmias, but only 20% exhibited complex forms (Fig. 25.6).[34]



FIGURE 25.4. Ventricular premature ectopic beats in a 13-year-old Maine Coon cat with familial hypertrophic cardiomyopathy. Note the presence of positive atrial deflections (P waves) with a normal atrioventricular conduction time (85 ms) and normal QRS complexes (40 ms) and the presence of premature ventricular ectopic beats (arrows) characterized by a wide QRS complex (65 ms) with a rS morphology. Note also a tall positive T wave and signs of atrioventricular dissociation such as a P wave inscribed in the ST segment of the 2nd and 7th beat and the presence of a fusion beat (fifth beat). Lead II; speed, 50 mm/s; calibration, 20 mm/1 mV.



FIGURE 25.5. Ventricular tachycardia in a 1-year-old domestic shorthair cat with familial hypertrophic cardiomyopathy. Note the wide QRS complex (75ms) tachycardia with a left bundle branch block–like appearance (280 bpm), with a normal axis in the frontal plane. The QRS complex shows a qR morphology in the inferior leads (II, III, aVF), and P waves dissociated from the QRS complex are present (arrows). Six limb leads (I, II, III, aVR, aVL, aVF); speed, 50 mm/s; calibration, 20 mm/1 mV.

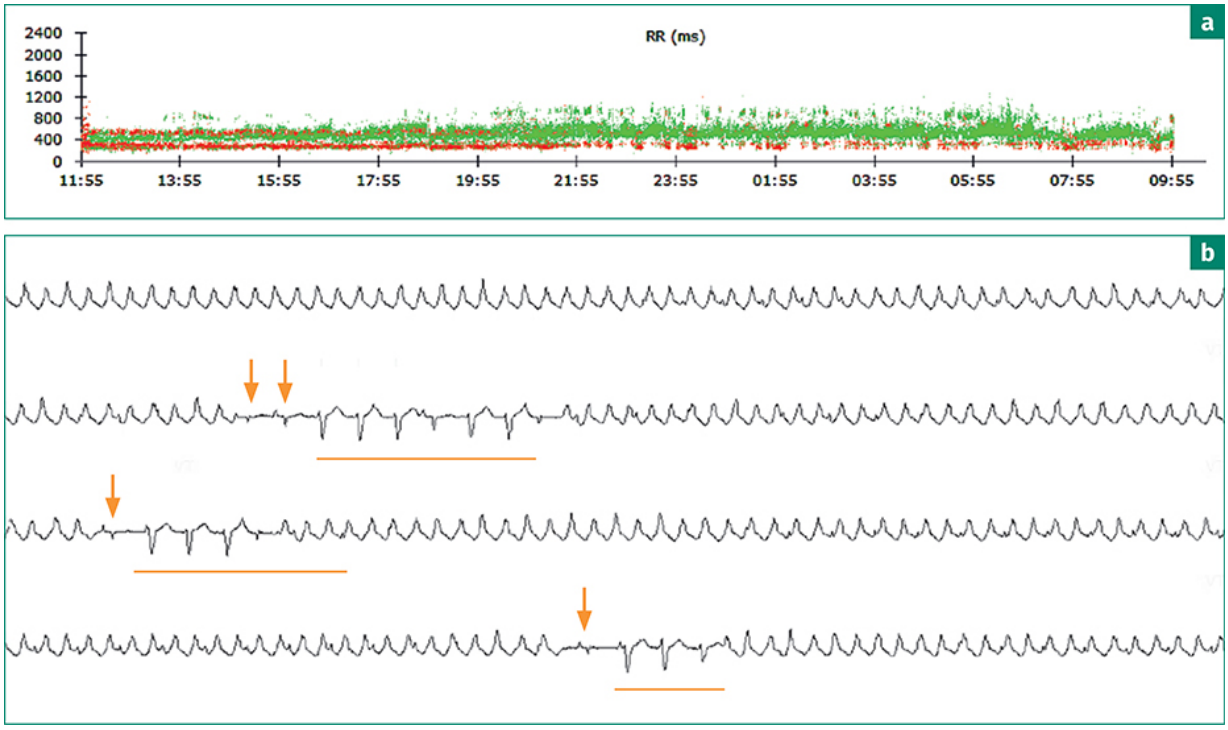


FIGURE 25.6. Holter monitoring in a 10-year-old domestic shorthair cat with familial hypertrophic cardiomyopathy and nonsustained monomorphic ventricular tachycardia. a) Twenty-four-hour tachogram showing the distribution of RR intervals during sinus rhythm (green dots) and the presence of ventricular ectopic beats (red dots). Y-axis, RR interval duration; x-axis, hours of the day and night. b) Electrocardiographic recording showing nonsustained monomorphic ventricular tachycardia characterized by wide QRS complexes and atrioventricular dissociation (P waves dissociated from the QRS complexes) interrupted by sinus beats (arrows) and nonsustained accelerated idioventricular rhythm (horizontal line). Each line corresponds to 10 seconds. Speed, 2.7 mm/s; calibration, 5 mm/mV.

ATRIOVENTRICULAR AND INTRAVENTRICULAR CONDUCTION BLOCKS

The familial form of hypertrophic cardiomyopathy in cats is also associated with conduction disturbances.

The presence of third-degree or complete atrioventricular blocks has been described in a population of cats with hypertrophic cardiomyopathy. Histological findings in cats with hypertrophic cardiomyopathy and atrioventricular and intraventricular conduction blocks have been demonstrated to be consistent with marked degeneration and fibrous replacement of the atrioventricular conduction system, extensive fibrosis of the central fibrous body, and endocardial and myocardial fibrosis in the upper border of the ventricular septum. These changes in the cardiac tissue

have been described to be secondary to a normal aging phenomenon and may have been exacerbated by abnormal mechanical forces due to cardiac hypertrophy.[31,39]

The familial form of hypertrophic cardiomyopathy has also been associated with left anterior fascicular block characterized by normal atrial activation, normal atrioventricular conduction times, and a leftward deviation of the mean electrical axis of the QRS complex in the frontal plane ranging from –30° and –60°. Typically, a qR morphology is present in leads I and aVL, with concomitant deep S waves in the precordial leads (Fig. 25.7). The correlation between structural heart disease and left anterior fascicular block is probably due to the abnormal forces on the left ventricular outflow tract in obstructive forms of hypertrophic cardiomyopathy.[31]

Cats with transient myocardial thickening have been described to be affected by different rhythm disturbances.[21–23] Transient intraventricular conduction disturbances have been reported in association with an increase in wall thickness and in cardiac troponin-I levels.[23] The reported intraventricular conduction disturbances are:

1. Complete left bundle branch block, characterized by normal atrial activation, normal atrioventricular conduction times, and increased QRS complex duration (>40 ms) with a normal mean electrical axis in the frontal plane.
2. Trifascicular block, which is characterized by an alternating pattern of complete right bundle branch block, left bundle branch block, and/or Mobitz type II second-degree atrioventricular block (see p. 323) (Fig. 25.8).

The presence of transient myocardial thickening has also been associated with repolarization abnormalities and ST segment elevation.[21]



FIGURE 25.7. Left anterior fascicular block in a 14-year-old domestic shorthair cat with familial hypertrophic cardiomyopathy. Note the presence of atrial deflections (sinus P waves), a normal atrioventricular conduction time (90 ms), narrow QRS complexes (42 ms) characterized by a leftward deviation of the mean electrical axis in the frontal plane (-30°), deep S waves in the inferior leads (II, III, aVF), and a qR morphology in leads I and aVL. Six limb leads (I, II, III, aVR, aVL, aVF); speed, 50 mm/s; calibration, 20 mm/1 mV.

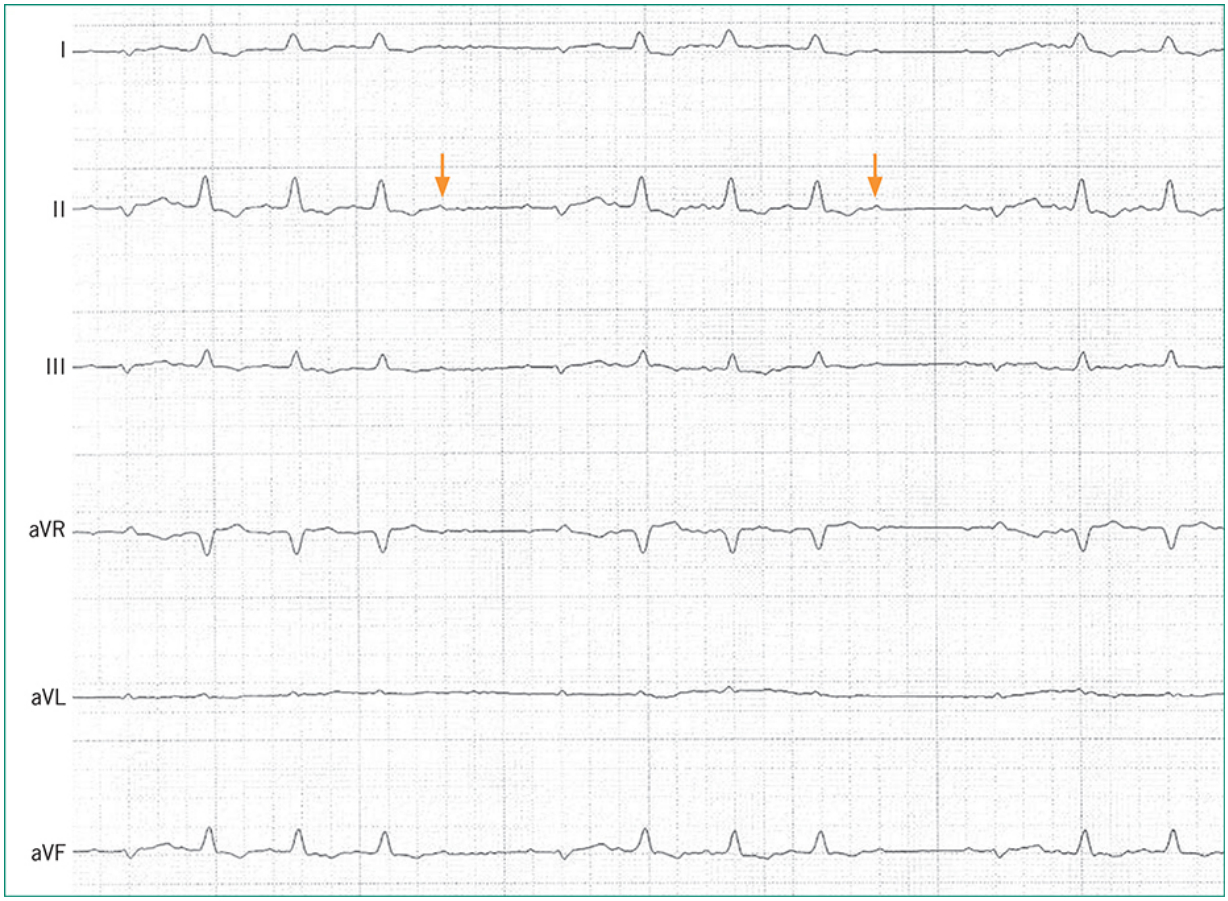


FIGURE 25.8. Trifascicular block in a 7-year-old domestic shorthair cat with transient myocardial thickening. Note the presence of an alternating pattern of complete right bundle branch block (1st, 5th, 9th beats), complete left bundle branch block (2nd, 3rd, 4th, 6th, 7th, 8th, 10th, 11th beats), and second-degree atrioventricular block (arrows). Six limb leads (I, II, III, aVR, aVL, aVF); speed, 50 mm/s; calibration, 20 mm/1 mV.

DIAGNOSIS

Echocardiography is considered the gold standard for diagnosing hypertrophic cardiomyopathy phenotypes.[1–3] It is now widely accepted that symmetric or asymmetric left ventricular hypertrophy must be present with a ventricular septal thickness 6 mm or greater and an equivocal zone between 5.5 and 5.9 mm to confirm a diagnosis of hypertrophic cardiomyopathy. Importantly, these values have to be interpreted on a patient-specific basis and include the use of breed and weight-based references values when available. The purpose of the echocardiographic examination is to determine the presence of left ventricular wall

hypertrophy, systolic anterior motion of the mitral valve leaflet and left ventricular outflow tract obstruction, systolic dysfunction, diastolic dysfunction, and left atrial dilation with decreased function, including the possible presence of smoke artefact or thrombotic lesions at the level of the left atrial chamber. In veterinary medicine, hypertrophic cardiomyopathy phenotypes can be obstructive or nonobstructive, while in human medicine multiple anatomical variants have been described. Left ventricular systolic function has been reported to be decreased in some cats with a hypertrophic cardiomyopathy phenotype.[1–3] The progressive myocardial fibrosis associated with hypertrophic cardiomyopathy leads to worsening of the left ventricular diastolic function. Doppler parameters such as transmitral flow and mitral annular tissue velocities are indispensable to assess diastolic function. In human medicine, cardiac magnetic resonance imaging has become the gold standard in patients with a hypertrophic cardiomyopathy phenotype, because this examination allows a complete assessment of the left and right ventricles and wall thickness as well as myocardial tissue characterization and evaluation of cardiac volumes.[40]

Even if echocardiography is still the gold standard, in veterinary medicine, biomarkers are now widely used for screening of hypertrophic cardiomyopathy phenotypes and diagnosis of respiratory distress secondary to cardiac disease. The most commonly used biomarker is NT-proBNP, a hormone released by the cardiomyocytes that causes natriuresis, diuresis, and vasodilation. The secretion of NT-proBNP is significantly upregulated in cardiac disease and congestive heart failure in response to myocardial stress and stretch. However, although cats with occult or overt cardiac disease have increased NT-proBNP levels, this parameter is not specific to hypertrophic cardiomyopathy. Another biomarker that can be considered is high-sensitivity cardiac troponin I, which is useful to identify affected patients. It is also a predictor of adverse cardiac outcomes in cats with hypertrophic cardiomyopathy.[1–3]

Electrocardiography is the gold standard technique to evaluate rhythm disturbances associated with hypertrophic cardiomyopathy phenotypes, such as ventricular rhythm disturbances, intraventricular conduction disturbances, and supraventricular rhythm disturbances. Holter monitoring is suggested to assess the number and complexity of supraventricular and ventricular rhythm disturbances.[34] Holter monitoring is used to identify

arrhythmias that might otherwise remain undetected and is recommended in cats experiencing episodes of weakness or transient loss of consciousness. Implantable loop recorders should also be considered for cats with intermittent and infrequent clinical signs that could be attributed to arrhythmias. Other options for recording a patient's cardiac rhythm and establishing correlations with the clinical signs include the use of a portable electrode plate (Kardia AliveCor) along with a smartphone to record electrocardiograms that can then be interpreted by a specialist.[1]

In dogs with subaortic stenosis and hypertrophic cardiomyopathy, echocardiography is the gold standard and is aimed at assessing the morphology of the valvular apparatus, confirming the findings obtained using Doppler techniques, and determining the severity of the left ventricular hypertrophy.[11–12]

Electrocardiography and thoracic radiography are rarely diagnostic, and echocardiography is required to establish a definitive diagnosis.

In dogs with congenital subaortic stenosis, the mildest lesions consist of small fibrous nodules located on the ventricular septum just below the aortic valve, while more advanced lesions appear as a distinct ridge, band, or complete ring of fibrous tissue that often involves the base of both the aortic and mitral valves. Based on the severity of the pressure gradient, different degrees of left ventricular hypertrophy can be detected. In some cases, functional mitral insufficiency and left atrial dilation can be identified.[11]

Most dogs with hypertrophic cardiomyopathy have symmetric hypertrophy (85%).[12] A minority of dogs are reported to display asymmetric septal hypertrophy. This hypertrophy pattern is similar to the left ventricular hypertrophy seen in cats with hypertrophic cardiomyopathy, but different from the symmetric septal hypertrophy exhibited by humans with the same condition. Although this was only evaluated subjectively by visual assessment, the right ventricular wall has also been reported to be hypertrophied in some dogs, with comparable right ventricular and left ventricular wall thicknesses. However, this is not a prominent feature of the disease in most dogs. Evidence of dynamic left ventricular outflow tract obstruction is observed in most dogs with hypertrophic cardiomyopathy, with systolic anterior motion of the mitral valve rather than muscular obstruction as the main mechanism.[12]

PROGNOSIS

The prognosis of the familial form of hypertrophic cardiomyopathy depends on the disease stage[1,2] and on several risk factors. Echocardiographic measurements of left atrial function, left ventricular hypertrophy, and left ventricular systolic function provide important prognostic information.[41,42]

In a study that examined the time from diagnosis of subclinical familial hypertrophic cardiomyopathy to the onset of heart failure, approximately 7% of cats developed heart failure within the first year, 20% within 5 years, and 25% within 10 years, regardless of the left atrial dimensions at the time of diagnosis.[43] Arterial thromboembolism is a fatal complication in many patients, and 70% die within a week. Thirty-seven percent of cats that survive the first week have an average survival time of 11.5 months and 20% of these cats live for one year or more.[44,45]

In cats with hypertrophic cardiomyopathy, the finding of transient ventricular arrhythmia on six-lead electrocardiograms has not been associated with poorer survival rates. In recent studies evaluating clinical risk markers for hypertrophic cardiomyopathy in people, nonsustained ventricular tachycardia proved to be a significant independent risk factor for sudden cardiac death, especially in young individuals.[2] In human medicine, sudden cardiac death is reported to occur in 1% of hypertrophic patients; however, in young athletes, hypertrophic cardiomyopathy is accountable for a considerable portion of sudden cardiac deaths.[46] In cats affected by familial hypertrophic cardiomyopathy, even mildly or moderately affected patients have significantly more frequent and severe ventricular arrhythmias and supraventricular arrhythmias than normal cats, which could lead to an increased risk of sudden cardiac death with a hazard ratio of 3.88.[34] It should be highlighted that even if male cats are more predisposed to the development of familial hypertrophic cardiomyopathy, the risk of sudden cardiac death does not seem to be higher in males than in females.[34]

In cats, atrial fibrillation is generally thought to portend a poor prognosis. However, 33% cats survived for 1 year after atrial fibrillation was diagnosed.[29]

The prognosis of cats affected by transient myocardial thickening is good if they survive hospitalization and the early recovery period. Recurrence

appears to be rare, although long-term studies are still lacking.[2,19–23]

The prognosis of dogs with subaortic stenosis mainly depends on the severity of the disease, which is determined based on the pressure gradient. A survival analysis demonstrated that dogs with mild to moderate subaortic stenosis and a pressure gradient ≤80 mmHg reached an older age than those in the severe and very severe categories, and the risk of death increased 1.6% for every 1 mmHg above 100 mmHg. No medical, interventional, or surgical therapy has been shown to improve survival in dogs with subaortic stenosis; however, information regarding the long-term survival of dogs undergoing combined cutting balloon and high-pressure balloon valvuloplasty is lacking, although a reduction in the pressure gradient has been demonstrated.[47]

The prognosis of dogs with hypertrophic cardiomyopathy is usually good, and most of them do not develop signs of congestive heart failure. Sudden cardiac death is not reported in this population of patients.[12]

TREATMENT

In cats affected by the familial form of hypertrophic cardiomyopathy, the administration of ß-blockers (atenolol) and calcium channel blockers (diltiazem) has been reported in subclinical phases of the disease.[2] The use of ß-blockers is an extrapolation from human medicine; in human patients, these drugs alleviate angina and exertional dyspnea, particularly in those with the obstructive form. In veterinary medicine, there is no evidence that cats with the familial form of hypertrophic cardiomyopathy may experience angina, and exertional dyspnea, considering their lifestyle, is rare. Atenolol has been reported to have no effects on cardiac performance.[48] In normal cats, a dose of 6.25–12.5 mg/cat of atenolol reduces the heart rate, peak myocardial velocity during systole (S'), peak myocardial velocity during early diastole (E'), left atrial shortening fraction, and left atrial ejection fraction, but it does not reduce systolic blood pressure.[2] The drug has shown to have the same effects in cats with familial hypertrophic cardiomyopathy and normal left atrial dimensions.[2] Atenolol administration does not prolong the 5-year survival in cats with subclinical hypertrophic cardiomyopathy[49] and does not reduce plasma NT-proBNP or cardiac

troponin I levels in this population.[50] However, atenolol reduces heart rate and murmur intensity in cats with systolic anterior motion of the mitral valve due to familial hypertrophic cardiomyopathy. In the opinion of several experts and based on most of the literature, there appears to be no justification for the use of ß-blockers in cats affected by the subclinical form of familial hypertrophic cardiomyopathy. ß-Blockers may only be useful in patients with severe left ventricular outflow tract obstruction due to systolic anterior motion of the mitral valve with a prolonged leaflet–interventricular septum contact time.[2]

Diltiazem was popular for decades in the treatment of subclinical and clinical familial hypertrophic cardiomyopathy in cats.[51] However, the administration of calcium channel blockers is no longer suggested due to their lack of efficacy and the gastrointestinal side effects of some of the extended-release formulations.[2]

Left ventricular outflow tract obstruction due to systolic anterior motion of the mitral valve may be a therapeutic target, and atenolol has been shown to be more effective in reducing the obstruction than diltiazem. This reduction in the dynamic obstruction of the left ventricular outflow tract is probably related to the negative inotropic effect of ß-blockers.[2] Dysopiramide is a different class I agent with a negative inotropic effect that is used to reduce left ventricular outflow tract obstruction in human patients in which atenolol has been ineffective.[52] The dynamic obstruction worsens in stressed cats during the examination and improves when the patients are resting or sleeping (75% of their life).[53] Therefore, in the opinion of several experts, it is illogical to try to lessen the degree of systolic anterior motion in cats if stress is not a common event in their life, particularly if drug administration itself is a source of stress in these patients.[2] With these considerations in mind, the suggested dose of atenolol in cats is 6.25–12.5 mg/cat per os (PO) every 12 hours.

Cats with familial hypertrophic cardiomyopathy are at risk of ventricular tachycardias. Ventricular tachycardias can be treated by administering a slow intravenous infusion of lidocaine at a dose of 0.25–1 mg/kg, which can be repeated 5–20 minutes later at a dose of 0.15–0.25 mg/kg, followed by a constant rate infusion (CRI) at 10–20 µg/kg/min. Another option is the administration of sotalol at a dosage of 2 mg/kg PO every 12 hours.[33] A potential adverse effect is neurotoxicity, which manifests as acute mental

dullness, ataxia, and lethargy.[33] A case report has described the successful treatment of ventricular fibrillation and ventricular tachycardia in a cat with defibrillation (2 joules/kg) and intravenous administration of amiodarone at 2 mg/kg over a 10-minute period, followed by a CRI at 0.8 mg/kg/h for 6 hours, and 0.4 mg/kg/h for an 18 additional hours. The cat was then administered oral amiodarone at a dosage of 12.5 mg/kg every 24 hours.[54]

In human medicine, gene therapy has recently gained interest, and different studies have hinted at the possibility of developing gene therapies for patients with inherited arrhythmias to control malignant arrhythmias and limit disease progression by targeting underlying disease mechanisms and to improve clinical outcomes. Gene therapy is broadly defined as therapy based on the introduction of material into cells; this material encompasses viral vectors, oligonucleotides, and modified RNA. In human hypertrophic cardiomyopathy patients, gene replacement therapy is of specific interest for pathogenic truncating *MYBPC3* mutations, and some studies have demonstrated that full-length *MYBPC3* replacement corrects pathogenetic functional abnormalities in cardiomyocytes and heart tissue.[55]

Treatment of subaortic stenosis in dogs with atenolol (0.5–1 mg/kg PO every 12 hours) or sotalol (1–2 mg/kg PO every 12 hours) has been reported.[56] Volumetric indices of left ventricular systolic function were reduced in dogs receiving sotalol when compared to those in dogs receiving atenolol, although no differences in linear indices of left ventricular systolic function were reported between the two groups. Furthermore, no differences were observed between the two drugs when assessing left ventricular outflow tract velocity or for any variable on 24-hour Holter monitoring.[56]

ß-Blocker administration has been reported to have no influence on survival time in dogs with severe subaortic stenosis, but a higher pressure gradient at diagnosis is associated with an increased risk of death.[57]

Sotalol does not have significant effects on overall survival but may increase the risk of sudden death in dogs with severe subaortic stenosis, unlike atenolol.[58]

The suggested treatment in dogs with hypertrophic cardiomyopathy and dynamic obstruction of the left ventricular outflow tract is atenolol at the standard dosages.[12]

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CHAPTER 26

Arrhythmias in dilated cardiomyopathy

Romain Pariaut

DEFINITION

Dilated cardiomyopathy is a phenotypic diagnosis based on structural and functional myocardial changes.[1] It is defined by the enlargement of the left or both ventricles and reduced systolic function in the absence of abnormal loading conditions.[1,2] Dilated cardiomyopathy can result from mutations, infection and autoimmunity, chemotherapy, metabolic dysfunction and nutritional deficiencies, and arrhythmias, among others. This chapter focuses on arrhythmias associated with idiopathic dilated cardiomyopathy, in other words, arrhythmias in animals with a dilated cardiomyopathy phenotype and no clearly identified etiology.

Idiopathic dilated cardiomyopathy has an overall prevalence estimated at 0.5% in dogs and is more commonly identified in large-sized dogs, with an overrepresentation of certain breeds, including Doberman Pinschers, Irish Wolfhounds, Deerhounds, Great Danes, Newfoundlands, Portuguese Water Dogs, Cocker Spaniels, and Welsh Springer Spaniels.[2–4] The prevalence, progression, and clinical expression of the disease shows some breed specificities. Dilated cardiomyopathy has been extensively studied in Dobermans and Irish Wolfhounds, and most of the information reported in this chapter comes from data collected in these two breeds. Dilated cardiomyopathy is sporadically diagnosed in cats, even in the absence a taurine deficiency.[5]

CLINICAL PRESENTATION

The disease typically has a preclinical (also referred to as occult, or latent) phase of variable duration and characterized by an absence of clinical signs. In Dobermans, this phase has been reported to occasionally last more than 3 years after the initial diagnosis.[6] It is followed by a clinical phase, which can take the form of left and right congestive heart failure, episodes of syncope, and the potential for sudden cardiac death.

Arrhythmias can be present during any phase of the disease. In one study, only 11% of dogs did not have an arrhythmia on the initial electrocardiogram at the time of diagnosis.[7] Hence, clinicians may come across the following scenarios:[8]

- Arrhythmias precede the onset of ventricular enlargement and reduced function.
- Arrhythmias appear or are identified simultaneously with the structural and functional changes of dilated cardiomyopathy.
- Arrhythmias only develop after dilated cardiomyopathy has progressed to advanced heart failure.

These three scenarios have been incorporated into a staging system (Table 26.1).[3] In Dobermans, it is estimated that approximately 30% of the dogs have an arrhythmia in the absence of echocardiographic changes, and 30% of dogs have electrocardiographic and echocardiographic changes at the time of diagnosis of occult cardiomyopathy.[9]

TABLE 26.1. Staging system for dilated cardiomyopathy (DCM).

DCM stage	Definition
A	Animals at risk for developing DCM in the future
B1	Arrhythmias present but no echocardiographic evidence of DCM Syncope possible
B2	Echocardiographic evidence of DCM Arrhythmias frequently present

	Syncope possible; no past or current signs of congestive heart failure
C	Past or current signs of congestive heart failure secondary to DCM
D	Advanced congestive heart failure not responding to standard therapy and requiring specialized interventions

Source: Modified from Wess G.[3]

In susceptible breeds, the initial diagnosis is often made as part of a screening program. It is advisable to conduct annual screenings in male dogs and every 2 years in females when they are used for breeding purposes. Considering the disease's natural progression, it is recommended to start screening dogs at 3–4 years of age.[3] A 24-hour Holter is indicated in breeds predisposed to ventricular arrhythmias, as they occur intermittently throughout the day and may not be detected on a short-duration electrocardiogram. Specific Holter criteria have been established to diagnose dilated cardiomyopathy in Dobermans (Table 26.2). An electrocardiogram should be sufficient to detect atrial fibrillation.[3]

TABLE 26.2. Proposed arrhythmia cutoffs for diagnosis of preclinical dilated cardiomyopathy.

Dobermans	>300 ventricular premature ectopic beats in 24 hours Or 50 to 300 ventricular premature ectopic beats in 24 hours on two Holter recordings obtained within 1 year (exclude accelerated idioventricular rhythms and ventricular rates <160 bpm)
Other breeds	>100 ventricular premature ectopic beats in 24 hours

Source: Modified from Wess G.[3]

An extensive diagnostic workup including an echocardiogram, abdominal ultrasound, bloodwork, electrocardiogram, and 24-hour Holter is

indicated to rule out secondary causes of dilated cardiomyopathy. Electrocardiographic abnormalities such as patterns of cardiac chamber enlargement and intraventricular conduction disturbances are frequently present in dogs with stage B2 and stage C dilated cardiomyopathy. Left bundle branch block is reported to occur in 25% to 30% of human patients with dilated cardiomyopathy, and in up to 50% of those with familial partial lipodystrophy with LMNA (lamin A/C) disease.[8]

SUPRAVENTRICULAR ARRHYTHMIAS IN DILATED CARDIOMYOPATHY

ATRIAL PREMATURE BEATS

It is not clear if isolated atrial premature beats represent an early manifestation of dilated cardiomyopathy in dogs with normal hearts.[9] A study in Dobermans indicated the presence of a low number of atrial premature beats on 24-hour Holter recordings in apparently healthy dogs. The number of atrial premature beats was higher in older dogs and in dogs with extracardiac disease, especially gastrointestinal diseases. Moreover, the number of atrial premature beats was not significantly higher in Dobermans that subsequently had a diagnosis of occult dilated cardiomyopathy, when this diagnosis was based on the detection of ventricular arrhythmias or echocardiographic changes consistent with cardiomyopathy. Finally, the number of atrial premature beats was higher in dogs with echocardiographic evidence of occult dilated cardiomyopathy combined with ventricular arrhythmias, but not in dogs with only echocardiographic changes at the time of diagnosis.[9]

ATRIAL FIBRILLATION

In humans, atrial fibrillation is identified in 30–50% of patients with inherited cardiomyopathies.[8] In people with early onset atrial fibrillation, the arrhythmia is frequently suspected to be the first manifestation of cardiomyopathy, before the onset of structural and functional changes. In a study, 10–16.7% of patients that developed atrial fibrillation before the age of 66 carried a mutation known to be associated with a genetic

cardiomyopathy, mainly dilated cardiomyopathy.[8] Atrial fibrillation has been reported in 45–50% of large populations of dogs with dilated cardiomyopathy.[7,10] It is more common in giant breed dogs with this disease.[7] In one study, it was present at the time of diagnosis in approximately 75% of Great Danes, Newfoundlands, and Saint Bernards.[7] Remarkably, 95–100% of Irish Wolfhounds with dilated cardiomyopathy have atrial fibrillation at the time of diagnosis.[7,11] Moreover, atrial fibrillation has been shown to be the first manifestation of dilated cardiomyopathy in some Irish Wolfhounds, although not all dogs with atrial fibrillation will end up developing dilated cardiomyopathy.[3,12] Atrial fibrillation is also frequently reported in large breed dogs with dilated cardiomyopathy (Fig. 26.1). In one retrospective study, 73% of German Shepherds with this disease had atrial fibrillation.[7]

Atrial size is known to have an important role in the patient's risk for developing atrial fibrillation. Atrial fibrillation occurs more commonly in dogs with left atrial or biatrial enlargement.[13] Right atrial enlargement was commonly identified in Dobermans with dilated cardiomyopathy and atrial fibrillation.[14] Dogs with atrial fibrillation were also more likely to show signs of right-sided congestive heart failure, with cavitary effusions being reported in approximately 75% of them.[15] It is unclear if right heart remodeling is an important contributor to the initiation of the arrhythmia, or if atrial fibrillation is responsible for the right heart changes.

Whenever a diagnosis of atrial fibrillation is made, a complete echocardiographic examination is indicated to determine if structural and functional changes are associated with the arrhythmia. In the presence of mild cardiac enlargement and slightly reduced systolic function, it can be difficult to distinguish a primary dilated cardiomyopathy phenotype from arrhythmia-induced cardiac changes (see p. 395) and from a limited ability to accurately assess cardiac size and function via echocardiography due to the rapid and irregular rhythm.[8]

Atrial fibrillation is typically not associated with syncope. In dogs with dilated cardiomyopathy and atrial fibrillation that experience syncope, another cause for these episodes should be investigated. Although ventricular arrhythmias are frequently suspected to be associated with

syncope, other rhythm abnormalities cannot be ruled out, including bradyarrhythmias such as paroxysmal atrioventricular block.[16]

The impact of atrial fibrillation on the prognosis of dilated cardiomyopathy is not yet fully understood. One study found that dogs with atrial fibrillation had a shorter life expectancy, while another study did not find any effect on survival.[17,18] In a group of Dobermans with dilated cardiomyopathy and congestive heart failure, survival time was shorter in the dogs that also presented with atrial fibrillation (median, 22 days; range, 42.1–134.4; vs. median, 98 days; range, 98.5–203). Dobermans with atrial fibrillation had a more than 50% mortality rate within the first 2 weeks of diagnosis, and their life expectancy was shorter than dogs in sinus rhythm.[18]

Out of a group of 50 cats diagnosed with atrial fibrillation, dilated cardiomyopathy was found in 6 of them.[19]

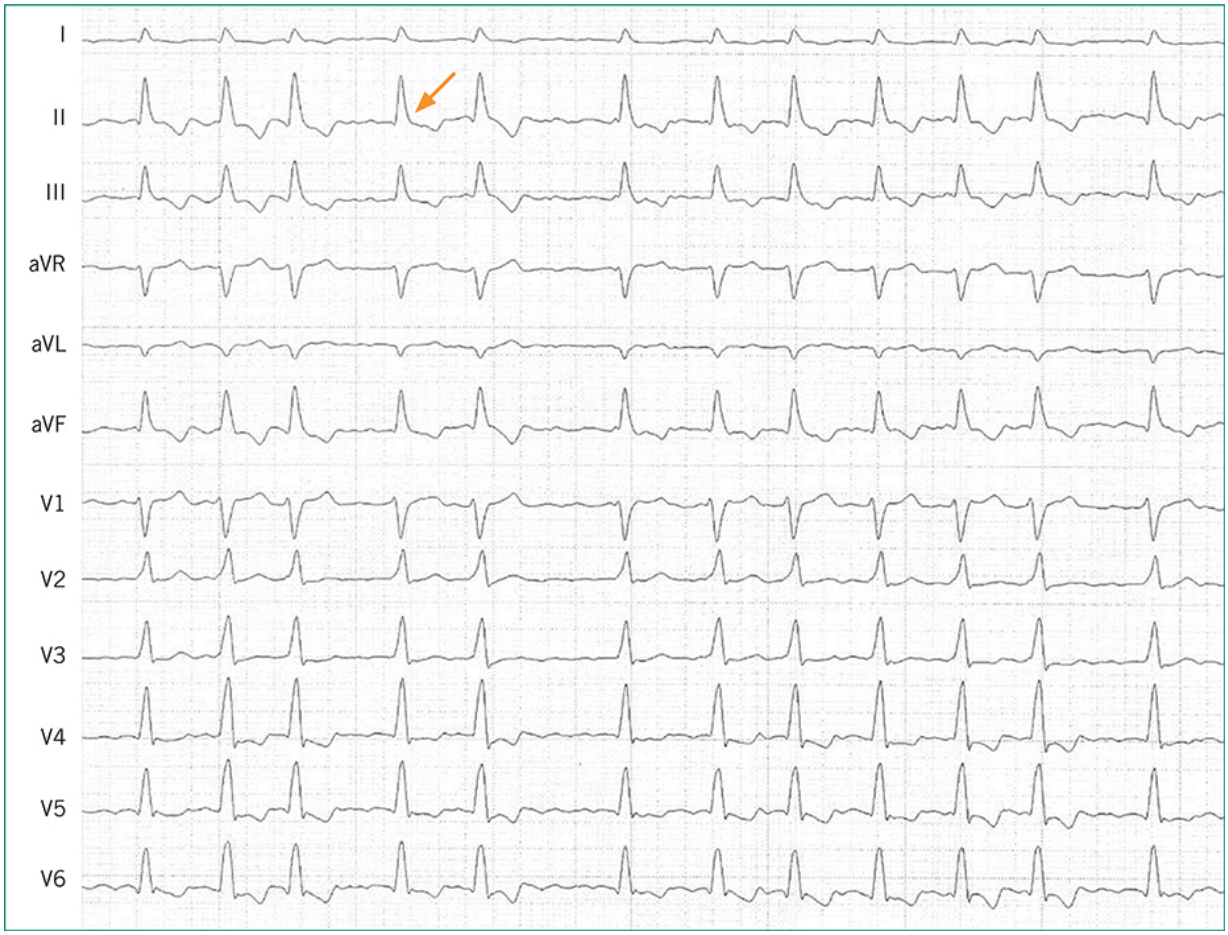


FIGURE 26.1. Persistent atrial fibrillation in a 7-year-old male Doberman with dilated cardiomyopathy. Note the presence of narrow QRS complexes (70 ms) with slurring (arrow), irregular RR intervals with an average rate of 140 bpm, and absence of P waves with coarse and irregular f waves. The precordial leads show interventricular dyssynchrony. The R-peak time of the left ventricle is 40 ms slower than the right one, that is, 20 ms. Twelve leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6); speed, 50 mm/s; calibration, 5 mm/1 mV.

VENTRICULAR ARRHYTHMIAS IN DILATED CARDIOMYOPATHY

ELECTROPHYSIOLOGICAL MECHANISM

There are many factors associated with the progression of dilated cardiomyopathy that can explain the occurrence of ventricular arrhythmias (Table 26.3), including myocardial fibrosis, electrical remodeling, neurohormonal activation, and electrolyte imbalances.[8] Myocardial fibrosis is considered a major contributor to ventricular arrhythmias, as it promotes automaticity and reentry.[8] Cardiac magnetic resonance imaging is used in human patients suspected of suffering from dilated cardiomyopathy. It can detect areas of fibrosis through late gadolinium enhancement, thus aiding in distinguishing between benign ventricular arrhythmias and arrhythmias associated with cardiomyopathy.[20]

TABLE 26.3. Factors associated with arrhythmias in dilated cardiomyopathy.

Increased cardiac chamber size
Elevated sympathetic tone and circulating catecholamines
Myocardial fibrosis
Cardiac chamber stretch ■ Reentry via heterogeneous shortening of tissue refractory period ■ Stretch-induced afterdepolarizations
Calcium homeostasis alteration ■ Afterdepolarizations
Intraventricular conduction delays
Hypokalemia and hypomagnesemia associated with diuretic use

Drugs (e.g., antiarrhythmics, sympathomimetics, digoxin)

VENTRICULAR PREMATURE BEATS

Ventricular premature beats are frequent in dogs with dilated cardiomyopathy, but they can go unnoticed during a routine physical examination or on a short electrocardiographic recording due to their varying frequency throughout the day. They can be identified on an electrocardiogram in approximately 30% of dogs at the time of diagnosis and can display various morphologies.[7] Typically, ventricular premature beats display a negative QRS complex in leads II, III, and aVF, and the left precordial leads. Although it has been suggested that the presence of one ventricular ectopy on a 5-min electrocardiogram in Dobermans is highly suggestive of an arrhythmia burden exceeding 100 ventricular premature beats per 24 hours, a 24-hour Holter remains a better tool to identify intermittent ventricular arrhythmias.[21]

Source: Modified from Zipes D. P. and Jalife J.[44]

In predisposed breeds, it might be challenging to establish a diagnosis of dilated cardiomyopathy when the disease initially manifests itself as an arrhythmia with no echocardiographic changes. In many cases, ventricular arrhythmias precede structural cardiac changes by months to years.[2] In Dobermans, it has been suggested that >300 ventricular ectopic beats on a 24-hour Holter, or 50 to 300 ventricular ectopic beats on two consecutive Holter recordings 1 year apart is considered diagnostic of occult dilated cardiomyopathy in the absence of another identifiable cause.[3] In this breed, it appears that >50 ventricular ectopic beats or one couplet/triplet per 24 hours is already associated with a high risk of developing dilated cardiomyopathy.[22,23] However, in all forms of cardiomyopathy, there is a high day-to-day variability of the arrhythmia, which can reach 100%, and a single Holter recording might fail to identify an affected dog. While it may not always be feasible in a clinical setting, extending the duration of a Holter recording to 4 or even 7 days would be beneficial in identifying a greater number of affected dogs.[24] Ventricular escape beats and periods of accelerated idioventricular rhythm should be excluded from the total ventricular beat count.[3]

Finally, when trying to determine if a low ventricular arrhythmia burden is an early indicator of dilated cardiomyopathy, it is important to consider sex and age differences in the predisposition to the disease. Dilated cardiomyopathy is more common in males and middle-aged to older dogs. For example, ventricular ectopic beats are more likely to indicate future development of dilated cardiomyopathy in a 5-year-old male Doberman than in a 2-year-old female of the same breed.[22]

VENTRICULAR TACHYCARDIA

Dilated cardiomyopathy has been associated with different types of ventricular tachycardia. It can manifest as either nonsustained or sustained ventricular tachycardia and can be either monomorphic, pleomorphic, or polymorphic (Figs. 26.2 and 26.3).[25] Bundle branch reentrant ventricular tachycardia is commonly identified in human patients with nonischemic cardiomyopathy. The reentrant circuit involves the His bundle, the left and right bundle branches, and the adjacent myocardium. Delayed or blocked left or right bundle branch conduction is required for this arrhythmia to occur. Bundle branch block ventricular tachycardia typically has a left or right bundle branch block morphology, and it is rapid and frequently associated with syncope. Patients with this form of tachycardia do not always have a bundle branch block pattern during sinus rhythm.[26]

A retrospective study examining the echocardiographic diagnosis in 106 cats with ventricular tachyarrhythmias revealed dilated cardiomyopathy in 6 of them.[27]

IDENTIFICATION OF ANIMALS AT HIGH RISK FOR SUDDEN DEATH

Sudden death accounts for 10% to 24% of deaths in dogs with dilated cardiomyopathy. In Dobermans, the percentage of dogs experiencing sudden cardiac death is estimated to be higher, ranging from 29% to 42%.[17,28] In humans, dilated cardiomyopathy is also the most common disease associated with sudden death, following coronary heart disease.[29] The natural history of dilated cardiomyopathy combines structural and

genetic substrates with physiological and environmental triggers that together increase the risk of ventricular arrhythmias, which serve as the leading cause of sudden cardiac death.[29]

Sudden cardiac death can be the first clinical manifestation of the disease or occur in dogs with preexisting congestive heart failure. The cause of sudden death is rarely documented. A retrospective study detailed the arrhythmias associated with sudden cardiac death in a small number of dogs who died during 24-hour Holter recording.[30] In 2 dogs with dilated cardiomyopathy and congestive heart failure and 3 dogs with dilated cardiomyopathy and documented arrhythmia or syncope, ventricular fibrillation was the cause of sudden death (Fig. 26.4). In some cases, the arrhythmia was triggered by runs of polymorphic ventricular tachycardia following a period of extreme bradycardia, suggesting triggered activity from early afterdepolarizations as the mechanism responsible for the ventricular arrhythmia. In other cases, ventricular fibrillation was induced by short-coupled ventricular premature beats, suggesting depolarization from an ectopic beat during the vulnerable period of ventricular repolarization as the initiator of ventricular fibrillation.[30] In another study, ventricular fibrillation was also identified to be the cause of sudden death in 3 Dobermans.[18]



FIGURE 26.2. Repetitive, monomorphic ventricular tachycardia runs in a 4-year-old male Doberman with dilated cardiomyopathy. Note the presence of wide QRS complexes (85 ms) with a monomorphic appearance, a rate of 300 bpm, and irregular RR intervals. Six limb leads (I, II, III, aVR, aVL, aVF); speed, 50 mm/s; calibration, 5 mm/1 mV.

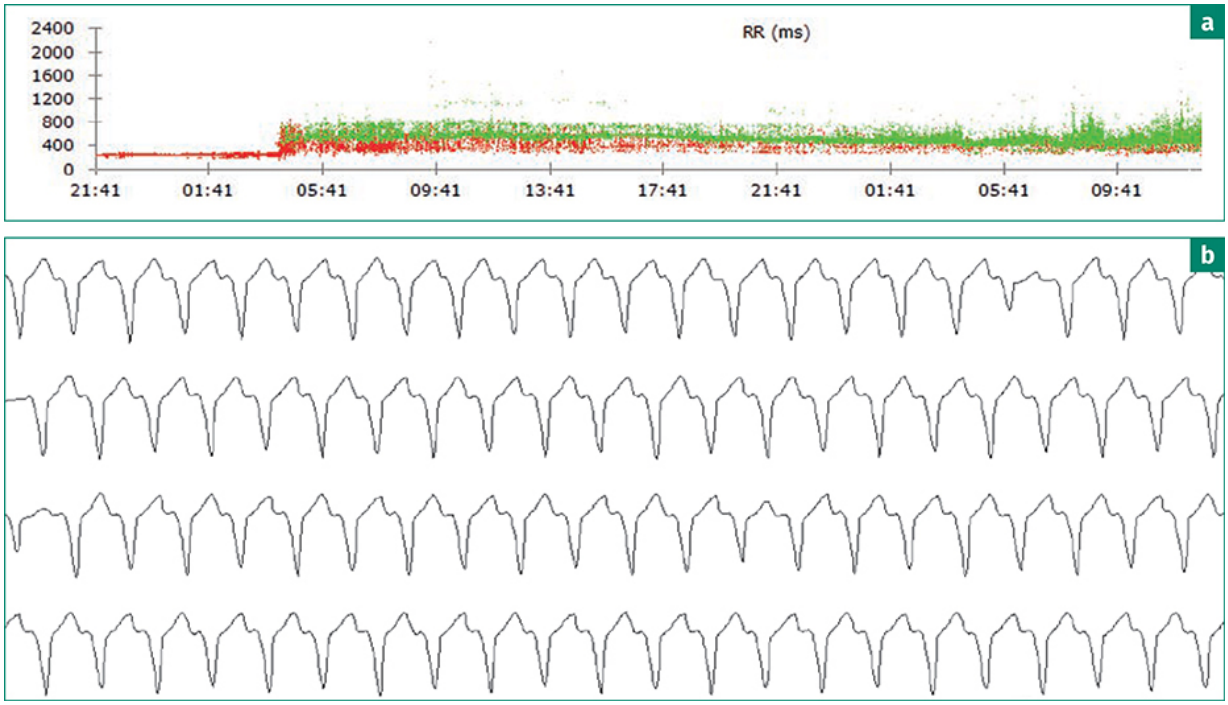


FIGURE 26.3. Holter recording from an 8-year-old male Cocker Spaniel with dilated cardiomyopathy and sustained monomorphic ventricular tachycardia. a) Twenty-four-hour tachogram showing the distribution of normal RR intervals (green) and RR intervals during ventricular arrhythmias (red). Y-axis, RR interval duration; x-axis, hours of day and night. Note, in the first hours of the tracing, the presence of a flat red line characteristic of a sustained ventricular tachycardia. b) Electrocardiographic recording showing a sustained monomorphic ventricular tachycardia as the dominant rhythm. Lead Y; each line corresponds to 5 seconds. Speed, 7.5 mm/s; calibration, 2 mm/mV.

When assessing the risk for arrhythmic sudden cardiac death, it might be useful to consider the presence or absence of left ventricular systolic dysfunction, the type of arrhythmia present (supraventricular or ventricular), and the characteristics of the arrhythmia (rate, coupling interval). The presence of left ventricular remodeling is thought to be a major contributor to the risk of sudden death. In Dobermans, the highest risk has been associated with the presence of cardiac enlargement (left ventricular end-diastolic volume/body surface area ratio [LVEDV/BSA] >91.3 mL/m^2; every 50 mL/m^2 increment increases sudden cardiac death risk 8.5-fold) and systolic dysfunction.[3] The presence of ventricular arrhythmias may also indicate a higher risk of sudden cardiac death. Among Dobermans with echocardiographic evidence of preclinical dilated cardiomyopathy, the presence of more than four ventricular premature beats on a 3-minute electrocardiogram identified a subset of dogs that developed

congestive heart failure or experienced sudden cardiac death at an earlier stage, particularly when the electrocardiogram also exhibited a sinus rate exceeding 110 bpm.[6] A greater number of ventricular premature beats and increased ventricular arrhythmia complexity on a 24-hour Holter recording was also associated with a worse outcome.[6] However, another study did not find an association between the number of ventricular premature beats and the risk of sudden cardiac death.[31] The pattern of ventricular arrhythmias might also be useful in identifying the dogs at risk of sudden cardiac death. Indeed, in Dobermans with left ventricular enlargement, the presence of ventricular premature beats with a coupling interval shorter than 230 ms might be a useful predictor of an increased risk.[32,33]

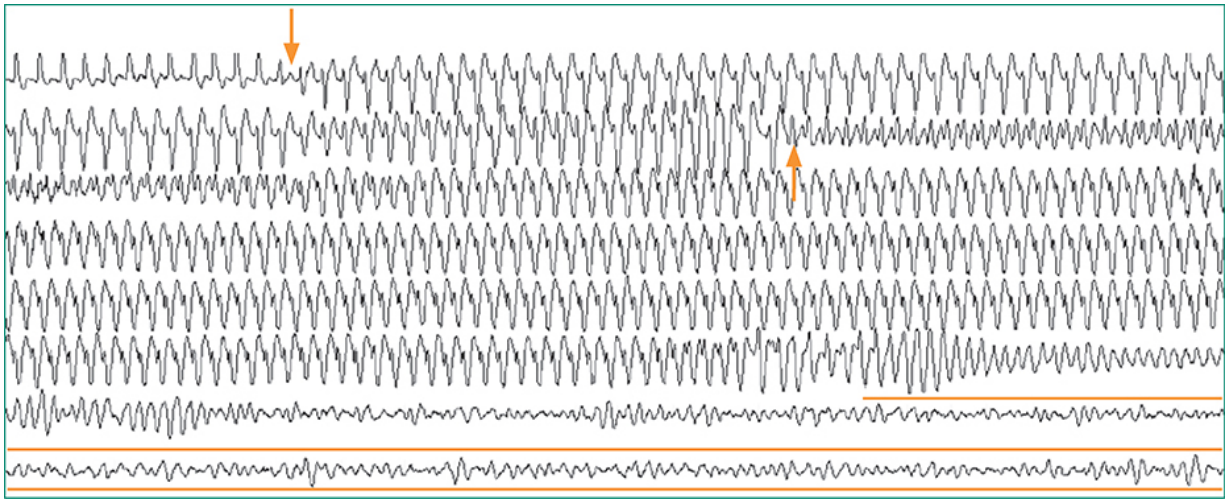


FIGURE 26.4. Holter recording from a 5-year-old female Great Dane with dilated cardiomyopathy that experienced sudden cardiac death. The dominant rhythm is a sustained pleomorphic ventricular tachycardia that degenerates into ventricular fibrillation. Note the changes in the QRS axis (arrows) with no changes in the tachycardia cycle length, characteristic of anatomical reentry with different exits points, that finally speeds up and then degenerates into ventricular fibrillation (horizontal line). Lead Y; each line corresponds to 30 seconds. Speed, 7.5 mm/s; calibration, 2 mm/mV.

In dogs with occult dilated cardiomyopathy and no evidence of cardiac enlargement, documentation of ventricular tachycardia, more than the number of ventricular ectopic beats, is also associated with an increased risk of sudden death, but to a smaller degree.[3,32] It seems that syncope is rarely documented in the weeks or months that precede sudden cardiac death.[33] Overall, approximately 50% of Dobermans with congestive heart

failure due to dilated cardiomyopathy experience a sudden cardiac death event.[34]

In a study, atrial fibrillation was not associated with an increased risk of sudden cardiac death in Dobermans with dilated cardiomyopathy and congestive heart failure.[14] In this study, ventricular arrhythmias were likely the cause of sudden cardiac death, which occurred in approximately 41% of the population.[14]

Electrocardiographic criteria during sinus rhythm are rarely useful to quantify the risk of sudden cardiac death. There is limited evidence that identification of ventricular late potentials via signal-averaged electrocardiography may indicate an increased risk of sudden cardiac death, although sudden death also occurs in dogs with no detectable abnormalities.[35,36]

Finally, circulating biomarkers might also be helpful to predict the risk of sudden cardiac death. Studies in Great Danes and Dobermans have shown a higher incidence of sudden cardiac death when the cardiac troponin I concentration is elevated, even in the absence of echocardiographic changes.[33,37]

THERAPY

PREVENTION OF SUDDEN CARDIAC DEATH

During the preclinical phase of dilated cardiomyopathy, the administration of pimobendan in Dobermans with echocardiographic evidence of left ventricular enlargement delayed the onset of congestive heart failure or sudden death by approximately 9 months.[6] A direct antiarrhythmic effect of the drug is unlikely. However, administration of pimobendan was associated with a reduction in left ventricular size, suggesting that reverse remodeling and improvement of systolic function with medical therapy could be associated with a lower incidence of sudden cardiac death. It is consistent with results of clinical trials in human patients with nonischemic cardiomyopathy that showed a reduction in the risk of sudden cardiac death and incidence of ventricular arrhythmias with optimal heart failure therapy.[38]

Antiarrhythmics are unlikely to decrease the risk of sudden cardiac death. In a study, Dobermans with dilated cardiomyopathy that received antiarrhythmics experienced a higher rate of sudden cardiac death than nontreated dogs. It is likely that the decision to treat those dogs was based on the identification of a frequent and complex ventricular arrhythmia that increased the risk of sudden cardiac death. However, it cannot be completely ruled out that the antiarrhythmic treatment was responsible for the higher number of sudden death events.[33]

In a small group of Dobermans with a history of syncope and documented ventricular arrhythmias in the absence of congestive heart failure, it was suspected that the addition of antiarrhythmics could have delayed the sudden cardiac death event, which occurred in all dogs whether they were treated or not. The antiarrhythmics used included amiodarone, quinidine gluconate, procainamide, tocainide, and mexiletine. A β-adrenergic blocking drug was also added in some dogs receiving tocainide or mexiletine.[39]

In humans, primary and secondary prevention of sudden cardiac death is based on implantable cardioverter defibrillator therapy.[40] However, this technology is currently unavailable for clinical use in veterinary patients.

ATRIAL FIBRILLATION

Standard rate control of the arrhythmia is typically recommended (see p. 224). One study evaluating the addition of spironolactone (50 to 75 mg twice daily) to standard congestive heart failure therapy in Dobermans with dilated cardiomyopathy found that dogs in the placebo group were 2.1 times (95% confidence interval: 1.01–4.57, P = 0.037) more likely to develop atrial fibrillation than those in the treatment group over the course of the disease.[34] This result could be related to the beneficial effects of spironolactone on atrial remodeling. In various experimental canine models of heart disease, the administration of spironolactone was associated with a reduction in apoptosis, myolysis, and fibrosis.[41]

VENTRICULAR ARRHYTHMIAS

Various antiarrhythmic protocols have been used empirically to manage ventricular arrhythmias in dogs, with limited evidence that it could delay a

sudden cardiac death event.[39] The antiarrhythmics commonly used include sotalol, mexiletine, amiodarone or a combination of drugs (see Chapter 7). Signs of toxicity have been described with chronic use of amiodarone in Dobermans and other breeds, which might limit its use for long-term management of ventricular arrhythmias.[42] In a study using a canine model of dilated cardiomyopathy and congestive heart failure, the effects of d,l-sotalol on cardiac repolarization were more pronounced than in control dogs, with a dose-dependent prolongation of the action potential duration.[43] The reverse use–dependent effect of sotalol was also more pronounced in the dilated cardiomyopathy group. However, sotalol was associated with a decrease in the mean arterial blood pressure, and some dogs did not tolerate a 3 mg/kg intravenous dose.[43] The effect on repolarization could contribute to both an antiarrhythmic and proarrhythmic effect of the drug. It could also suggest that a lower dose of sotalol could be effective in dogs with dilated cardiomyopathy and congestive heart failure.

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CHAPTER 27

Arrhythmias in myocarditis and inflammatory cardiomyopathy

Roberto Santilli

DEFINITION

Myocarditis is an inflammatory disease of the atrial and ventricular myocardium mainly caused by infectious cardiotropic pathogens. In dogs and cats, it can occur in a subclinical form, which is often underdiagnosed, or manifest clinically with different types of arrhythmias at different stages, severe and permanent myocardial damage that can lead to congestive heart failure, and the patient's death.[1–7]

The diagnosis of myocarditis in humans should be based on established histological, immunological, and immunohistochemical criteria. Histological changes should meet the Dallas criteria, with signs of inflammatory infiltrates (≥14 leucocytes/mm^2, including up to 4 monocytes/mm^2 with the presence of CD3-positive T lymphocytes ≥7 cells/mm^2) within the myocardium associated with myocyte degeneration and necrosis of nonischemic origin. When a diagnosis of myocarditis is established in a patient with a dilated cardiomyopathy phenotype, the term inflammatory cardiomyopathy or inflammatory dilated cardiomyopathy (DCMi) should be used.[8,9]

ETIOLOGY OF MYOCARDITIS

The causes of myocarditis in dogs and cats are similar to those reported in humans, although knowledge is more limited due to the sporadic use of diagnostic screening methods allowing a precise in vivo diagnosis. For this reason, most of the published studies are limited to case reports or case series of necropsies.

Myocarditis can be caused by viral, bacterial, protozoal, and parasitic infections, or it can be induced by immune-mediated diseases, drugs and toxins, heat stroke, hemodynamic shock, and idiopathic noxae (Table 27.1).

The gold standard for the in vivo diagnosis of myocarditis is endomyocardial biopsy obtained from the right and left ventricles, followed by histological, immunohistochemical, and molecular analysis.[9,10] To date, only one prospective study evaluated the presence of cardiotropic pathogens through the use of right ventricular endomyocardial biopsy in a population of 37 dogs with myocardial disease (i.e., dilated cardiomyopathy) and/or arrhythmic disorders (i.e., atrioventricular blocks, ventricular and supraventricular arrhythmias) of unknown etiology and in 10 dogs that underwent invasive procedures for congenital heart disease.[6] These biopsy samples were obtained in vivo by endomyocardial biopsy and sent for histological, immunohistochemical, and PCR examination for canine adenovirus 1 and 2, canine coronavirus, canine herpesvirus 1 and 2, distemper virus, West Nile virus, *Bartonella* spp., *Borrelia burgdorferi*, *Toxoplasma gondii*, and *Leishmania infantum*. Fifty-seven percent of these patients tested positive for one or more etiological agents, a percentage similar to that reported in humans. Of the 21 dogs with a positive PCR, 14 tested positive for RNA viruses, 8 for DNA viruses, 4 for bacteria (*Bartonella* spp.) and 1 for protozoa (*L. infantum*). Fifteen dogs showed nucleic acids from a single pathogen, while nucleic acids of multiple agents were demonstrated in 6 dogs. The absence of inflammatory infiltrate and a negative PCR result in 9/10 dogs of the control group indicated the possibility of a cause-and-effect link in sick dogs with myocardial or arrhythmic disorders and positive for myocardial pathogens. Simultaneously with this work, two other articles were published that described the postmortem search for cardiotropic pathogens, with discordant results.[11,12] In these studies, the presence of pathogens was detected both in samples of myocardial tissue with a histological diagnosis of myocarditis[11,12] and in myocardial samples from dogs that died of other

pathologies.[12] Particularly, while in the first study 30% of the dogs with histologically proven myocarditis were found to be positive for canine parvovirus 2, in the second study, 53% of the dogs diagnosed with myocarditis had a negative PCR test for canine parvovirus 2, distemper virus, herpesvirus canine, *Borrelia* spp., West Nile virus, adenovirus, parainfluenza virus, pneumovirus, respiratory coronavirus, influenza virus, *Bartonella* spp., *Rickettsia* spp., *Mycoplasma* spp., and *Neospora caninum*. On the other hand, 47% of animals in the control group were negative for these etiological agents. However, the main limitation of these studies lies in the fact that the samples for PCR testing were collected in a nonsterile manner during necropsy. They had been fixed in formalin and then cut with a microtome; therefore, contamination of the samples in one of the phases of this process cannot be ruled out.

TABLE 27.1. Etiology of infectious myocarditis in dogs and cats.

Phylum	Animal	Etiological agent	References	Geographical area
Viruses	Dog	Canine parvovirus 1 and 2	PM, IV[6]	USA, Italy
	Cat	Feline parvovirus (FPV)	PM[13]	USA
	Dog	West Nile	PM[34,35]	USA
	Dog	Canine adenovirus	PM[1, 12], IV[6]	USA, Italy
	Dog	Canine distemper virus	PM[36], IV[6]	USA, Italy
	Dog	Canine enteric coronavirus	IV[6]	Italy
	Cat	Feline coronavirus (FIP)	PM[13]	Italy
	Dog	Herpes virus	PM[12], IV[6]	USA, Italy
	Dog	Parainfluenza virus	PM[12]	USA
	Cat	Feline immunodeficiency virus (FIV)	PM[14]	Brazil
	Dog, cat	Coronavirus 2 (SARS-CoV-2)	IV[37]	United Kingdom
Protozoa	Dog	*Neospora caninum*	PM[7,38-40]	USA, Australia
	Dog	*Trypanosoma cruzi*	PM[7, 22, 23]	USA
	Dog	*Leishmania infantum*	PM[41-43], IV[6]	Brazil, Spain, Italy
	Dog	*Hepatozoon canis*	PM[44]	USA
	Cat	*Hepatozoon silvestris*	PM[45]	Switzerland
	Dog, cat	*Toxoplasma gondii*	PM[7,40], IV[6,17]	USA, Italy, Russia
	Cat	*Sarcocystis felis*	PM[46]	USA
Bacteria	Dog, cat	*Bartonella* spp.	PM[3,7,47,48], IV[4,6]	USA, Italy
	Dog	*Borrelia burgdorferi*	PM[49]	Czech Republic
	Dog	*Citrobacter koseri*	PM[50]	United Kingdom
	Dog	*Clostridium piliforme*	PM[51]	Japan
	Dog	*Mycoplasma haemocanis*	PM[12]	USA
	Dog	*Leptospira* spp.	PM[7]	USA
	Cat	*Streptococcus canis*	PM[52]	USA
	Cat	*Salmonella typhimurium*	PM[53]	Italy
	Cat	*Streptococcus suis*	PM[54]	USA
Fungi	Dog	*Inonotus tropicalis*	PM[55]	USA
	Dog	*Blastomyces dermatitidis*	PM[56]	USA
Algae	Dog	*Prototheca* spp.	PM[57]	Australia
Nematoda	Dog	*Dirofilaria immitis*	PM[7]	USA

FIV, feline immunodeficiency virus; FIP, feline infectious peritonitis; FPV, feline panleukopenia virus; IV, in vivo diagnosis; PM, postmortem diagnosis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; USA, United States of America.

Most of the cats with histologically proven myocarditis were suffering from concomitant pathologies or immunosuppression, mainly related to the feline leukemia and immunodeficiency viruses, feline infectious peritonitis, *Mycoplasma* infection, and immunosuppressant drugs.[13,14] Interestingly, a study reported the identification of the feline parvovirus in the hearts of cats with hypertrophic, restrictive, and dilated cardiomyopathies.[15] In one of the previously mentioned studies, antigens of the feline immunodeficiency virus were identified in the hearts of cats with myocarditis and hypertrophic cardiomyopathy, but a correlation between the two pathological entities

could not be demonstrated.[14] In another study published in the same year (2016), viral genome was not found in samples of myocardium from cats with endomyocardial restrictive cardiomyopathy collected at necropsy, thereby decreasing interest in this research subject, with studies now being more directed towards the immune-mediated forms.[16] To date, only one case report described the use of endomyocardial biopsy in a cat with *Toxoplasma gondii*-induced myocarditis.[17]

PATHOPHYSIOLOGY OF MYOCARDITIS

Study models of rats experimentally infected with enteroviruses enabled the study and characterization of the three-phase course of myocarditis (Fig. 27.1).[9,18]

The *acute phase (hot phase)* lasts only a few days. Virus entry and replication cause acute damage to myocytes, leading to myocardial necrosis. The resulting exposure of intracellular antigens is followed by activation of the host's immune system, which leads to tissue invasion by natural killer cells, macrophages, and T lymphocytes.

The *subacute phase* of myocarditis, which can last from a few weeks to a few months after the initial infection, is characterized by myocardial inflammation mediated by the immune system cells and by the direct action of antibodies against myocardial cells.

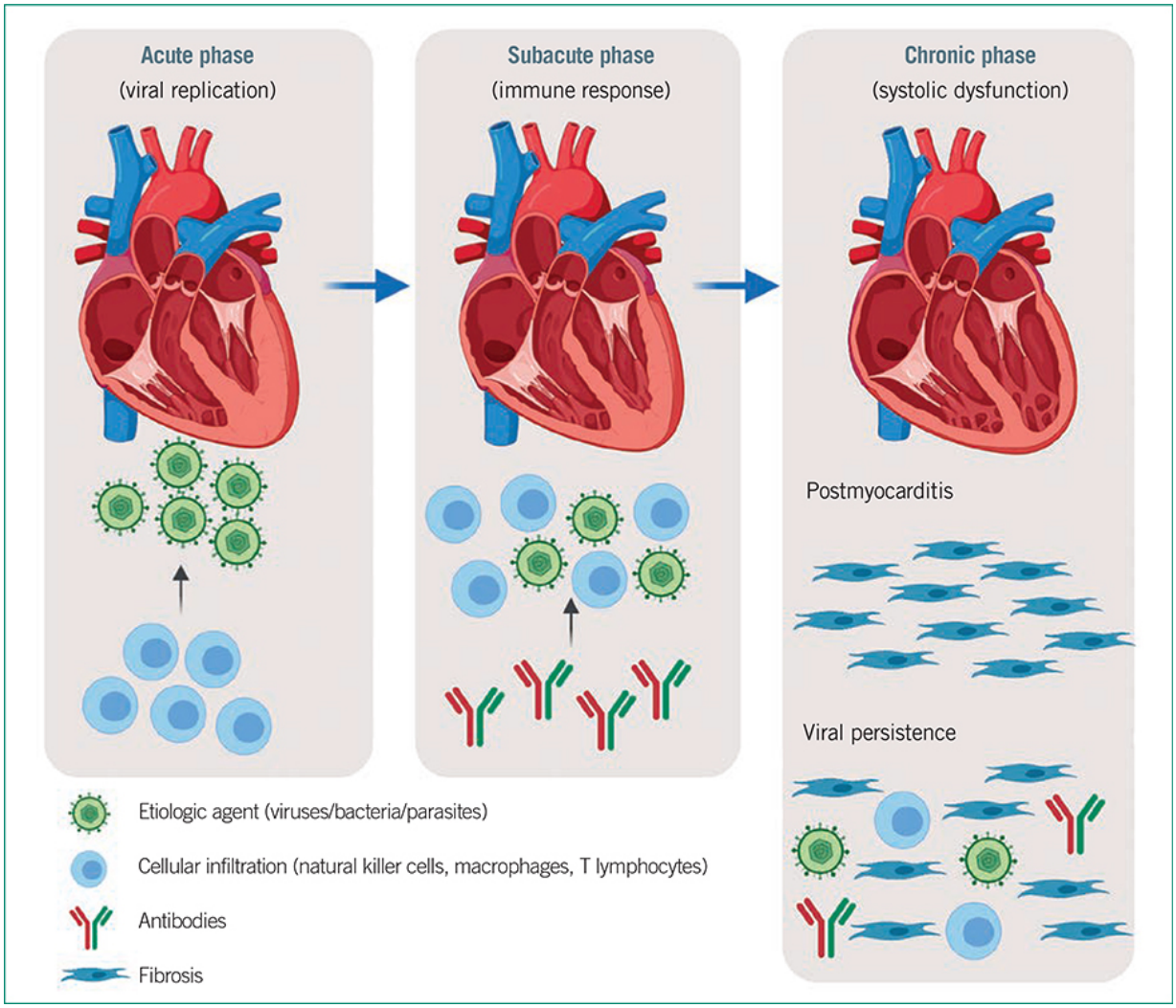


FIGURE 27.1. Schematic representation of the stages of myocarditis. The acute phase lasts only a few days, while the subacute and chronic phases can last from a few weeks to several months.

The *chronic phase (cold phase)* is characterized by a process of multifocal replacement of myocardial tissue with fibrous tissue, systolic dysfunction, and development of hypokinetic-dilating clinical pictures (inflammatory cardiomyopathy or DCMi).[3,9] Such a stage can be characterized by a complete disappearance of the signs of viral infection (i.e., virus, cell infiltration, and antibodies) (postmyocardial phase) or by a persistence of the pathogen in the myocardium (viral persistence).

CLINICAL AND INSTRUMENTAL FINDINGS

The clinical signs of myocarditis vary depending on the stage of the disease and include upper respiratory tract, gastrointestinal system, and cardiovascular signs as well as signs secondary to severe bacterial sepsis. There is no specific clinical sign on which to base the diagnosis; the owners of dogs with myocarditis often report nonspecific signs such as fever, anorexia, cough, muscle pain, exercise intolerance, and diarrhea.[6,7] As for cardiovascular signs, affected dogs may present with severe dyspnea due to new-onset pulmonary edema or cavity effusions, severe depression with cardiogenic shock secondary to systolic dysfunction or tachyarrhythmias, or syncope caused by new-onset atrioventricular blocks.[6,7] Cats with acute myocarditis are usually referred for acute-onset severe pulmonary edema and syncope.[4,5,19]

ECHOCARDIOGRAPHY

The most common echocardiographic change reported in humans with myocarditis consists in acute systolic dysfunction, which can lead to an increase in the sphericity of the left ventricle and in the thickness of the interventricular septum. In people with a viral infection demonstrated by endomyocardial biopsy, a progressive worsening of left ventricular function was observed in association with chronic viral persistence, while the absence of viral material in control biopsies was associated with significant restoration of systolic function.[9,20] However, in experimental rat models, autoimmune processes persisted regardless of the presence or absence of viral genome and were responsible for the progression towards clinical pictures of dilated cardiomyopathy.[21] This condition has also been demonstrated in dogs with Chagas disease, in which severe acute damage of the myocardium was observed although the burden of intracellular parasites was relatively low, and was caused by the immune response.[22,23]

In a recent study, 52% of dogs with left ventricular systolic dysfunction undergoing endomyocardial biopsy were positive for viral or bacterial myocarditis. The distemper virus appeared to be the most represented pathogen in these dogs (Fig. 27.2).[6] In another study in which the diagnosis of myocarditis was confirmed postmortem, 56% of the dogs had decreased left ventricular systolic function, 34% had subjective left ventricular myocardial heterogenicity, 14% had focal left ventricular hypokinesia, and

16% presented with a small amount of pericardial effusion without cardiac tamponade.[7] Myocardial hypertrophy, which has been observed in humans, has also been described in cats. A recent retrospective study assessed a population of cats that presented with transient myocardial thickening associated with congestive heart failure and showed that after a mean of 3.3 months, reverse remodeling had occurred, with a reduction in ventricular wall thickness and left atrial dimensions.[19] Interstitial myocardial edema secondary to myocarditis was suspected to be at the origin of the thickening. The occurrence of stressful events in the period prior to heart failure in a significant percentage of patients (71%) has led to the suspicion of a particular form of stress-induced cardiomyopathy. Transient myocardial thickening associated with atrioventricular and intraventricular conduction abnormalities was also reported in a cat with *Toxoplasma gondii* myocarditis diagnosed by endomyocardial biopsy,[17] and in one cat that tested positive for *Bartonella henselae* [4] (Fig. 27.3).

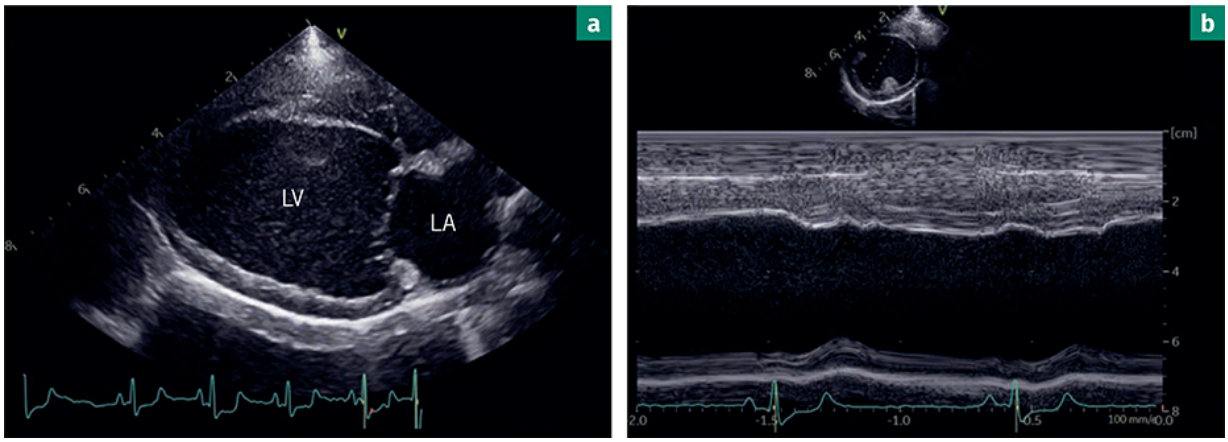


FIGURE 27.2. Five-year-old male mongrel with chronic myocarditis and distemper virus persistence demonstrated by endomyocardial biopsy. a) Right parasternal four-chamber echocardiographic view. Note the left ventricular volume overload secondary to moderate to severe systolic dysfunction (left ventricular two-dimensional ejection fraction: 31%). b) M-mode view of the left ventricle showing increased end-diastolic and end-systolic left ventricular diameters with moderate to severe left ventricular systolic dysfunction (shortening fraction: 20%). LA, left atrium; LV, left ventricle.

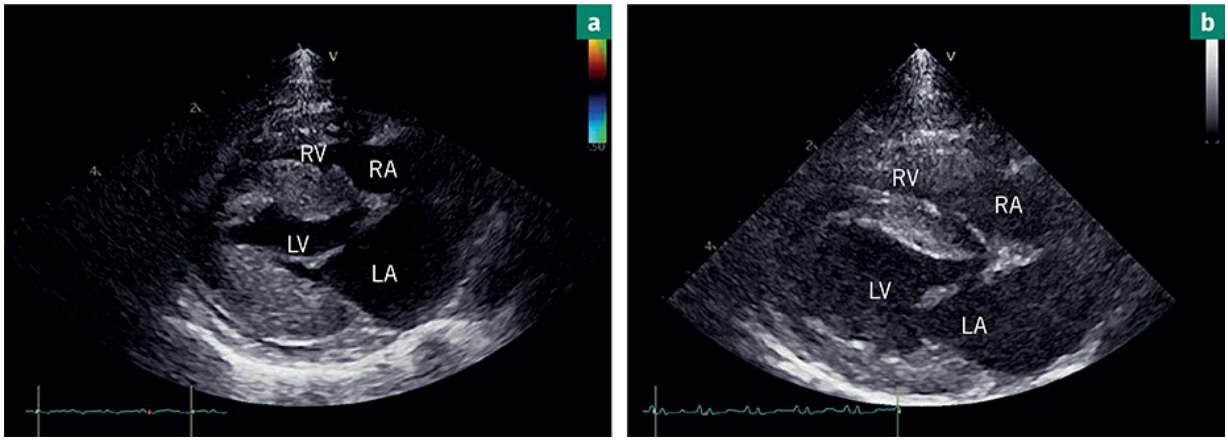


FIGURE 27.3. Acute myocarditis due to *Bartonella* spp. and transient myocardial thickening in a 2-year-old female Siamese cat. a) Day 1, right parasternal long-axis echocardiographic view of the left ventricle at the end of diastole presenting severe concentric symmetric hypertrophy and decreased myocardial echogenicity. The patient's cardiac troponin I concentration was 13.9 ng/dL. b) Day 32, right parasternal long-axis echocardiographic view of the left ventricle at the end of diastole, showing complete reverse remodeling of the left ventricle with regression of hypertrophy and disappearance of myocardial thickening. The patient's cardiac troponin I concentration was 0.32 ng/dL. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

ARRHYTHMIAS IN MYOCARDITIS

Many types of arrhythmias may occur in humans and animals with myocarditis at any stage of the disease: hot-phase arrhythmias occur during the onset of the myocardial disorder (acute or fulminant myocarditis), while cold-phase arrhythmias appear in the chronic stage or postmyocarditis.[24]

In the acute phase of myocarditis, the most common arrhythmias encountered are atrioventricular and intraventricular conduction abnormalities and supraventricular arrhythmias, while in the chronic phase ventricular arrhythmias predominate.[9] The electrocardiograms of dogs with postmortem proven myocarditis revealed 54% had ventricular premature complexes, 33% ventricular tachycardia, and 13% both, while 7% had supraventricular tachycardias and another 7% had atrioventricular block (Figs. 27.4 and 27.5).[7]

Several papers described the association between conduction disturbances and myocarditis in the dog.[3,6,25,26] The follow-up of a large number of dogs after pacemaker implantation for third-degree atrioventricular block demonstrated a complete or partial regression of the conduction disturbance over a period of one month postprocedure, thus

suggesting, for the first time in this species, that acute myocarditis was a possible cause of transient atrioventricular block.[27] In a 2019 study, out of 6 dogs with third-degree atrioventricular block that underwent endomyocardial biopsy, 3 were found to be affected by canine coronavirus and *Leishmania infantum*.[6]

In cats, a few case reports have documented the association of atrioventricular and intraventricular conduction disturbances with suspected acute myocarditis, with complete resolution of the clinical signs as the myocardial disorder resolved.[4,5] Trifascicular block characterized by intermittent block of the three bundle branches or by bifascicular block associated with second-degree atrioventricular block was diagnosed in 3 cats in which myocarditis was suspected on the basis of cardiac troponin I (cTnI) elevation and resolution of conduction disturbance at follow-up (Fig. 27.6).[5]

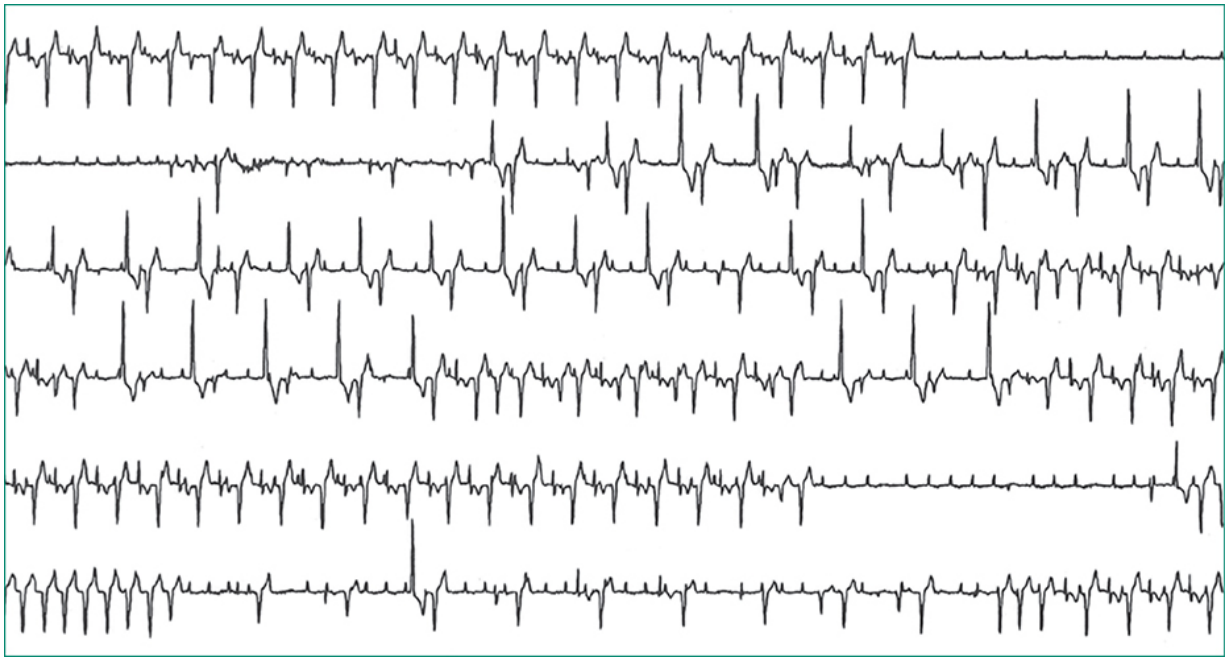


FIGURE 27.4. Paroxysmal atrioventricular block secondary to acute myocarditis in a 3-year-old female domestic shorthair cat. The first part of the Holter tracing shows a ventricular bigeminy followed by a sudden ventricular arrest of 7.9 seconds due to paroxysmal atrioventricular block. The atrioventricular block persisted for part of the following tracing, with variable escape rhythms and ventricular ectopies. Ventricular bigeminy then recurred, followed by a new ventricular arrest of 3.4 seconds due to a new episode of paroxysmal atrioventricular block that was interrupted by monomorphic ventricular tachycardia. Lead Y; each line corresponds to 30 seconds. Speed, 7.5 mm/s; calibration, 5 mm/mV.

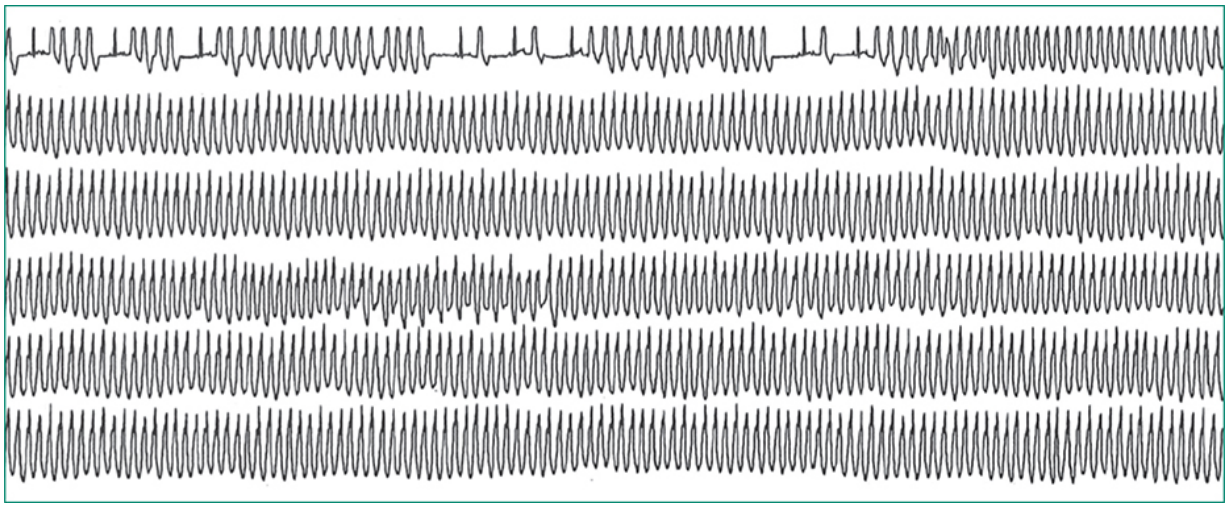


FIGURE 27.5. Chronic myocarditis and endocardial biopsy-proven parvovirus persistence in a 2-year-old male Australian Shepherd. The first part of the Holter tracing shows repetitive monomorphic ventricular tachycardia with left bundle branch morphology, which for the rest of the tracing becomes sustained. The documented arrhythmia is related to an anatomical scar-related reentrant circuit. Lead Y; each line corresponds to 30 seconds. Speed, 7.5 mm/s; calibration, 5 mm/mV.

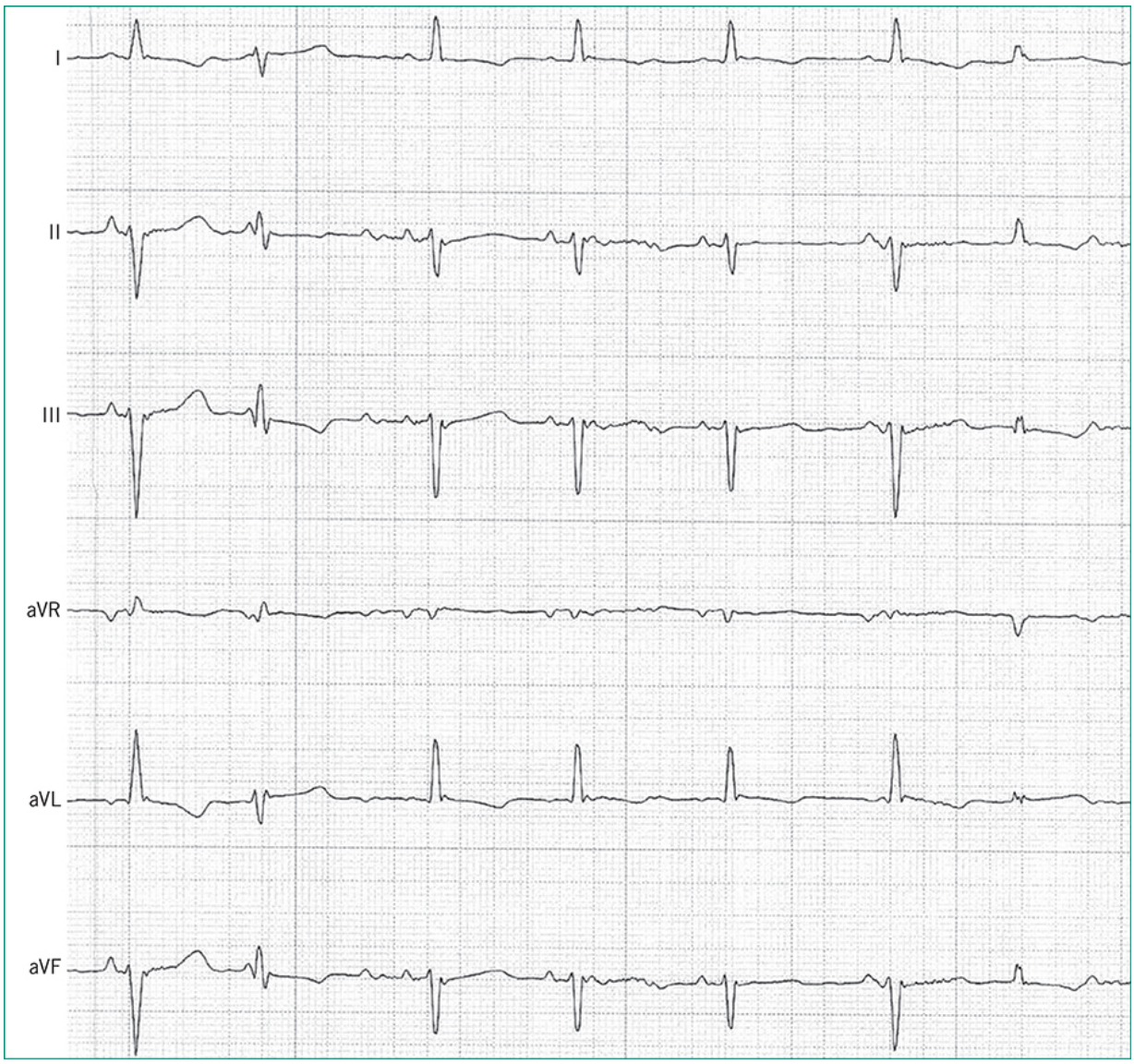


FIGURE 27.6. Acute myocarditis due to *Bartonella* spp. and transient myocardial thickening and trifascicular block in a 2-year-old female Siamese cat (same animal as in Fig. 27.3). The first beat is a sinus beat conducted with bifascicular block (left anterior fascicular block and right bundle branch block) followed by a second-degree atrioventricular block and then by a sinus rhythm conducted with left anterior fascicular block. The presence of a bifascicular block and second-degree atrioventricular block is diagnostic of a trifascicular block. Six limb leads (I, II, III, aVR, aVL and aVF). Speed, 50 mm/s; calibration, 10 mm/1 mV.

Several hypotheses have been postulated to explain hot-phase arrhythmias:

1. A direct cytopathic effect leading to electrical instability secondary to myocyte membrane lysis.
2. Ischemia from coronary macrovascular or microvascular disorders.

3. Gap junction dysfunction and impaired myocardial expression of connexins.
4. Abnormal calcium handling and ion channel impairment particularly when in association with arrhythmogenic cardiomyopathy.[24]

In humans, transient conduction disturbances have been explained by compressive damage of the conduction tissue secondary to inflammatory interstitial edema.[28] Supraventricular arrhythmias can be found mainly during the hot phase when pericardial inflammation is also present.[24]

Cold-phase arrhythmias include ventricular and supraventricular arrhythmias, which may result from either persistent inflammation or postinflammatory myocardial scar.[24] Persistent inflammation may derive from a combination of persistent viral genome and/or an immune dysregulating phenomenon. However, postinflammatory fibrosis and scar-related arrhythmias such as monomorphic ventricular tachycardias can develop even if the pathogen has been cleared.[24]

Ventricular arrhythmias have been reported in dogs in association with myocarditis and myocardial ischemia, sepsis, anemia, and metabolic diseases; these arrhythmias are therefore not very specific of a disease.[7] However, in a study in dogs suffering from unexplained myocardial or arrhythmic disorders in which endomyocardial biopsy was performed, 3 of 4 dogs with symptomatic ventricular tachycardias that required pharmacological treatment showed histological evidence of myocarditis caused by different pathogens.[6]

Supraventricular arrhythmias were associated in the same study with viral persistence secondary to distemper.[6] A study conducted in humans showed an association between atrial myocarditis and ventricular myocarditis in patients with myocardial inflammation from various causes, suggesting that myocarditis patients are predisposed to the development of supraventricular tachycardias together with ventricular arrhythmias inducing congestive heart failure and sudden cardiac death.[29]

BIOMARKERS AND VIRAL SEROLOGY

Cardiac troponin I is a protein released by damaged cardiomyocytes and can therefore be used with a good sensitivity and specificity as a marker of myocardial damage.[30] Increases in cTnI (>0.2 ng/mL) were described in dogs with infiltrative myocardial diseases, including myocarditis, with a good diagnostic and prognostic value.[31,32] Cardiostructural disorders such as dilated cardiomyopathy or chronic mitral valve disease cause only mild to moderate increases in cTnI (up to 1.57 ng/mL), since the etiopathogenesis of these disorders does not involve myocyte destruction.[31] More significant increases in cTnI likely reflect direct myocardial damage or ischemia.[30] However, to date there is no large-scale accepted cutoff value above which acute infiltrative or ischemic myocardial damage can be suspected. According to some authors, a cTnI concentration cutoff value of >1.405 ng/mL is a relatively sensitive indicator of myocarditis.[32] In a 2020 study, cTnI was assessed at initial evaluation in 29 dogs. The median initial cTnI concentration was 12.2 ng/mL (range, 0.2–808.0 ng/mL); individual values exceeded the upper end of the laboratory's reference interval (>0.2 ng/mL) in all cases. Initial cTnI exceeded 1.0 ng/mL in 90% dogs and 1.405 ng/mL in 83% of dogs. Cardiac troponin I was retested at a subsequent follow-up examination (median, 26 days later; range, 0–827 days) in 26 dogs: cTnI levels had decreased in 76% of cases and increased in 24%.[7]

Other biomarkers such as creatine kinase, white cell count, and C-reactive protein have low specificity and low sensitivity in the diagnosis of myocarditis.[9]

The utility of viral serology in patients with suspected myocarditis remains unclear and is currently not included in the standard diagnostic protocol of human patients with suspected myocarditis.[9] In a study aimed at clarifying the diagnostic value of serology when compared to viral genome analysis of endomyocardial biopsy samples, serological evidence of the infection detected with endomyocardial biopsy was found in only 4% of patients.[33]

ENDOMYOCARDIAL BIOPSY

Endomyocardial biopsy is currently recognized in human medicine as a fundamental step for confirmation of myocarditis, and histological analysis

of the samples combined with molecular biology techniques and immunohistochemistry often plays a critical role in the identification of those patients needing specific treatment.[9]

In veterinary medicine, endomyocardial biopsy is rarely used. In a recent study conducted in 47 dogs, a modified technique was performed by inserting, using the Seldinger method, a vascular sheath (7 Fr, length 40 cm) with a curved tip in the left jugular vein at a 70-degree angle approximately (Fig. 27.7). Under fluoroscopic guidance, the introducer was advanced into the right ventricle through the cranial vena cava and right atrium, with the tip passing through the tricuspid valve to limit potential valve damage caused by the passage of the bioptome. In this study, three biopsy samples were taken from the right ventricular apex and three from the interventricular septum to perform histology, immunohistochemistry, and molecular biology.[6] Specific histological criteria were used for the diagnosis of myocarditis, defined by the presence of ≥14 leukocytes/mm^2, and ≥7 CD3-positive T lymphocytes/mm^2.[8,9] The most common diagnosis in dogs with unexplained myocardial and rhythm disorders (monomorphic ventricular tachycardia and/or supraventricular tachycardias including lone atrial fibrillation) was chronic myocarditis with viral persistence (40% of dogs) characterized by the presence of lymphocytic/plasma cell infiltrates and a PCR test positive for a cardiotropic virus. The other dogs had primary cardiomyopathies (15%), acute/subacute myocarditis associated or not with a positive PCR test (10.6%), 1 dog had chronic myocarditis with a negative PCR test (postmyocardial phase), while no or mild nonspecific histological findings were observed in the remaining dogs.[6] Another study showed the presence of neutrophils in 47% of the hearts examined postmortem and a concomitant valvular endocarditis was found in 14.5% of the cases.[7]

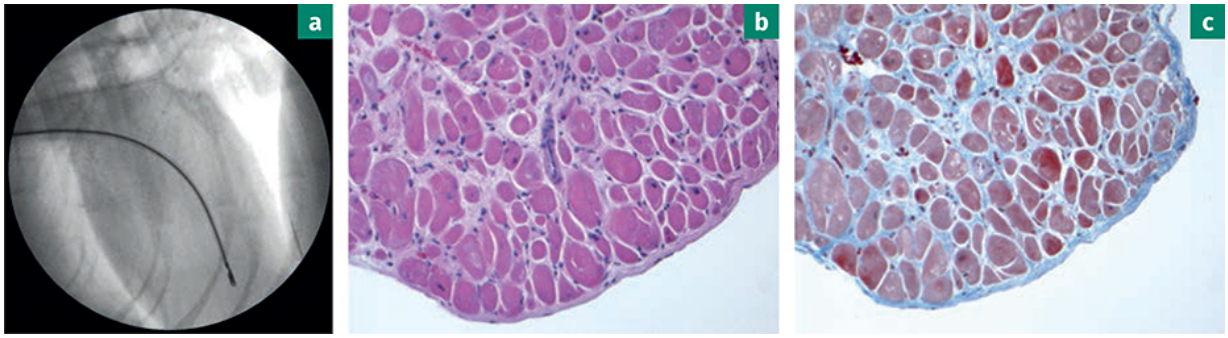


FIGURE 27.7. a) Right lateral fluoroscopic view of the heart during right ventricular endomyocardial biopsy. A 7 Fr sheath is first advanced along a hydrophilic wire into the right ventricle, then a bioptome is placed at different levels of the right ventricle to obtain 3–6 myocardial samples. b) Myocardial sample from the right ventricular apex of a 3-year-old male Giant Schnauzer with chronic myocarditis due to a canine parvovirus, stained with eosin and hematoxylin. The stain shows lymphoplasmacellular infiltrates (×10). c) Myocardial sample of the right ventricular apex from the same dog stained with Masson's trichrome showing interstitial and endocardial fibrosis (×10). Image courtesy of Dr. M. Tursi, University of Turin, Italy.

THERAPY

The three crucial points of the treatment of myocarditis in humans are pathogen inhibition, modulation of the immune system, and control of heart failure. The treatment must take into consideration the etiological diagnosis and staging of the disease clarified by endomyocardial biopsy.[9]

As regards the inhibition of the pathogen during acute viral myocarditis in humans, the early use of antivirals such as interferon have shown positive effects on systolic function and survival in some clinical trials. Immunosuppression can be considered safe in case of virus-negative myocarditis, and in some etiopathogenetic categories such as eosinophilic and giant cell myocarditis and forms associated with connective tissue diseases.[9]

Potential targets for new biological therapies are under evaluation in humans and involve blocking inflammatory cells and cytokines in the hot phase and inhibiting myofibroblasts in the cold phase.[24]

In dogs and cats, all specific treatments are empirical and controversial. If myocarditis is not associated with a systemic infectious disease (e.g., viral diseases such as parvovirus, or bacterial, parasitic, or fungal diseases), the indications are currently limited to management of the clinical signs of congestive heart disease, drug treatment of symptomatic supraventricular and ventricular arrhythmias, and electrical treatment of bradyarrhythmias with a permanent cardiac stimulator. There is evidence from experimental studies in rats that drugs commonly used to treat heart failure in dogs and cats can also have a beneficial effect on myocarditis. For example, it appears that angiotensin-converting enzyme inhibitors reduce the extent of myocardial inflammation. Furthermore, the activation of cytokines secondary to the inflammatory process leads to an increase in the synthesis of nitric oxide by the damaged myocytes; theoretically, this effect could be

minimized through the use of pimobendan and amlodipine. Digoxin, however, is contraindicated due to its ability to stimulate the production of proinflammatory cytokines, cause vascular spasm, worsen the extent of myocardial damage, induce arrhythmias, and increase mortality. The use of ß-blockers could reduce the extent of myocardial damage and increase survival.[7,9]

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CHAPTER 28

Arrhythmias in arrhythmogenic cardiomyopathy

Romain Pariaut

DEFINITION

Arrhythmogenic cardiomyopathy is an arrhythmogenic muscle disorder most commonly identified in Boxers and English Bulldogs, with occasional occurrences in other dog breeds and cats.[1–3] It is still commonly referred to as "arrhythmogenic right ventricular cardiomyopathy" because it resembles the initial description of the disease in humans: the ventricular arrhythmias have a typical morphology that suggests a right ventricular origin, and pathological alterations predominantly affect the right heart.[2–4] However, left ventricular and biatrial involvement has been recognized in dogs, cats, and humans.[1,4–9] In addition, in certain instances, a segmental form of the disease has been documented, with only a specific section of the heart muscle being affected, typically the right ventricular outflow tract.[10] This expanded understanding has led to a preference for the more encompassing term "arrhythmogenic cardiomyopathy", rather than the previous designation that placed the focus on the right ventricle.

PATHOPHYSIOLOGY

Evidence points towards dysfunction of the desmosome as the most common cause of arrhythmogenic cardiomyopathy in humans and dogs.

The desmosome is a component of the intercalated disc, along with the adherens junction, the gap junction, and several ion channels.[5] Desmosomal abnormalities have been identified in Boxer dogs and manifest as a reduction of the immunofluorescent signal for plakoglobin on postmortem histopathology and endomyocardial biopsies.[6,11,12] In humans, 5 out of the 8 genes most frequently linked to arrhythmogenic cardiomyopathy encode for desmosomal proteins.[5] In Boxer dogs, the disease is inherited as an autosomal dominant trait, but to this day only one genetic mutation has been associated with the condition in some animals.[13,14] This mutation affects a gene that encodes for striatin, a protein that coexists with desmosomal proteins and the intermediate filaments.[14] The question of whether the disease is directly caused by the striatin deletion or if the striatin gene is associated with an unidentified gene responsible for the condition remains unresolved.[15] In humans and animals, arrhythmogenic cardiomyopathy has variable penetrance and expression, which suggests the contribution of modifier genes and environmental factors to the phenotypic expression of the disease.[5]

How desmosomal abnormalities ultimately lead to the pathological and clinical manifestations of arrhythmogenic cardiomyopathy is not completely understood. A plausible explanation is that desmosomes provide mechanical coupling between myocytes, and that desmosomal protein alteration may disrupt normal myocardial function. Consequently, myocardial damage occurs, with secondary inflammation, fibrosis, and adipocytosis due to increased myocardial strain.[3,5] Indeed, there is strong evidence that exercise is the main environmental factor that influences the phenotypic expression of arrhythmogenic cardiomyopathy in people with desmosomal mutations linked to the disease. Notably, athletes have a higher incidence of arrhythmogenic cardiomyopathy than the general population.[4] The link between exercise and disease severity has not been established in dogs. However, the structural and electrical alterations in arrhythmogenic cardiomyopathy likely stem from multiple causes, primarily due to the complex interactions between intercalated disc proteins. Certain proteins and striatin are involved in signaling pathways linked to adiposis, fibrosis, and apoptosis, while others interact with connexin-43 (Cx43, a major constituent of the gap junction) and ion channels, and play a role in calcium

homeostasis.[5,16] Oxford et al. showed differences in the intracellular distribution of the striatin protein between control and affected Boxers and provided some evidence that disruption of the canonical Wnt/β-catenin pathway, which is involved in cell proliferation and differentiation in the developing heart and in remodeling of the adult heart, may be involved in the process of fibrofatty accumulation.[17]

Arrhythmias in arrhythmogenic cardiomyopathy are likely influenced by several factors, such as compromised structural integrity of the myocardium, impaired gap junction function, altered inward Na^+ current, and abnormal intracellular Ca^{2+} handling.[5] The normal architecture of the tissue is disrupted by atrial and ventricular fatty and fibrofatty myocardial replacement, which first takes place in the epicardium (Fig. 28.1). In animals, the right ventricle appears to be affected earlier based on the origin of the arrhythmias, echocardiographic changes, and necropsy findings. Traditionally, the "triangle of dysplasia" in the right ventricle, which comprises the inflow tract, outflow tract, and apex, has been recognized as the primary area of cardiac involvement. However, recent studies in people indicate that the left ventricle might be affected earlier in the course of the disease.[3,5] The accumulation of fibrous and fatty tissue within the myocardium creates a substrate for reentrant arrhythmias. Abnormal intracellular calcium cycling can lead to arrhythmias triggered by delayed afterdepolarizations during high catecholamine states, such as exercise.[18–20]

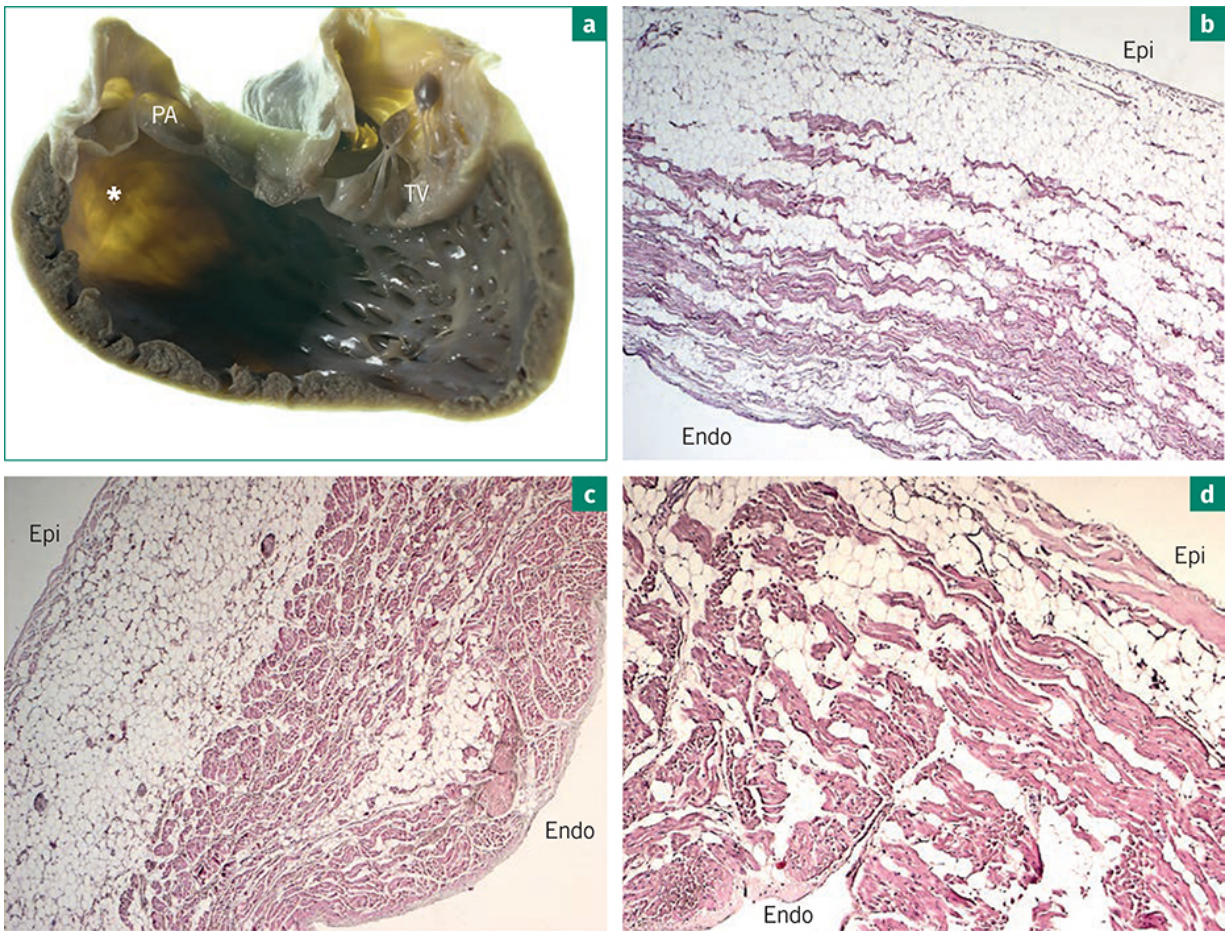


FIGURE 28.1. Transillumination testing. Endocardial view of the free wall of the right ventricular outflow tract in an 8-year-old male English Bulldog with arrhythmogenic cardiomyopathy. Due to fibrofatty tissue replacement, a large area at the level of the infundibulum allows the passage of light (*). PA, pulmonary artery; TV, tricuspid valve (a). Histology images showing the right ventricular wall (×2.5) (b), right atrial wall (×2.5) (c) and left auricle (×5) (d) from the same dog. Extensive transmural fatty infiltration from the epicardium (Epi) to the endocardium (Endo). Hematoxylin–eosin staining. Images courtesy of Dr. Massimiliano Tursi, Department of Veterinary Sciences, University of Turin (Italy).

CLINICAL PRESENTATION

Arrhythmogenic cardiomyopathy has an adult onset. The median age at the time of diagnosis in Boxers has been reported to be 6 years, with a range of 1 to 11 years.[21] Two retrospective studies found that English Bulldogs tended to be older at initial presentation.[9,22] Males are overrepresented in most studies, though there are some exceptions.[9,22,23] Historically, and derived from studies in Boxer dogs, arrhythmogenic cardiomyopathy has

been categorized into three temporal phases. However, it is important to note that these phases may not always occur in sequence in all dogs affected by the disease.[24] Phase 1 is the subclinical or "concealed" phase of the disease and is characterized by the presence of ventricular arrhythmias and no obvious clinical signs. During this period, the arrhythmia is detected incidentally on auscultation, an electrocardiogram, or a 24-hour Holter recording during screening of a predisposed animal. During phase 2, clinical signs are associated with the arrhythmia. Syncope is the most common manifestation of the disease, followed by exercise intolerance and weakness.[21] Studies report that syncope is the first presenting clinical sign in up to two thirds of Boxers with arrhythmogenic cardiomyopathy.[25,26] Some dogs experience sudden death as the first overt sign of the disease. Cunningham et al. reported that during this phase, the echocardiogram suggests a mild reduction in right ventricular systolic function, whereas the left ventricular systolic function remains normal.[27,28] Right ventricular systolic dysfunction was also identified by magnetic resonance imaging in the absence of morphological changes.[29] Nevertheless, other researchers failed to detect a decline in right ventricular function in affected dogs when assessing multiple echocardiographic parameters.[30] Phase 3 is reached when a dilated cardiomyopathy phenotype accompanies the arrhythmia. In this phase, left, right, or biventricular congestive heart failure occurs.[2] Boxer dogs with the striatin mutation may be at higher risk of developing a dilated cardiomyopathy phenotype.[31] It is important to distinguish phase 3 arrhythmogenic cardiomyopathy, which corresponds to the end stage of the disease, from arrhythmia-induced cardiomyopathy (see p. 395), which can occur in dogs with frequent, repeated episodes of tachycardia and sometimes in animals with a high percentage of ventricular premature complexes in the absence of sustained tachycardia. In these animals, cardiac chamber size and function typically improve weeks after initiation of effective antiarrhythmic therapy.

In cats, right-sided congestive heart failure is the most common presentation of arrhythmogenic cardiomyopathy. Nonspecific signs of lethargy and anorexia have also been reported, and the author has diagnosed arrhythmogenic cardiomyopathy in an apparently healthy cat after incidental detection of an arrhythmia.[1]

SUPRAVENTRICULAR ARRHYTHMIAS IN ARRHYTHMOGENIC CARDIOMYOPATHY

Supraventricular arrhythmias, including premature beats, nonspecific supraventricular tachycardia, and atrial fibrillation, were reported in 24% of a heterogeneous population of English Bulldogs with a clinical diagnosis of arrhythmogenic cardiomyopathy.[9] Clinically significant supraventricular arrhythmias are more commonly documented in dogs with concurrent signs of cardiac enlargement and congestive heart failure. These arrhythmias could result from cardiac remodeling associated with heart failure or from a combination of both.[6,22,23] However, supraventricular arrhythmias have been documented in dogs with confirmed arrhythmogenic cardiopathy via histopathology in the absence of atrial enlargement, suggesting that the cardiomyopathy itself may contribute to these arrhythmias (see Figs. 28.1c and 28.1d).[6]

Arrhythmias are also common in cats with arrhythmogenic cardiomyopathy. Fox et al. identified atrial fibrillation in 4 of 12 animals with this disease, and a supraventricular tachycardia in another affected cat. All these cats had marked right heart enlargement.[1]

VENTRICULAR ARRHYTHMIAS IN ARRHYTHMOGENIC CARDIOMYOPATHY

ELECTROPHYSIOLOGICAL MECHANISM

Various electrophysiological mechanisms may be responsible for ventricular arrhythmias at different stages of the disease. Studies in a murine model of arrhythmogenic cardiomyopathy suggested that triggered activity secondary to calcium cycling dysregulation could be responsible for ventricular arrhythmias during the concealed phase (phase 1) of the disease.[16,18] However, ventricular arrhythmias in dogs with arrhythmogenic cardiomyopathy are usually considered to be caused by anatomical reentries. Late potentials, which can result from areas of slow electrical conduction in the ventricular myocardium and may contribute to the substrate for reentrant arrhythmias, have been identified via signal-averaged

electrocardiography in Boxers with ventricular arrhythmias.[32] A reentrant mechanism for ventricular tachycardia has been confirmed in some dogs that underwent radiofrequency ablation.[10]

VENTRICULAR PREMATURE COMPLEXES

Meurs et al. demonstrated that affected Boxers exhibit significant day-to-day and yearly fluctuations in the number of ventricular premature complexes, which can vary by over 80%.[21,33] In certain cases, the number of ventricular premature complexes may drop below the standard cutoff of 100 to 300 ventricular premature complexes per 24 hours on a follow-up Holter recording after an initial positive diagnosis.[21] Temporal variability is also present over the course of the day, with a lower number of ventricular premature complexes during nighttime than in the morning and late afternoon hours.[34] This variation is likely attributable to increased sympathetic activity during times of the day when the animal is more active and interacting with its owners (Fig. 28.2).

Most Boxers with a clinical diagnosis of arrhythmogenic cardiomyopathy have been reported to exhibit a single ventricular premature complex morphology on the electrocardiogram.[24] However, when analyzing 24-hour long electrocardiographic tracings, Visher et al. found ventricular premature complexes of various morphologies in 91.7% of dogs (Fig. 28.3).[35] They also reported a short coupling interval (so-called R-on-T phenomenon) between ventricular premature complexes and the preceding sinus beat in 76.7% of animals.[35]

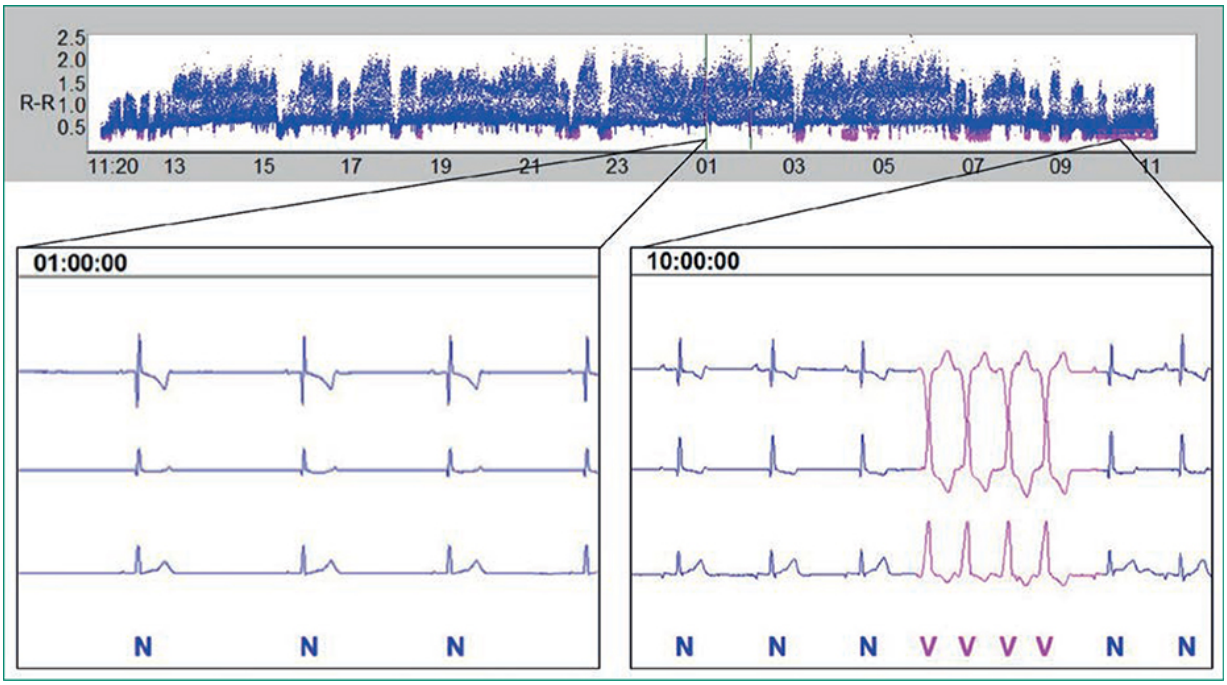


FIGURE 28.2. Twenty-four-hour heart rate tachogram illustrating the temporal variability of ventricular arrhythmias and the influence of adrenergic stimulation in arrhythmogenic cardiomyopathy. Ventricular arrhythmias (pink, V) are clustered around periods of elevated adrenergic tone, which can be identified by the increased rate of the underlying sinus rhythm (blue, N). Conversely, during periods of elevated vagal tone and sinus arrhythmia (for example from 23:00 to 03:00), only rare ventricular premature beats occur. X-axis, time; y-axis, R-R intervals in seconds.

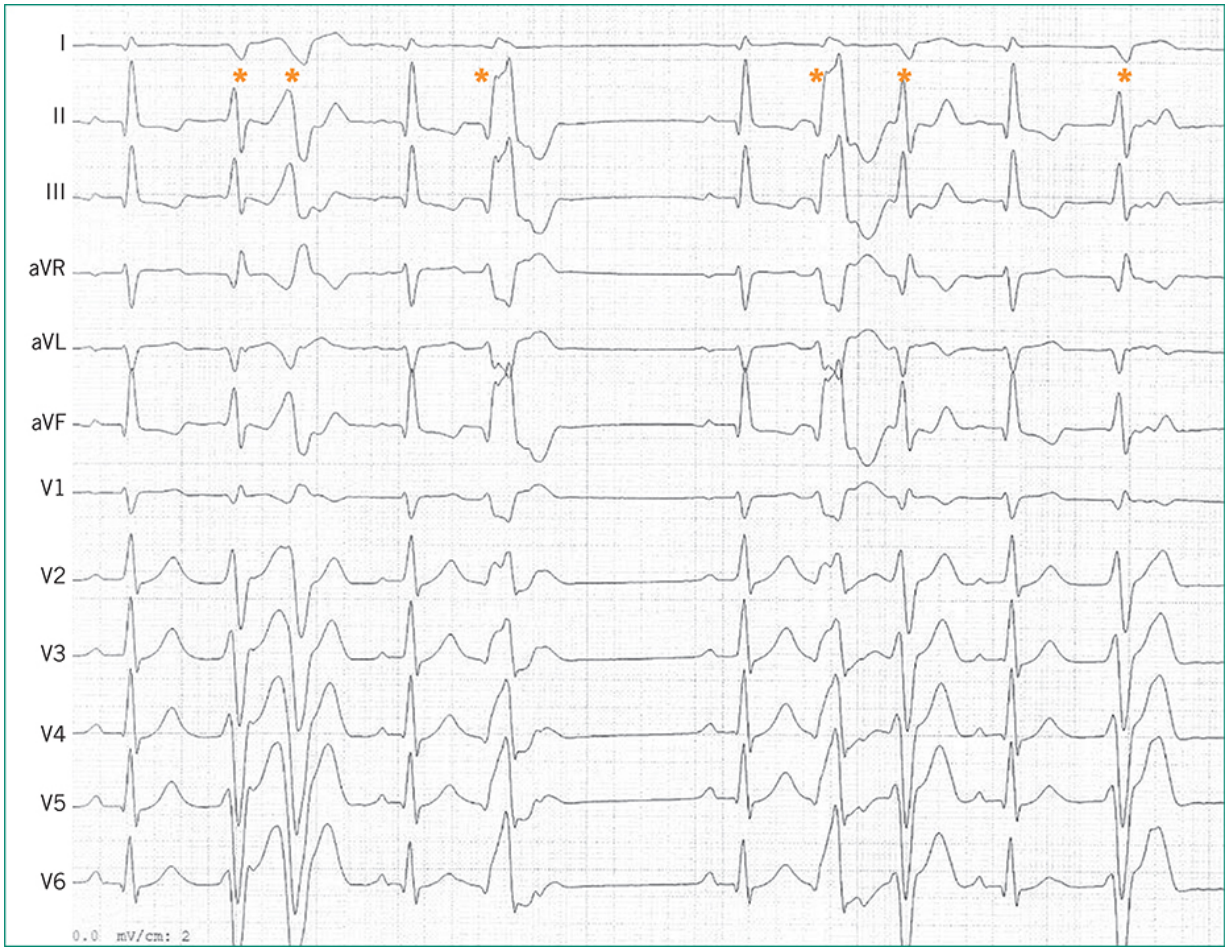


FIGURE 28.3. Sinus rhythm interrupted by frequent multiform ventricular ectopic beats (*) in a 7-year-old male Boxer with arrhythmogenic cardiomyopathy. Note the third and fourth ventricular ectopic beats present the typical left bundle branch morphology characteristic of this myocardial disorder. Twelve leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6). Speed, 50 mm/s; calibration, 2 mm/1 mV.

VENTRICULAR TACHYCARDIA

The typical ventricular tachycardia is monomorphic with a left bundle branch block–like pattern (Fig. 28.4).[3] In the veterinary literature, ventricular tachycardia is usually considered to have a left bundle branch block morphology if a positive and prolonged QRS complex is observed in the inferior leads (II, III, and aVF).[3] It differs from the criteria used in human cardiology, which include a wide QRS complex and a predominantly negative QRS deflection in lead V1.[36] In a group of English Bulldogs, Santilli et al. identified the mechanism of the arrhythmia as an anatomical reentry, with its origin in the right ventricular outflow tract.

They were also able to determine with greater precision the location of the site of origin of the tachycardia based on the morphology of the QRS in lead I: a negative QRS complex indicated the arrhythmia originated from the anterior portion of the right ventricular outflow tract, while a positive QRS complex was associated with an arrhythmia originating from the posterior portion of the right ventricular outflow tract. Finally, a negative QRS complex in aVL indicated that the ventricular tachycardia arose near the pulmonic valve (Fig. 28.5).[10] In dogs with advanced disease, it is not uncommon, however, to observe several QRS morphologies during different episodes of ventricular tachycardia.[23]

Ventricular arrhythmias are also common in cats with arrhythmogenic cardiomyopathy.[1]

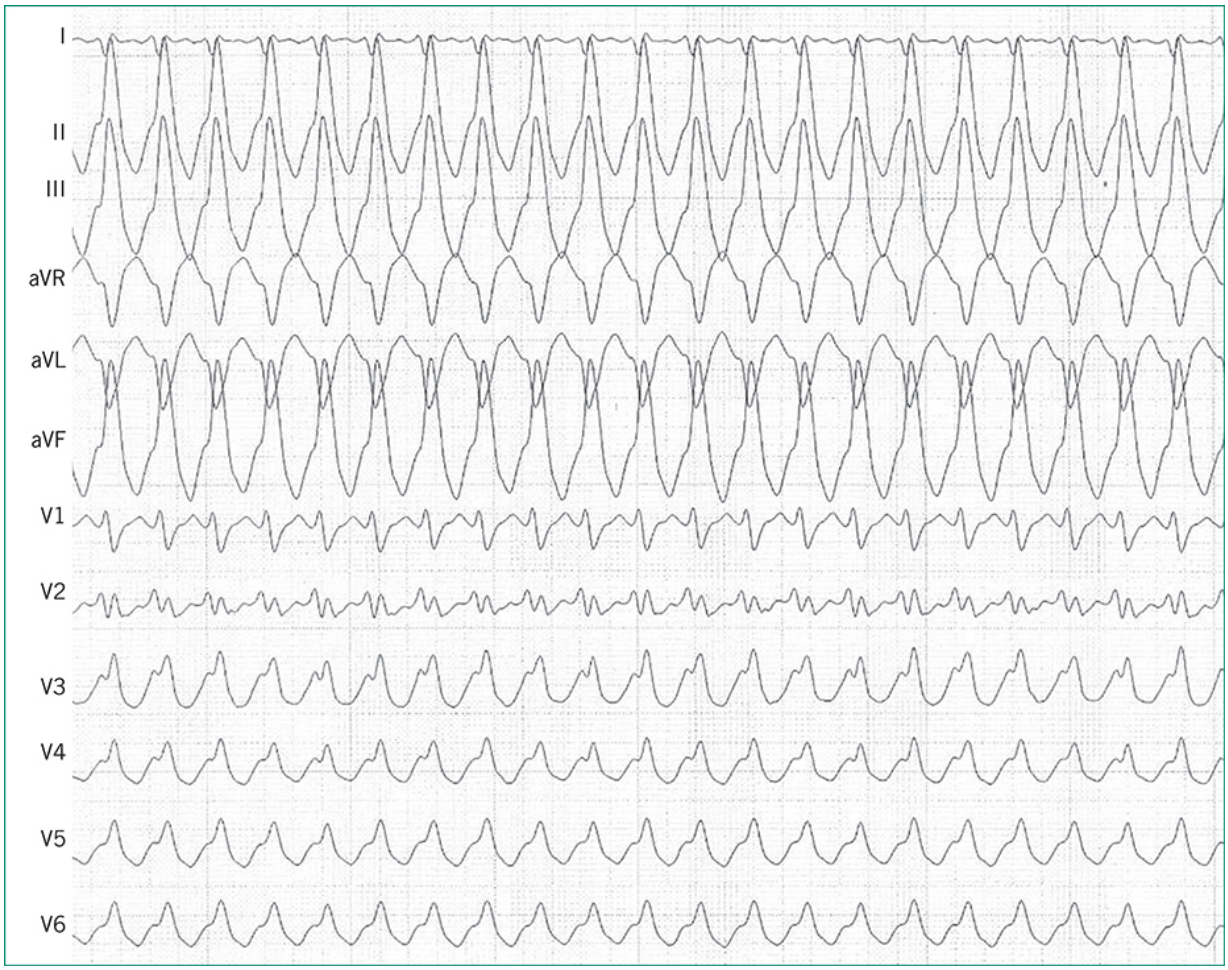


FIGURE 28.4. Sustained monomorphic ventricular tachycardia arising from the anterior portion of the right ventricular outflow tract in a 9-year-old female English Bulldog with arrhythmogenic cardiomyopathy. Note the presence of wide monomorphic QRS complexes (80 ms) with a left bundle

branch block morphology and a normal axis in the frontal and horizontal planes. Note also the negative QRS complexes and regular ventricular rate of 340 bpm in lead I. Twelve leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6). Speed, 50 mm/s; calibration, 2 mm/1 mV.

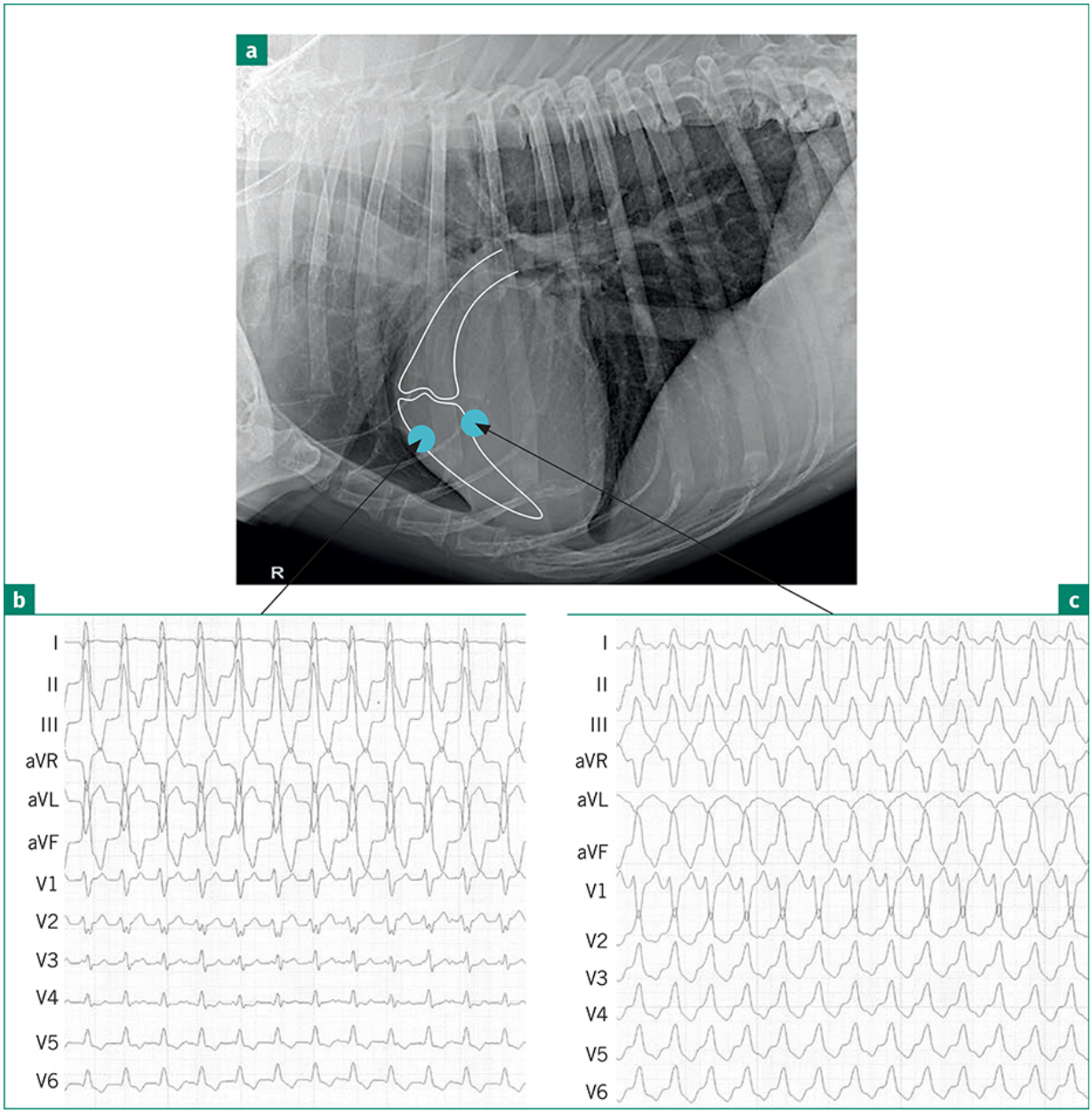


FIGURE 28.5. a) Anatomical representation of the right ventricular outflow tract in the dog's chest. b) Monomorphic ventricular tachycardia arising from the anterior portion of the right ventricular outflow tract, with a left bundle branch morphology in the frontal and horizontal planes and a negative morphology in lead I; c) Monomorphic ventricular tachycardia arising from the posterior portion of the right ventricular outflow tract with a left bundle branch morphology in the frontal and horizontal planes and a positive morphology in lead I. Twelve leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6). Speed, 50 mm/s; calibration, 2 mm/1 mV).

IDENTIFICATION OF ANIMALS AT HIGH RISK FOR SUDDEN DEATH

In a prospective study investigating the natural history of arrhythmogenic cardiomyopathy in Boxers, Meurs at al. observed that a large proportion (30.6%) of Boxers with this disease experienced sudden death. However, there was no difference in survival between the affected dogs and the age-matched control group, with a median age of affected dogs at the time of death of 11 years following a median follow-up period of 5 years.[21]

Various studies investigated the link between syncope and a shorter survival time, with conflicting results. These discrepancies likely stem from variations in the canine populations studied. Caro-Vadillo et al. found that Boxers with syncope and normal left ventricular dimensions had a 4.875 times increased likelihood of dying within a year.[25] Another retrospective study reported that English Bulldogs with documented syncope had a shorter median survival time (4.9 months) than the overall median survival time of 8.3 months.[22] Palermo et al. found a higher risk of death if the syncopal dogs also had an increased left ventricular systolic diameter.[23] However, the presence of syncope did not correlate with a shorter survival time in a study by Mõtsküla et al., although it is worth noting that this study included younger Boxers that may have suffered from neurocardiogenic syncopal events. [26]

Even in the absence of syncope, dogs with left ventricular enlargement have a shorter survival time than dogs with a normal left ventricle.[26] In these dogs, in which left ventricular enlargement likely represents a more advanced stage of the disease, death can be secondary to congestive heart failure or sudden cardiac death.

There is limited evidence that associates arrhythmia frequency and complexity with an increased risk for sudden cardiac death. In the study by Mõtsküla et al., in dogs with arrhythmogenic cardiomyopathy and normal left ventricular dimensions, the presence of ventricular tachycardia was associated with a shorter survival time, in some cases because of an arrhythmic death.[26] Caro-Vadillo et al. reported the risk of cardiac-related mortality (defined as sudden death within the first year following diagnosis) to be 4.8 times higher in dogs with syncope and 5.43 times higher in those

with over 10,000 ventricular premature complexes daily. In dogs with more than 200 episodes of ventricular tachycardia per day, the risk was 20 times higher.[25] Conversely, Holdt et al. found that increased ventricular arrhythmia complexity was not associated with a higher incidence of sudden cardiac death in a group of English Bulldogs with arrhythmogenic cardiomyopathy.[9]

DIAGNOSIS

It is currently not possible to establish a definitive clinical diagnosis of arrhythmogenic cardiomyopathy. The gold standard for diagnosis still relies on postmortem histopathology.[3] A 2021 pilot study reported the feasibility of endomyocardial biopsy and the use of immunofluorescent techniques to identify affected dogs.[12] However, these results need to be confirmed in a larger group of animals to establish this technique as a possible diagnostic tool. A scoring method that integrates major and minor criteria, using abnormalities observed in cardiac imaging, electrocardiography, and family history, is employed to diagnose arrhythmogenic cardiomyopathy in human patients.[4] A comparable scoring system has not yet been developed for dogs.

In most cases, the diagnosis is made by identifying ventricular arrhythmias in a middle-aged dog of a predisposed breed (Boxer or English Bulldog) after ruling out other cardiac diseases, metabolic causes, and abdominal masses. The traditional cutoff for ventricular arrhythmias to distinguish affected from healthy dogs has been set at more than 100 ventricular ectopies on a 24-hour Holter recording.[37] However, other authors have proposed incorporating evidence of arrhythmia complexity to better distinguish affected from unaffected dogs. A cutoff of 100 ventricular ectopies was suggested, with the presence of couplets and beats with a short coupling interval abutting on the previous T wave as additional criteria.[35] In nonpredisposed breeds, arrhythmogenic cardiomyopathy can be suspected in the presence of a ventricular arrhythmia with characteristics resembling reentrant ventricular tachycardia originating from the right ventricular outflow tract region. Echocardiographic evidence of structural and functional cardiac changes may also aid in the diagnosis, although right

heart changes are usually too mild to be useful as standalone criteria.[27] Echocardiographic studies in dogs suspected of arrhythmogenic cardiomyopathy should include a detailed assessment of the right heart. A mild reduction in tricuspid annular plane systolic excursion or TAPSE (<15.1 mm), an echocardiographic marker of right ventricular function, was reported to be associated with a shorter time to cardiac death in Boxers, even in the absence of left ventricular dysfunction.[38] Additionally, in some dogs, especially English Bulldogs, a focal aneurysmal dilation of the outflow tract can be another abnormality supporting the diagnosis.[39,40]

In cats, right heart changes are more pronounced and include marked right atrial and ventricular enlargement as well as focal areas of aneurysmal dilation in the apical and subtricuspid region (Fig. 28.6).[1]

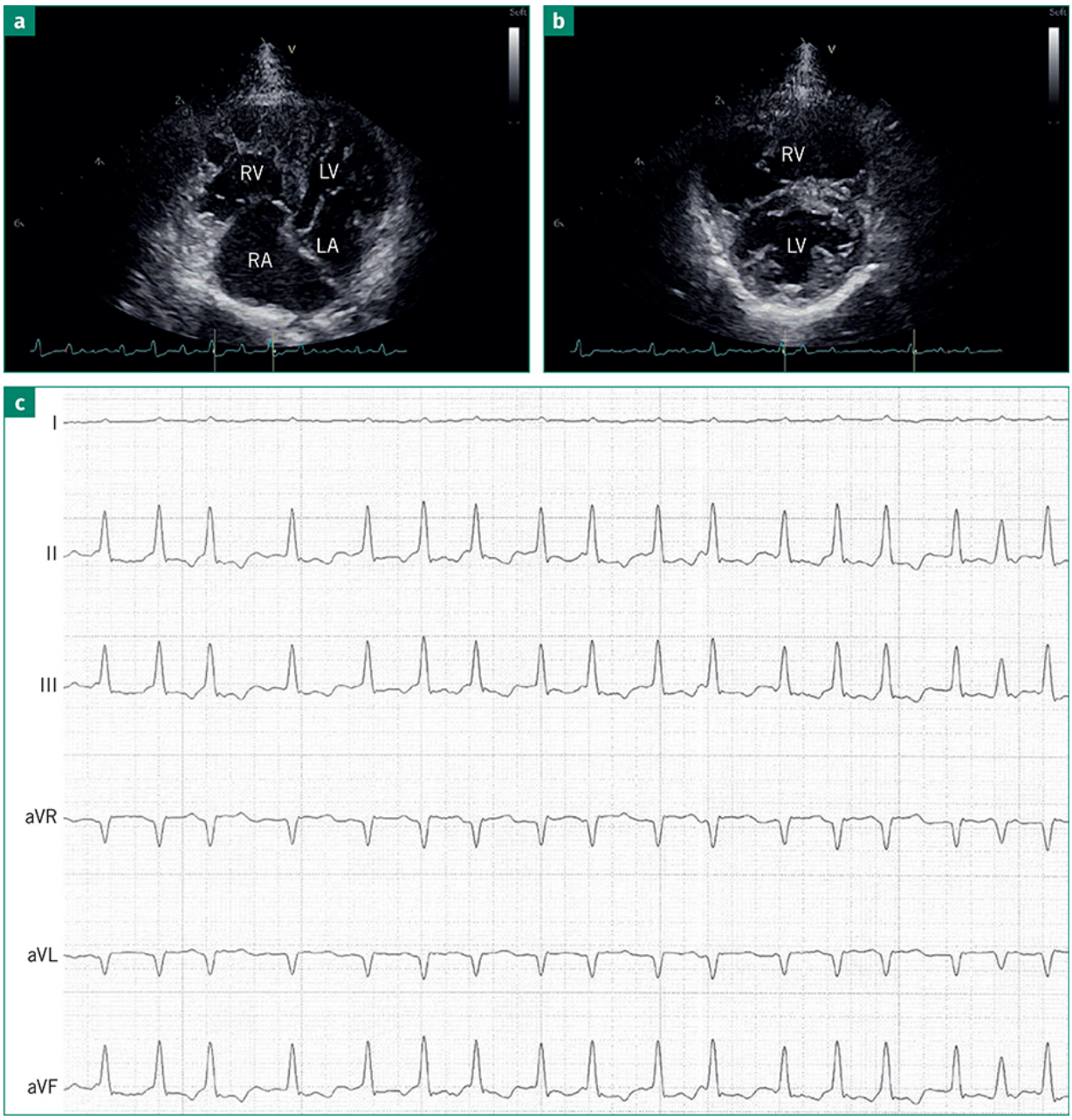


FIGURE 28.6. Echocardiogram and electrocardiogram from a cat with arrhythmogenic cardiomyopathy. a) Two-dimensional left parasternal long-axis four-chamber view. Severe dilation of the right atrium and right ventricle. There is also moderate enlargement of the left heart chambers. b) Two-dimensional right parasternal short-axis mid-ventricular view. The right ventricle is severely dilated. There is septal flattening in diastole due to right-sided chamber volume overload. LA, left atrium; RA, right atrium; LV, left ventricle; RV, right ventricle. c) This cat's rhythm was persistent atrial fibrillation, which is rare in this species but more commonly reported with this condition. Six limb leads (I, II, III, aVR, aVL, aVF). Speed, 50 mm/s; calibration, 10 mm/mV.

THERAPY

Treatment goals revolve around alleviating the burden of arrhythmias, controlling the clinical signs, and preventing sudden cardiac death. Strategies to slow disease progression have not been investigated in veterinary medicine. In humans, the clear association between exercise and earlier phenotypic expression of arrhythmogenic cardiomyopathy has led to lifestyle modification recommendations in the current guidelines.[4] It is advised that people with a diagnosis of arrhythmogenic cardiomyopathy or at risk of developing the disease should refrain from high-intensity endurance exercise and most competitive sports.[4]

MEDICAL THERAPY

Some dogs with arrhythmogenic cardiomyopathy present with rapid monomorphic ventricular tachycardia that can persist for several hours, or repeated episodes of ventricular tachycardia over the course of several days. These arrhythmic events can be described as electrical storms.[41] In arrhythmogenic cardiomyopathy, it has been suggested that acute inflammation could trigger some of those episodes. Indeed, a higher serum cardiac troponin I (cTnI) concentration was reported in Boxers with arrhythmogenic cardiomyopathy, and a correlation as found between the cTnI concentration and the number of arrhythmias and arrhythmia grade.[42] Moreover, inflammatory infiltrates have been found in histopathological studies in dogs and cats.[1,3,6] A high sympathetic tone is also thought to contribute to the initiation of electrical storms.[41] The standard approach to managing ventricular tachyarrhythmias should be used to manage these events, starting with the identification of triggers that can be eliminated, such as electrolyte imbalances or proarrhythmic drugs. Then, antiarrhythmic drugs usually constitute the first-line treatment. In the absence of prospective clinical studies, the choice of antiarrhythmics mainly depends on the clinician's experience and drug availability. Commonly used drugs include lidocaine, injectable procainamide, and amiodarone HCl. Lidocaine, which reduces electrical excitability and slows conduction, was shown to provide adequate arrhythmia control in 19/25 Bulldogs with arrhythmogenic cardiomyopathy.[9] The author sometimes administers oral sotalol (2 to 3 mg/kg), with an anticipation that the tachycardia will resolve within 2 to 3 hours after giving the medication. Use

of a β-blocker or sedation to block sympathetic stimulation might be considered.[41] In refractory cases, electrical cardioversion (see p. 139) and radiofrequency ablation (see p. 164) should be considered.

Dogs with syncope and ventricular arrhythmias are usually given long-term oral antiarrhythmic therapy. Twenty-four-hour Holter monitoring is recommended prior to initiation of treatment to quantify and grade the severity of the ventricular arrhythmia and rule out neurocardiogenic syncope as the cause for syncopal events.[43] To assess the effectiveness of treatment and identify potential proarrhythmic effects, it is essential to compare Holter recordings before and after treatment. A positive response to treatment is most reliably determined by observing a reduction in ventricular premature complex numbers by at least 80–85% and a decrease in arrhythmia complexity in the post-treatment Holter.[33] Meurs et al. systematically assessed the efficacy of four distinct oral antiarrhythmic protocols in a group of Boxers. The primary objective was to determine the most effective therapeutic interventions for reducing ventricular arrhythmia frequency in this specific canine population. Two of the treatment regimens demonstrated notable success in mitigating the burden of ventricular arrhythmias. Sotalol, administered as a monotherapy at dosages ranging from 1.5 to 3.5 mg/kg every 12 hours, exhibited significant effectiveness. Additionally, the combination of mexiletine (5 to 8 mg/kg every 8 hours) and atenolol (0.3 to 0.6 mg/kg every 12 hours) proved to be efficacious in reducing ventricular arrhythmia incidence. However, the use of procainamide and atenolol as standalone therapeutic agents did not yield discernible improvements in ventricular arrhythmia burden within this specific Boxer dog population.[44] In current veterinary practice, sotalol stands out as the main first-line antiarrhythmic agent in the management of ventricular arrhythmias associated with this specific disease. Based on the author's clinical experience, approximately 30% of Boxer dogs exhibit a satisfactory response to sotalol therapy alone. In cases in which the response to sotalol remains insufficient, a common strategy employed by practitioners involves the adjunctive use of mexiletine, administered at dosages ranging from 5 to 7 mg/kg every 8 hours.[45] It is important to note that when arrhythmias do not respond to the initial therapeutic measures, the administration of oral amiodarone may be considered for the management of affected dogs. Interestingly, based on evidence from rodent

models of arrhythmogenic cardiomyopathy, flecainide has been proposed as a potential treatment due to its ability to regulate calcium cycling and decrease calcium outflow by blocking the opening of ryanodine receptors. In a study conducted by Erkamov et al., effective arrhythmia control was achieved in a small group of human patients treated with a combination of flecainide and sotalol or metoprolol.[46] A large observational study reaffirmed the effectiveness of combining flecainide with a β-blocker, with a significant reduction in ventricular ectopies and sustained ventricular tachycardia episodes in human patients treated with this drug combination. Additionally, there was a notable decrease in ventricular tachycardia inducibility as assessed through programmed ventricular stimulation.[47] Further research is required on the use of flecainide in dogs with arrhythmogenic cardiomyopathy.

Apart from antiarrhythmic drugs, a study suggested that fish oil supplementation (780 mg EPA/497 mg DHA per day) for 6 weeks reduced the number of ventricular premature complexes in a small group of asymptomatic Boxers with a clinical diagnosis of arrhythmogenic cardiomyopathy. Further investigations are needed to confirm this finding and ascertain an optimal dosage and duration of treatment.[48]

RADIOFREQUENCY CATHETER ABLATION

Radiofrequency catheter ablation might be considered in dogs with ventricular arrhythmias that are refractory to medical therapy and suspected to have a segmental form of the disease. Santilli et al. showed the feasibility of radiofrequency catheter ablation of a ventricular tachycardia reentry circuit in the right ventricular outflow tract region of an English Bulldog with arrhythmogenic cardiomyopathy.[10] Subsequently, Crooks et al. conducted a study to assess the feasibility of radiofrequency ablation in 5 Boxers with presumptive arrhythmogenic cardiomyopathy. They used electroanatomic mapping to investigate the arrhythmia mechanisms and identify the appropriate site for ablation. The study encountered certain challenges, such as difficulties in inducing ventricular arrhythmia under anesthesia, inconsistent identification of low voltage areas that were expected to be associated with fibrofatty scars, and the induction of ventricular fibrillation in 2 dogs. Ablation targets were successfully located in specific regions of the right and left ventricles. Following the ablation

procedure, all dogs experienced a reduction in ventricular tachycardia episodes and saw an improvement in syncopal episodes. However, the reduction in the total number of ventricular ectopies varied among the dogs.[49]

IMPLANTABLE DEVICES

In human patients with arrhythmogenic cardiomyopathy and a high risk of sudden cardiac death, the use of implantable cardioverter defibrillators (ICDs) has become standard of care. These devices can deliver three types of therapy in addition to a pacemaker function: antitachycardia pacing to terminate episodes of reentrant ventricular tachycardia by overdrive pacing, low-energy cardioversion shocks to terminate ventricular tachycardia episodes that do not respond to antitachycardia pacing, and high-energy shocks delivered in the event of rapid ventricular tachycardia and ventricular fibrillation. It is worth noting that while the first two modes of therapy are typically imperceptible to the patient, high-energy shocks can induce extreme discomfort. The implantation of an ICD in a Boxer with suspected arrhythmogenic cardiomyopathy was reported in 2006, with successful termination of some ventricular tachycardia episodes by antitachycardia pacing. Regrettably, complications emerged in the form of recurrent inappropriate delivery of high-energy shocks and device-related infection necessitating device removal (see p. 152).[50]

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CHAPTER 29

Arrhythmia-induced cardiomyopathy

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DEFINITION

Arrhythmia-induced cardiomyopathy is a subform of the nonfamilial dilated cardiomyopathy described in human beings and dogs and cats; it is defined as reversible atrial and/or ventricular dysfunction secondary to rapid and/or asynchronous/irregular myocardial contraction.[1–11] Arrhythmia-induced cardiomyopathy can be caused by a rhythm disturbance with an incessant, sustained, or paroxysmal behavior, even though some studies have shown that this condition can also result from highly frequent single premature ectopic beats, right apical ventricular pacing, or a complete bundle branch block.[1–11] Arrhythmia-induced cardiomyopathy can be divided into two categories:[1–11]

1. Pure arrhythmia-induced cardiomyopathy, in which the arrhythmia is accepted as the absolute reason for ventricular dysfunction and is totally reversible after successful treatment of the arrhythmia.
2. Impure arrhythmia-induced cardiomyopathy, in which the arrhythmia exacerbates the atrial or ventricular dysfunction in the presence of a concomitant structural heart disease. In these patients, treatment of the arrhythmia is correlated with partial reverse remodeling.

The risk of developing arrhythmia-induced cardiomyopathy depends not only on the origin of the arrhythmia (supraventricular or ventricular) but also on the duration and rate of the rhythm disturbance. It has been shown that faster tachycardia rates and ventricular arrhythmias in dogs generally

cause a more severe arrhythmia-induced cardiomyopathy.[1,11] In both human and veterinary medicine, the overall prevalence and incidence of this disease are unclear and likely underestimated.[1]

PATHOPHYSIOLOGY

Arrhythmia-induced cardiomyopathy is characterized by structural and functional cardiac changes. Based on studies conducted in animal models, electrical remodeling and alterations in Ca^{2+} homeostasis are thought to be responsible for the impaired excitation–contraction coupling and diastolic dysfunction.[1] The three main factors that appear to cause arrhythmia-induced cardiomyopathy are a fast heart rate, irregular RR intervals, and dyssynchrony, with a significant overlap between the different mechanisms leading to this condition.[3,4]

In animal models, rapid artificial cardiac stimulation (tachy-pacing) has been shown to result in left ventricular systolic dysfunction within weeks.[3] Three phases have been defined in this process. The first phase (first 3–7 days of rapid pacing), called compensatory phase, is characterized by a normal end-systolic volume, a severely increased left ventricular end-diastolic volume associated with significant neurohormonal activation, and defects in Ca^{2+} handling. In this phase, myocardial energy store depletion, increased oxidative stress, and a blunted response to β-adrenergic stimulation are all involved in the pathogenesis of arrhythmia-induced cardiomyopathy. In addition, structural and functional alterations in the myocardial capillary network result in an impaired myocardial blood flow reserve and induce myocardial ischemia. All these mechanisms can be seen in several forms of heart failure and are related to elevated filling pressures and a decreased cardiac output.[3,7]

Cessation of tachy-pacing results in a significant recovery of left ventricular systolic function and cardiac output after 48 hours and full normalization after a period ranging from 1 to 2 weeks. The abnormalities in Ca^{2+} handling significantly normalize within 4 weeks, while some changes such as fibrosis appear to persist despite cessation of tachy-pacing and normalization of left ventricular systolic function (Table 29.1).[1]

TABLE 29.1. Summary of the pathophysiological mechanisms involved in arrhythmia-induced cardiomyopathy in experimental animal models.

Within 1 week	**Compensatory phase**
	Normal left ventricular systolic function Sympathetic system activation
Within 1–3 weeks	**Left ventricular dysfunction phase**
	Left ventricular systolic dysfunction Myocardial contractile dysfunction Neurohormonal activation
After 3 weeks	**Heart failure phase**
	Severe left ventricular systolic dysfunction Significant neurohormonal activation Systemic hemodynamic compromise Pulmonary edema, pleural/abdominal effusion

Irregular sequences of RR intervals, as can be seen in atrial fibrillation, produce adverse hemodynamic changes that depend on heart rate. The Frank–Starling mechanism (which relates myofiber length to the strength of ventricular contraction) and the force–interval relationship are two potential mechanisms connecting RR interval irregularity, reduced systolic function, and decreased cardiac output.[7]

Intraventricular and interventricular dyssynchronous myocardial contraction (e.g., due to right apical artificial ventricular pacing, a bundle branch block, or premature ventricular ectopic beats) prevents normal ventricular activation through the His–Purkinje system. In these cases, beyond the anomalous electrical activation of the ventricles, the mechanical activation pattern changes simultaneously, with a redistribution of

myocardial strain and myocardial work leading to poorer myocardial contractile efficiency.[7]

The absence of synchrony may also be atrioventricular, as occurs in atrial fibrillation. Atrioventricular asynchrony results in a 15–20% reduction in cardiac output and in alterations in the left ventricular filling times.[7]

Cardiac remodeling is not just limited to the ventricular myocardium but also extends to the atrial myocardium. This process is called atrial arrhythmia-induced cardiomyopathy. The mechanisms contributing to atrial dilation and reduced systolic function of the atrial myocardium are similar to those previously described for the ventricular myocardium. Alterations in Ca^{2+} handling together with tissue apoptosis, inflammatory cell infiltration, and myocyte death in the atria have been demonstrated in experimental animal models.[7]

CLINICAL PRESENTATION

The prevalence of arrhythmia-induced cardiomyopathy are difficult to estimate due to the small number of retrospectively designed studies available and of patients included in these studies in both human and veterinary medicine.[7–11]

The clinical presentation of arrhythmia-induced cardiomyopathy, both in puppies and in adults, can vary from asymptomatic to end-stage congestive heart failure. Many patients do not show signs of an arrhythmia, or the owner only describes subtle or unspecific signs that make an early diagnosis extremely difficult. Once signs of heart failure appear, worsening of the clinical condition is inevitable if treatment of the arrhythmia and heart failure is not initiated.[7–11] The clinical signs associated with the arrhythmia include dyspnea, exercise intolerance, and chest discomfort, and those related to heart failure include dyspnea or orthopnea due to pulmonary edema and/or pleural effusion, and abdominal distension due to abdominal effusion. It can be argued that patients presenting higher heart rates and ventricular tachycardia often present first with tachycardia-related signs. The clinical features that should raise suspicion of arrhythmia-induced cardiomyopathy can be categorized as follows:[7–11]

- Tachycardia or frequent ectopies associated with systolic dysfunction in a patient without preexisting structural heart diseases.
- Asymptomatic nonfamilial cardiomyopathy in the setting of a persistent arrhythmia or frequent ectopies.
- Tachycardia in a patient with a known structural heart disease with worsening of systolic function and heart failure.

DIAGNOSIS

A definitive diagnosis of arrhythmia-induced cardiomyopathy is often difficult to make. The key diagnostic criterion is the detection of rhythm disturbances in conjunction with decreased left ventricular systolic function that cannot otherwise be explained.[1–7] A number of arrhythmias can provoke arrhythmia-induced cardiomyopathy; these are listed in Table 29.2. Although the duration of the rhythm disturbance and ventricular rate are important factors, no threshold values are available for these parameters.

TABLE 29.2. Rhythm disturbances that can trigger arrhythmia-induced cardiomyopathy.

Supraventricular tachycardias	Atrial fibrillation Atrial flutter Focal atrial tachycardia Focal junctional tachycardia Orthodromic atrioventricular reciprocating tachycardia Permanent junctional tachycardia Frequent atrial premature ectopic beats
Ventricular tachycardias	Frequent ventricular premature ectopic beats Ventricular tachycardia

Relevant arrhythmias cannot always be detected with a surface 12-lead electrocardiogram, and Holter monitoring is often required to reach the correct diagnosis. A Holter study will allow the identification of: nonsustained tachycardias; maximum, minimum, and mean ventricular

rates; heart rate variability; and frequency of atrial and ventricular premature ectopic beats.[1–7]

The echocardiographic examination is characterized by mild-to-severe biventricular systolic dysfunction with normal septal and posterior wall thickness. Functional mitral and tricuspid valve insufficiency may be present due to dilation of the annuli and lack of leaflet coaptation.[1–7]

The link between arrhythmia and reduced systolic function is often difficult to assess, because any form of decreased left ventricular systolic function can lead to rhythm disturbances (the egg–chicken question). In human medicine, clinical trials have shown that left ventricular systolic dysfunction and end-diastolic dilation in patients with arrhythmia-induced cardiomyopathy are less pronounced than in patients with dilated cardiomyopathy complicated by rhythm disturbances. A possible diagnostic algorithm is provided in Figure 29.1 for those cases in which arrhythmia-induced cardiomyopathy may be suspected.[1–7] In an experimental study, 4 week–pacing in dogs led to left ventricular dysfunction associated with severe neurohormonal activation. This condition has been shown to be associated with a decrease in all normal strain components and in left ventricular twist. The decrease in strain is more prominent at the left ventricular apex. A loss of apex-to-base gradient of circumferential strain has also been shown in arrhythmia-induced cardiomyopathy. A possible explanation is that the initial decrement in ventricular contraction affects the longitudinal axis, whereas the radial axis is relatively preserved in the early phase, regardless of the physiological model.[12]

Once a basic diagnostic workup has been performed, use of targeted diagnostic methods is recommended.

The histopathological examination and comparison of myocardial biopsies from human patients with arrhythmia-induced cardiomyopathy or cardiomyopathies of other origins (familial, inflammatory) revealed arrhythmia-induced cardiomyopathy was characterized by mild or absent fibrosis and macrophage infiltration.[3]

The diagnosis of arrhythmia-induced cardiomyopathy is considered conclusive if it is completely or partially reversed (depending on whether there is a preexisting structural heart disease) within a few days or weeks of successful treatment of the arrhythmia (Figs. 29.2 and 29.3).[1–7]

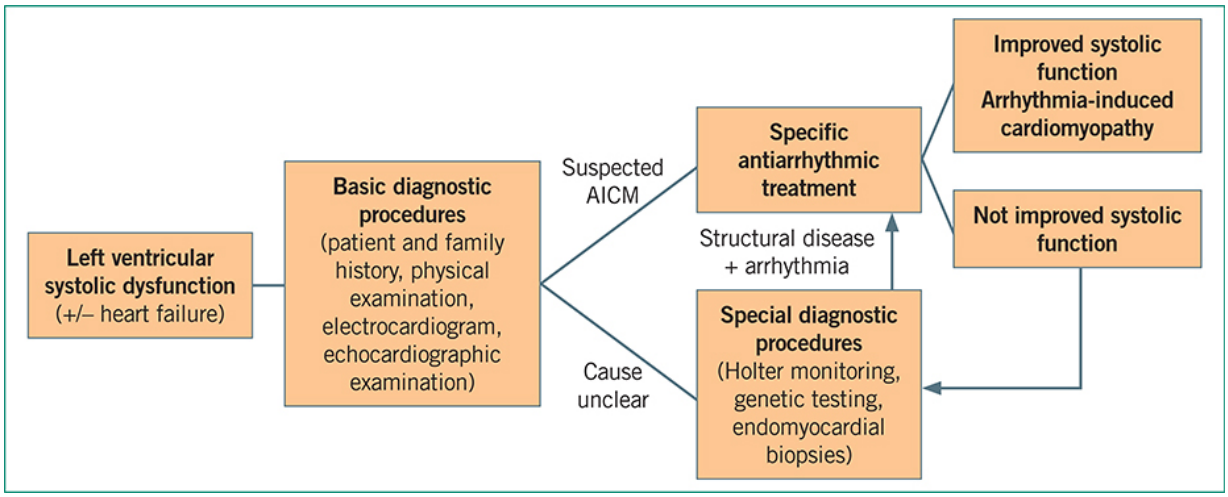


FIGURE 29.1. Proposed algorithm for the diagnosis of arrhythmia-induced cardiomyopathy (AICM).

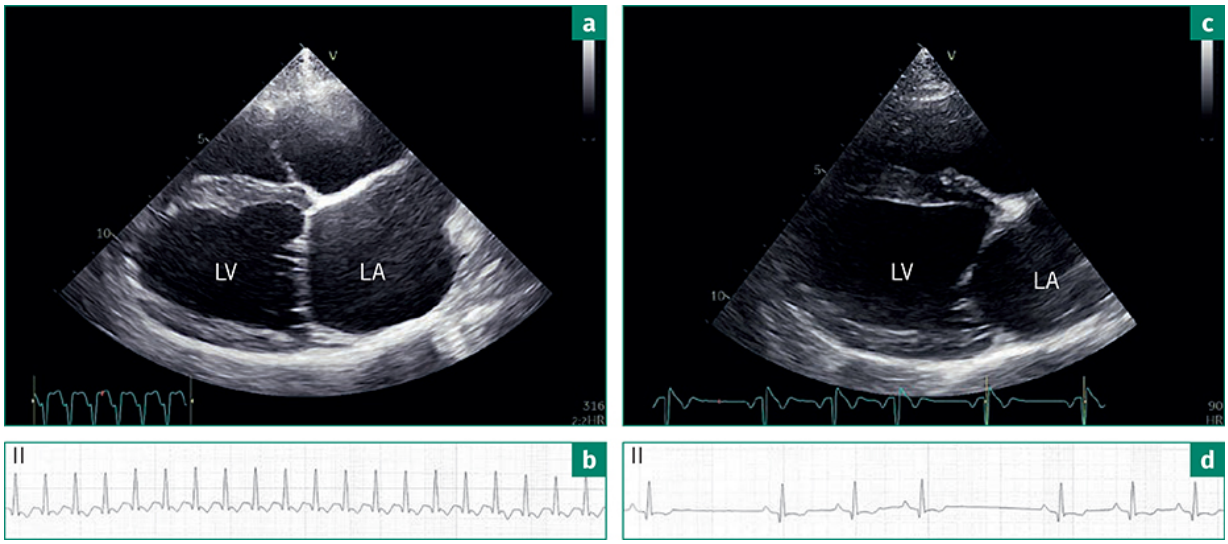


FIGURE 29.2. Orthodromic atrioventricular reciprocating tachycardia and arrhythmia-induced cardiomyopathy in a 9-month-old male Labrador Retriever. Echocardioghic view (a) and electrocardiogram during orthodromic atrioventricular reciprocating tachycardia (b): note the increased left ventricular end-diastolic internal dimensions and left atrial dimensions. Echocardiographic view (c) and electrocardiogram (d) 2 weeks after radiofrequency catheter ablation of the posteroseptal accessory pathway: sinus rhythm is restored. Note the reverse remodeling of the left ventricular and left atrial dimensions. LA, left atrium; LV, left ventricle. Lead II; speed, 50 mm/s; calibration, 10 mm/1mV.

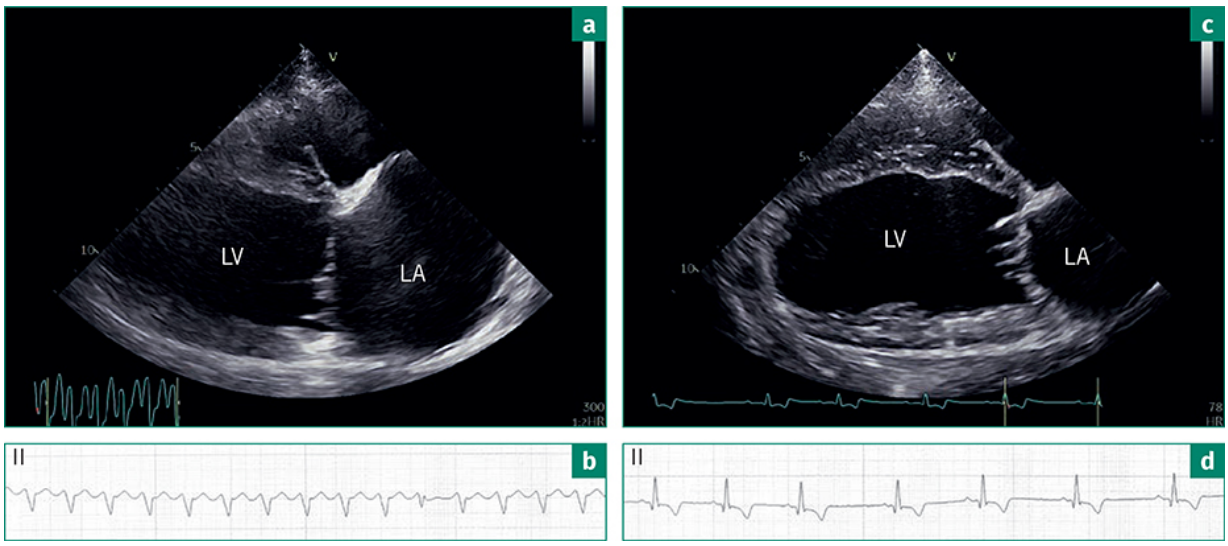


FIGURE 29.3. Ventricular tachycardia and arrhythmia-induced cardiomyopathy in an 8-month-old male mixed-breed dog. Echocardioghic view (a) and electrocardiogram during monomorphic ventricular tachycardia (b): note the increased left ventricular end-diastolic internal dimensions and left atrial dimensions. Echocardiographic view (c) and electrocardiogram (d) after pharmacological treatment when sinus rhythm is restored, with reverse remodeling of the left ventricular and left atrial dimensions. LA, left atrium; LV, left ventricle. Lead II; speed, 50 mm/s; calibration, 10 mm/1mV.

THERAPY

Treatment of arrhythmia-induced cardiomyopathy is mainly aimed at eliminating or controlling the rhythm disturbance using a pharmacological approach or ablative techniques, with the goal of reversing systolic dysfunction and improving the associated signs. The correct approach should be selected depending on the underlying arrhythmia. In general, definitive ablation is the method of choice.[1–7]

Nevertheless, the initial treatment of arrhythmia-induced cardiomyopathy should include initiation and optimization of medical treatment to control heart failure and left ventricular systolic dysfunction, with the administration of drugs such as diuretics, angiotensin-converting enzyme inhibitors, aldosterone blockers, and pimobendan to optimize reverse remodeling. Elimination of the arrhythmia improves not only systolic function within 4–12 weeks but also the signs of heart failure in most patients. In human medicine, it has been proven that age, tachycardia rate, baseline left ventricular ejection fraction, and left ventricular end-diastolic dimensions were predictors of recovery in a pediatric population.[1–7]

ARRHYTHMIA-SPECIFIC DIAGNOSTIC TESTS AND TREATMENT

Atrial fibrillation

Atrial fibrillation is the most common persistent arrhythmia in both human beings and veterinary patients. In human medicine, it is the most common cause of arrhythmia-induced cardiomyopathy. Rapid and irregular ventricular depolarizations associated with a loss of atrial contraction are the proposed pathophysiological mechanisms to explain the development of arrhythmia-induced cardiomyopathy. The characteristic irregularity of the RR intervals during atrial fibrillation causes Ca^{2+} mishandling, while the loss of atrial contraction/emptying associated with sympathetic activation contributes to limited ventricular filling and increased filling pressures, functional atrioventricular valve regurgitation, and diastolic dysfunction.[1–4] It is not uncommon for atrial fibrillation to be diagnosed for the first time in association with left ventricular systolic dysfunction, making the link between both unclear. In such cases, the first aim should be pharmacological control of the ventricular rate of atrial fibrillation (with digitalis +/– diltiazem) (see p. 224), associated with pharmacological treatment of congestive heart failure. Optimal heart rates have not yet been definitively established in human or veterinary medicine, although rates of 60–100 bpm at rest and <110 bpm during mild exercise have been suggested in humans. The Holter-derived mean heart rates of dogs with structural heart disease and atrial fibrillation have been shown to be correlated with these dogs' survival time. Dogs with a mean heart rate <125 bpm lived longer than those with a mean heart rate ≥125 bpm.[13]

Holter monitoring is key to evaluate the 24-hour ventricular rate. Based on the disease follow-up and on the diagnostic test results, it is possible to distinguish pure arrhythmia-induced cardiomyopathy, which is characterized by the absence of an underlying structural heart disease and associated with complete reverse remodeling of the heart after arrhythmia treatment, from impure arrhythmia-induced cardiomyopathy, which is characterized by the presence of a structural heart disease complicated by atrial fibrillation and associated with partial reverse remodeling after arrhythmia treatment.[1–4]

Atrial fibrillation can also be treated by electrical cardioversion to achieve rhythm control. Different studies in human medicine have shown

that compared with rate control, rhythm control using electrical cardioversion associated with the administration of amiodarone improved left ventricular systolic function and quality of life but did not reduce the mortality risk.[1–4]

Another treatment option is catheter ablation. In human medicine, ablation of atrial fibrillation has been shown to be correlated with a significant improvement in left ventricular systolic function with normalization of the ejection fraction, even in cases of prior optimal pharmacological rate control.[1–4]

In cases of treatment-refractory atrial fibrillation with a noncontrolled ventricular rate, a combination of atrioventricular node ablation and biventricular pacemaker implantation can be considered in selected patients (ablate and pace technique).[1–4]

Atrial flutter

Atrial flutter is one of the common causes of arrhythmia-induced cardiomyopathy in both humans and animals. In human medicine, the prevalence of arrhythmia-induced cardiomyopathy associated with atrial flutter is estimated to be 8%.[2,3] Arrhythmia-induced cardiomyopathy patients present a higher ventricular rate compared to those with left ventricular systolic dysfunction of a different etiology. Pharmacological control of the ventricular rate is more challenging in atrial flutter than in atrial fibrillation, and rhythm control is frequently required. Electrical cardioversion represents an effective option to restore sinus rhythm. However, radiofrequency catheter ablation should be considered given the high recurrence rate in patients with atrial flutter after electrical cardioversion. In human medicine, normalization of left ventricular systolic function has been demonstrated in approximately 75% of patients after atrial flutter ablation.[2,3]

Premature atrial ectopic beats and other supraventricular tachycardias

A correlation between premature atrial ectopic beats and arrhythmia-induced cardiomyopathy has been demonstrated in both animal models and human medicine.[14] In human medicine, frequent atrial ectopic beats have

been shown to be associated with an increased risk of developing atrial fibrillation and atrial and ventricular arrhythmia-induced cardiomyopathy.[14]

Arrhythmia-induced cardiomyopathy has essentially been associated with any frequent and sustained supraventricular tachycardia.[1–7] Supraventricular tachycardias frequently trigger arrhythmia-induced cardiomyopathy in both puppies and adult patients. Incessant supraventricular tachycardias are the underlying disorder in approximately 90% of pediatric cases of arrhythmia-induced cardiomyopathy.[2] The most common supraventricular tachycardias associated with left ventricular dysfunction in dogs are orthodromic atrioventricular reciprocating tachycardia and permanent junctional tachycardia.[8,9] The elevated heart rate associated with these rhythm disturbances and their incessant behavior are responsible for arrhythmia-induced cardiomyopathy (Fig. 29.2). In all the reported cases, the arrhythmia was treated with radiofrequency catheter ablation, which led to complete reversal of left ventricular systolic dysfunction.[8,9] Arrhythmia-induced cardiomyopathy has also been reported in one cat suffering from supraventricular tachycardia; reverse remodeling was achieved after drug therapy with sotalol.[10]

Arrhythmia-induced cardiomyopathy due to focal atrial tachycardia has been described in human medicine. Focal atrial tachycardia has been reported to be commonly refractory to medical treatment, and ablation of the arrhythmic substrate is considered the first-line treatment option.[3]

Left ventricular dysfunction has also been described in about 50% of Labrador Retrievers affected by focal junctional tachycardia with isorhythmic atrioventricular dissociation and type I or II synchronization.[15] Because these rhythm disturbances are difficult to control pharmacologically, the degree of reverse remodeling that can be achieved is difficult to evaluate.

Frequent premature ventricular ectopic beats and ventricular tachycardias

In human medicine, idiopathic ventricular arrhythmias in the absence of a structural heart disease are considered a benign entity. Premature ventricular ectopic beats have been recorded in up to 75% of normal healthy people on 48-hour Holter monitoring. However, there is a clear association between

frequent premature ventricular ectopic beats and arrhythmia-induced cardiomyopathy.[1,4]

In human medicine, the burden of premature ventricular ectopic beats considered to be associated with arrhythmia-induced cardiomyopathy is 15–26% of the total cardiac beats.[1,4] Studies in experimental animal models have demonstrated that left ventricular systolic function declined linearly as the burden of premature ventricular ectopic beats increased. Arrhythmia-induced cardiomyopathy developed in some dogs with a burden of premature ventricular ectopic beats of 25%, but it developed in all animals included in the study with a burden of 50%.[16] The probability of developing arrhythmia-induced cardiomyopathy increases with the frequency of premature ventricular ectopic beats, although many other risk factors have been suggested, such as the presence of retrograde atrial activation after the premature ventricular ectopic beats, the presence of interpolated premature ventricular ectopic beats, a wide QRS complex duration that correlates with the degree of ventricular dyssynchrony, and an epicardial origin of the premature ectopic beats.[1–4]

Even if the precise underlying electrophysiological mechanism is not completely known, various cellular and clinical mechanisms have been proposed. Premature ventricular ectopic beats are associated with increased wall stress because propagation of the depolarization wavefront does not occur through the specialized conduction system and leads to a slower and dyssynchronous activation of the individual wall segments. In addition, the abnormal coupling interval of premature ventricular ectopic beats may be followed by a post-extrasystolic pause, leading to an increased filling pressure caused by the long diastolic period.[17–20] In human medicine, premature ventricular ectopic beats with a short coupling interval and a consequently long post-extrasystolic pause have been found to be an adjunctive risk factor for the development of arrhythmia-induced cardiomyopathy.[17–20]

At the cellular level, the calcium current (I_{CaL}), the rapid component of the delayed rectifier potassium current (I_{Kr}), and the inward rectifier potassium current (I_{K1}), have been found to be decreased in a canine model. There is a decrease in Ca^{2+} release from the sarcoplasmic reticulum, which leads to impaired excitation–contraction coupling.[17–21]

In human medicine, ventricular tachycardia is only rarely associated with arrhythmia-induced cardiomyopathy, likely because it generally causes acute signs, thereby leading to treatment initiation.[2] In veterinary medicine, it has been proven that deterioration of the left ventricular ejection fraction and dilation of the left ventricle are more marked in cases of chronic ventricular tachycardia than in those of chronic supraventricular tachycardia, even with a lower heart rate.[11] The abnormal sequences of activation causing ventricular dyssynchrony and atrioventricular asynchrony are likely the two major factors inducing more severe left ventricular function impairment in dogs with ventricular tachycardia (Fig. 29.3).[11] In the experimental setting, recovery from arrhythmia-induced cardiomyopathy is complete with both atrial pacing and ventricular pacing.[11]

In human medicine, radiofrequency catheter ablation is considered to be the preferred treatment option with respect to pharmacological therapy.[3,4] Successful ablation is correlated with a significant improvement in cardiac function, and the burden of premature ventricular ectopic beats before and after ablation is the main predicting factor of left ventricular ejection fraction recovery.[1–4] Radiofrequency catheter ablation is also considered the best treatment option for ventricular tachycardia and is correlated with partial or complete recovery depending on the presence of an underlying structural heart disease.[1–4]

Abnormal conduction–induced cardiomyopathies

The past years have seen an increasing interest in the identification of reversible causes of dilated cardiomyopathy. Right ventricular pacing, left bundle branch block, and preexcitation syndrome have been identified as additional etiologies of arrhythmia-induced cardiomyopathy.[22] The three entities are associated with abnormal ventricular activation resulting in abnormal ventricular contraction, which is referred to as dyssynchrony.[22]

Right ventricular pacing cardiomyopathy is defined as left ventricular systolic dysfunction solely correlated with a high percentage of ventricular pacing. Among the possible artificial pacing sites, the right ventricular apex is the most common choice.[22,23] Although in human medicine, most patients undergoing pacemaker implantation remain clinically stable for

years with a good quality of life, artificial electrical stimulation of the myocardium and artificially induced ventricular dyssynchrony due to cardiac pacing have been associated with the development of decreased left ventricular systolic function, increased left ventricular end-diastolic dimensions, and clinical manifestations of heart failure.[22,23] Even if the definition of decreased left ventricular systolic function varies from one study to another, a 10% reduction in left ventricular ejection fraction from baseline or an absolute value of left ventricular ejection fraction below 50% are the most sensible cutoffs for early diagnosis and treatment in human medicine.[22,23] Several risk factors other than the percentage of artificial stimulation have been reported in human medicine for the development of right ventricular pacing cardiomyopathy, such as the duration of the paced QRS complex and presence of an underlying structural heart disease.[22] Based on these findings, it is recommended that patients have a baseline echocardiographic examination before undergoing pacemaker implantation; it is also suggested to repeat the test annually.[23] The main mechanism inducing right ventricular pacing cardiomyopathy is the asynchronous electrical stimulation, which disrupts the timing of the cardiac cycle and causes left ventricular mechanical dyssynchrony. This condition is suspected to have adverse effects on ventricular function by inducing cardiac remodeling due to changes in myocardial metabolism and perfusion.[23] In human medicine, the true incidence of right ventricular pacing cardiomyopathy is unclear, but it is widely acknowledged to occur mostly in patients with a right ventricular pacing burden >40%.[23] However, for reasons still unclear, most patients with a pacing burden close to 100% do not develop left ventricular dysfunction and remodeling.[23] Conventional right ventricular pacing causes myocardial activation almost in reverse compared with the normal activation wavefront, which travels in an intrinsic physiological antegrade fashion through the His–Purkinje system. This phenomenon causes delayed and abnormal ventricular myocardial activation (electrical dyssynchrony), which is associated with nonphysiological ventricular contraction (mechanical dyssynchrony); this indicates that right ventricular pacing causes interventricular dyssynchrony (between the right and left ventricle). Interventricular dyssynchrony results from a delay in the electrical activation of the left ventricular posterolateral wall with respect to the right ventricular apex, whereas intraventricular

dyssynchrony results from a delay in the activation of some regions of the ventricle compared with others.[23] Electrical and mechanical dyssynchrony results in prolongation of the systolic phase and shortening of the diastolic phase, thus compromising stroke volume, reducing diastolic filling, and causing functional mitral regurgitation.[23] Chronic right ventricular pacing has also been associated with sympathetic activation and increased oxidative stress linked with a reduction in nitric oxide production in the cardiomyocytes.[23] In dogs, atrioventricular conduction disturbances requiring pacemaker implantation may be due to acute myocarditis mainly secondary to viral infections. This etiology must be taken into consideration when evaluating left ventricular function in patients with chronic right ventricular pacing, since it can alone induce a reduction in left ventricular systolic function (inflammatory dilated cardiomyopathy). This condition can also reduce the life expectancy of affected dogs.[24,25]

Prevention is the best way of managing any disease, including arrhythmia-induced cardiomyopathy. Therefore, in addition to careful patient selection, a patient-tailored choice of pacemaker and programming are crucial to reduce the incidence of the disease. Since the pacing burden is considered one of the factors with the greatest impact on pacemaker-induced cardiomyopathy, correct programming of the implant is important. Programming a VVIR pacing mode at a lower rate than the intrinsic rate when possible is the only way to prevent burden-related pacemaker induced-cardiomyopathy. In case of biventricular pacemaker implantation, proper programming of the atrioventricular conduction time is essential to allow intrinsic conduction when possible by a simple interval prolongation or by using device algorithms intended for this purpose.[23] However, for patients requiring chronic ventricular pacing, the choice of ventricular lead implantation site may be the only way of preventing pacemaker-induced cardiomyopathy. Ventricular contraction by direct activation of the specialized conduction system at the His bundle to capture the myocardium with a normal wavefront direction is a good strategy to maintain ventricular syncytium synchrony.[23] These new physiological pacing sites in human medicine are aimed at preserving natural ventricular depolarization and preventing right ventricular pacing dyssynchrony.[23]

In the experimental setting, left ventricular pacing or biventricular pacing has been shown to improve left ventricular function in clinically normal

dogs. Given the evidence of the detrimental effects of right ventricular pacing and the superiority of left ventricular pacing or biventricular pacing, these pacing sites could be considered for dogs with a structural cardiac disease such as mitral valve regurgitation or systolic dysfunction and low cardiac reserve, as these patients might not tolerate additional decreases in left ventricular function caused by right apical ventricular pacing. In these dogs, left ventricular pacing or biventricular pacing may preserve or possibly even increase left ventricular function and improve the outcome.[26]

Abnormal conduction–induced cardiomyopathy can also be the consequence of *complete left bundle branch block*. In human medicine, complete left bundle branch block is uncommon in the general population (<1%), but its prevalence increases with age. Unlike complete right bundle branch block, left bundle branch block portends an increased risk of developing arrhythmia-induced cardiomyopathy and heart failure.[22] Left bundle branch block cardiomyopathy is caused by a persistent complete left bundle branch block that frequently responds to cardiac resynchronization therapy, with partial or complete resolution of the cardiomyopathy.[22] Complete left bundle branch block is characterized by a significant prolongation of the left ventricular activation time and a marked delay in the activation of the basal free wall. The result on left ventricular mechanics is a global discoordination of the contraction–relaxation process, defined as intraventricular and interventricular dyssynchrony. The deleterious effect of complete left bundle branch block on mechanical synchrony affects the entire cardiac cycle. The pre-ejectional leftward shift of the septum and its subsequent paradoxical septal motion to the right indicate abnormal activation of the ventricles.[27] The delayed deformation of the lateral wall also affects the kinetics of the papillary muscles and mitral valve apparatus. Lastly, diastolic filling is shortened. All these factors cause left ventricular remodeling characterized by impaired systolic and diastolic function (Fig. 29.4).[27] Although these mechanisms are known, the relationship between complete left bundle branch block and left ventricular remodeling is complex and still poorly understood. Complete left bundle branch block could appear in the natural course of familial dilated cardiomyopathy, representing a marker of disease severity associated with an increased risk of mortality, or it may play a causative role in the development of a "dyssynchronopathy".[27] In dogs, it has been proven that complete left

bundle branch block is associated with an abnormal interventricular dyssynchrony index (evaluated with the precordial lead system) and with a reduced life expectancy.[28]

The key mechanism of *ventricular preexcitation–related cardiac dysfunction* is electrical–mechanical dyssynchrony caused by ventricular preexcitation, which may lead to remodeling and progressive left ventricular dilation and decreased systolic function. Human patients with ventricular preexcitation-related cardiac dysfunction usually develop a specific type of dilated cardiomyopathy called preexcitation-induced dilated cardiomyopathy, which is mainly associated with right-sided accessory pathways.[29] A possible mechanism is that long-term discordant left ventricular myocardial contraction and inefficient cardiac pumping leads to changes in excitation–contraction coupling. Preexcitation-induced dilated cardiomyopathy is characterized by intra–left ventricular dyssynchrony, which may persist even after successful ablation of the accessory pathway.[29] Segmental myocardial thinning and wall motion abnormalities associated with ventricular preexcitation have also been described in veterinary medicine.[29] Early segmental activation during ventricular preexcitation results in segmental contraction under low preload conditions, which is unopposed by activation of the remaining left ventricular myocardium. The decreased workload of the preexcited myocardium leads to physiological thinning and displacement of the weak myocardial segment towards the low-pressure right ventricle, resembling an aneurysmatic lesion.[30]

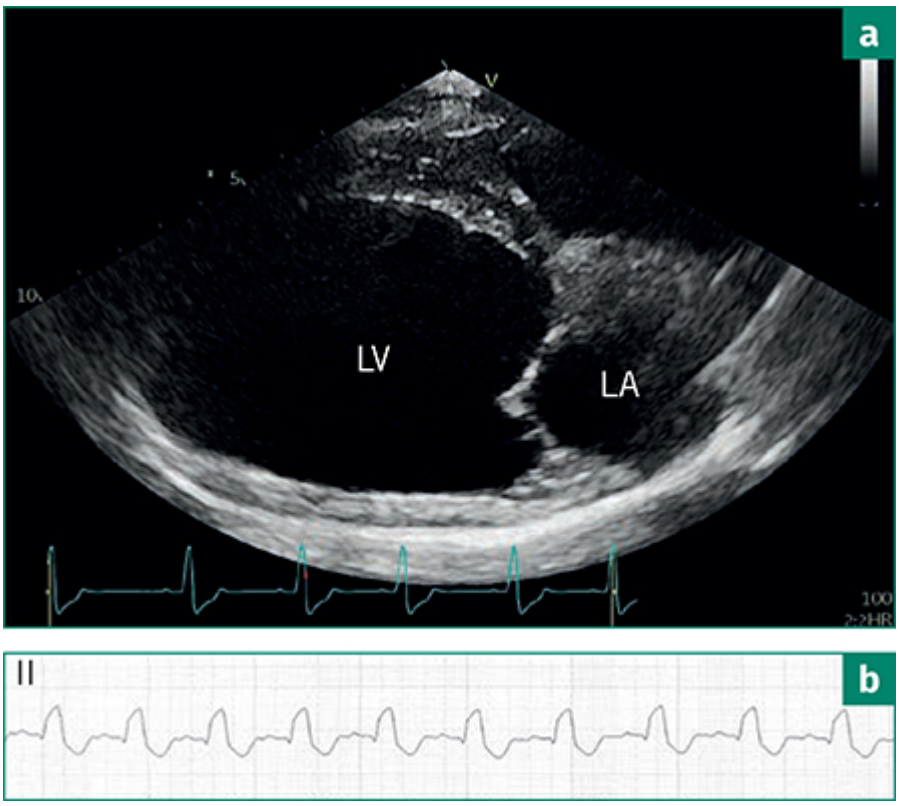


FIGURE 29.4. Predivisional or troncular left bundle branch block and abnormal conduction-induced cardiomyopathy in a 12-month-old female Golden Retriever. Echocardiographic view (a) and electrocardiogram (b) showing complete left bundle branch block. Note the increased left ventricular end-diastolic internal dimensions associated with the conduction disturbance and interventricular dyssynchrony. LA, left atrium; LV, left ventricle. Lead II; speed, 50 mm/s; calibration, 10 mm/1mV.

Ventricular preexcitation is probably underestimated in veterinary medicine, as only 31% of accessory pathways conduct antegradely in dogs, and these are usually associated with accessory pathway–mediated tachycardia, with the resulting arrhythmia-induced cardiomyopathy possibly masking the echocardiographic findings typical of ventricular preexcitation.

PROGNOSIS

Following effective treatment, the left ventricular pump function normally recovers within a few weeks or months.[1–4] The initial follow-ups should be frequent and include an electrocardiogram, an echocardiogram, and Holter monitoring. In human medicine, arrhythmia recurrence despite successful ablation depends on the underlying arrhythmia, but it is estimated to range

from 5% for supraventricular tachycardias to 50% for atrial fibrillation. Arrhythmia recurrence could be a cause for incomplete recovery of left ventricular function at follow-up. Even in cases in which arrhythmia control has been completely achieved, treatment with disease-modifying drugs (angiotensin-converting enzyme inhibitors, pimobendan) plays an important role. Discontinuation of these drugs following recovery of left ventricular systolic function is controversial. In general, it is advised to continue these medications after recovery of systolic function considering the persistence of subtle remodeling in patients with arrhythmia-induced cardiomyopathy.[1–4] The prognosis of the disease is also associated with the repolarization abnormalities described in human medicine and animal models.[31] Prolongation of the repolarization time has been described in animal models in conjunction with spatial dispersion of repolarization and an increased risk of sudden death. Although the causative mechanism has not been completely established, prolongation of the QT interval is present in 8.3% of patients with arrhythmia-induced cardiomyopathy and heart failure.[31] The prolongation of the action potential duration may be correlated with ventricular arrhythmias due to the increased heterogeneity of repolarization, which leads to a nonexcitable gap reentry.[31]

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CHAPTER 30

Arrhythmias in mitral valve disease

Romain Pariaut

DEFINITION

Mitral valve disease, also known as myxomatous valve degeneration, is the most common heart disease in dogs. It is more prevalent in small breed dogs (<15 kg) but is also observed in medium and large breed dogs. Arrhythmias are present in both groups with some differences, including a higher occurrence of atrial fibrillation and ventricular arrhythmias in the larger breeds.[1]

Holter recordings in dogs with preclinical disease typically reveal occasional supraventricular ectopies, but these rarely exceed 50 over a 24-hour period. In dogs with clinical disease, the number of supraventricular arrhythmias remains low, although some dogs develop atrial ectopic beats, self-limiting runs of focal atrial tachycardia, and atrial fibrillation (Fig. 30.1). Atrial fibrillation is an uncommon complication of mitral valve disease that affects less than 3% of small to medium-sized dogs, and typically occurs at a late stage of the disease (stages C and D).[2,3] It is more common in dogs of larger breeds with mitral valve disease.[4] Atrial fibrillation was reported to be present in 31% of dogs in a group of German Shepherds with mitral valve disease.[4]

The ventricular arrhythmia burden is mild in the early stage of the disease and rarely exceeds 50 ectopies per day; it increases in dogs with clinical disease but typically remains below 400 to 500 ectopies over a 24-hour period.[5,6] Pimobendan, a key drug in the management of mitral valve disease, was initially suspected to increase the risk of arrhythmias due to its

effects on calcium metabolism, but subsequent investigations did not confirm a proarrhythmic effect.[7,8] Importantly, in dogs with mitral valve disease, clinical signs are rarely associated with ventricular ectopies.[5]

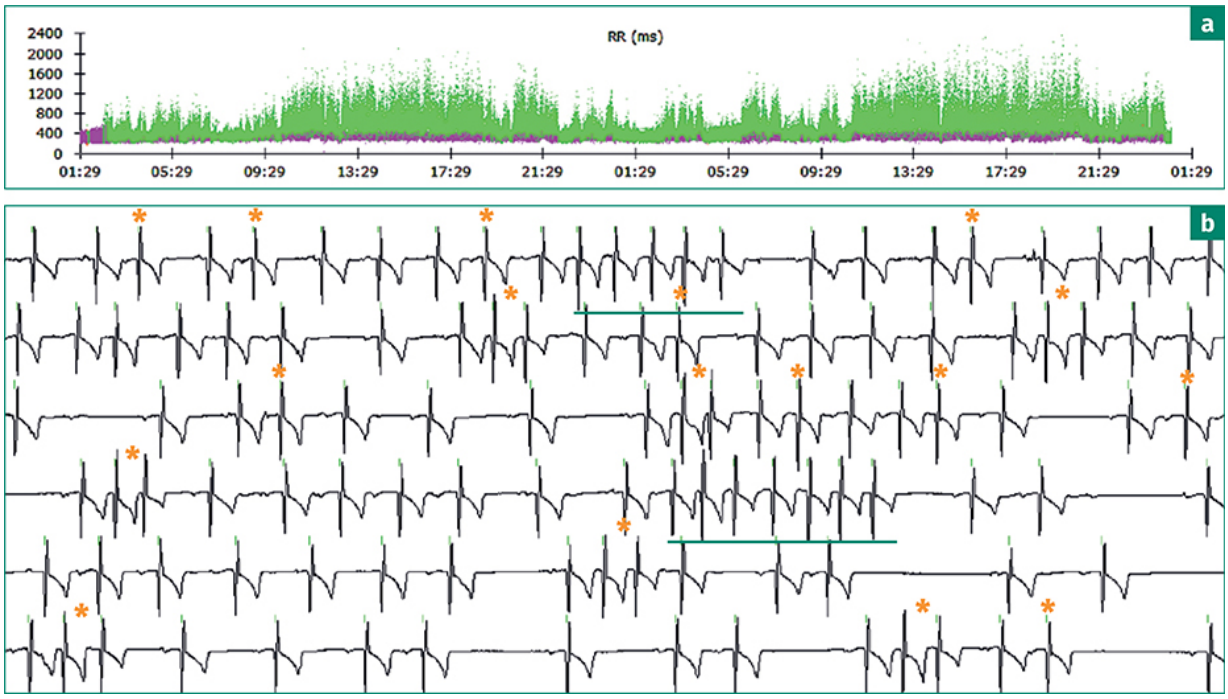


FIGURE 30.1. Holter recording from a 12-year-old female Yorkshire Terrier with myxomatous mitral valve disease and frequent atrial arrhythmias. a) Twenty-four-hour tachogram with distribution of normal RR intervals (green) and abnormal RR intervals during atrial arrhythmias (purples). Y-axis, RR interval duration; x-axis, hours of day and night. b) Electrocardiographic recording showing a dominant sinus rhythm interrupted by frequent atrial ectopies and couplets (*) and self-limiting runs of focal atrial tachycardia (horizontal lines). Lead Y; each line corresponds to 30 seconds. Speed, 7.5 mm/s; calibration, 2 mm/mV.

Mitral valve disease is commonly identified in dogs exhibiting atrioventricular block and sinus node dysfunction. While these conditions affect the same population of dogs, they are not believed to be interconnected.

ELECTROPHYSIOLOGICAL MECHANISM

Studies have been conducted to explain the association between mitral valve disease and atrial fibrillation. Left atrial enlargement with elevated chamber pressure is the main factor associated with a higher risk of atrial

fibrillation in dogs with mitral valve disease (Fig. 30.2). Indeed, a larger body weight, an increased left atrial size, and the presence of decompensated heart failure are associated with a higher risk of developing atrial fibrillation. Not surprisingly, several echocardiographic parameters reflecting an increased atrial size or elevated pressure are also indicators of a higher risk of atrial fibrillation, including an increased left atrial to aortic root ratio (LA/Ao) and an increased mitral inflow E wave velocity, as well as decreased fractional shortening (%FS) (Table 30.1).[2] Experimental canine models of mitral regurgitation have only revealed small alterations in the electrophysiological properties of the atria, and mainly attribute the higher inducibility of atrial fibrillation to an increased left atrial size.[9,10] A modest amount of fibrosis that is heterogeneously distributed among the atria might influence electrical impulse conduction velocities and increase susceptibility to atrial fibrillation.[11]

The mechanisms of ventricular arrhythmia in the presence of mitral valve disease in dogs are still unclear. In animals with late-stage mitral valve disease, ventricular remodeling secondary to volume overload, and in many cases pulmonary hypertension, likely results from a combination of elevated adrenergic tone, altered architecture of the ventricular muscle, and electrolyte imbalances. The presence of ventricular ectopies is more difficult to understand in the early stages of the disease. Interestingly, ventricular arrhythmias are reported in people with mitral valve prolapse with or without regurgitation. In this population, the risk of sudden cardiac death is higher if mitral regurgitation is present, and markedly increased in patients with heart failure and left ventricular dysfunction. The suspected mechanisms include fibrosis affecting the subvalvular apparatus, the papillary muscles, and the adjacent myocardium, and mechanical stretch of the papillary muscles leading to altered repolarization and stretch-induced early afterdepolarizations.[12] The electrocardiographic parameters of ventricular repolarization suggest some ventricular repolarization abnormalities are present in dogs with mitral valve disease. These abnormalities are more pronounced at the advanced stages of the disease and may indicate a higher risk of ventricular arrhythmias.[6,13]

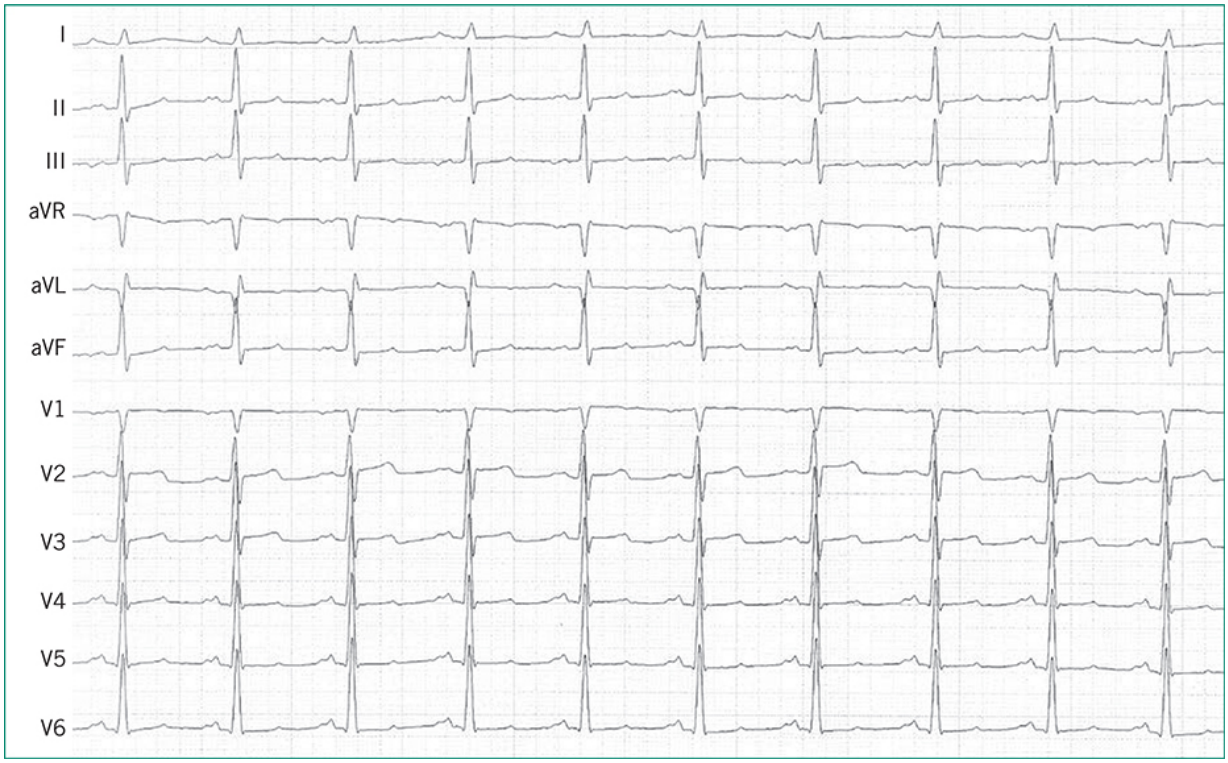


FIGURE 30.2. Interatrial conduction delay in a 12-year-old female Cavalier King Charles Spaniel with severe left atrial remodeling secondary to myxomatous mitral valve disease. Notice the bifid P wave morphology on the frontal plane, typical of interatrial conduction delay due to severe myocardial fibrosis. Twelve leads (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6); speed, 50 mm/s; calibration, 5 mm/1 mV.

TABLE 30.1. Prediction of atrial fibrillation (AF) risk in dogs with mitral valve disease.

LA diameter (cm)*	5× increased risk of AF per each cm increase
LA/Ao	14× increased risk of AF per increment unit
E max (m/s)	2× increased risk of AF per 1 m/sec increase
Body weight (kg)	9% increased risk of AF per each kg increase
ACVIM stage	5× increased risk in stage C and D
%FS	8 to 10% increased risk per 1% decrease

*LA diameter: early diastole on a bidimensional short-axis image.
LA, left atrium; Ao, aortic root; %FS, fractional shortening.
Source: Jung S. W. et al.[1]

CLINICAL PRESENTATION

Arrhythmias remain benign and of no clinical significance in most dogs over the course of the disease. However, in medium to large breed dogs with mitral valve disease and congestive heart failure, the presence of atrial fibrillation has been associated with a decreased survival time by 3 to 4 months. In addition, the median survival time of dogs with inadequate control of the ventricular response rate was only 60 days compared to almost 6 months for dogs with a ventricular response rate below 160 bpm on an electrocardiogram after treatment.[1] Moreover, right-sided congestive heart failure is present in most dogs with mitral valve disease and atrial fibrillation. It is suspected that the increase in atrial pressure secondary to the loss of atrial contraction and associated atrioventricular dyssynchrony is a contributor to the onset of right heart failure.[14]

Syncope is a common clinical sign in small breed dogs (<15 kg) with mitral valve disease. It is reported in approximately 25% of dogs and is more common in the advanced stages of the disease.[15] The cardiac rhythm during a syncopal event is rarely documented. In 4 dogs that had a syncope during a Holter recording, sinus arrest followed by a slow escape rhythm was documented in 1 dog, and sinus rhythm was documented in the 3 other dogs.[16] Although tachyarrhythmias, sinus node dysfunction, and atrioventricular blocks should be considered as possible causes for syncope in older small breed dogs with mitral valve disease, most episodes of syncope likely result from autonomic dysfunction initiated by a triggering event such as excitement or cough (Fig. 30.3) (see p. 425). Sinus arrhythmia has been reported in some dogs with mitral valve disease and in some humans with mitral valve prolapse; however, it is more pronounced in dogs and could indicate autonomic system imbalance in both species.[17,18]

Sudden cardiac death from arrhythmias is thought to be rare in dogs with mitral valve disease. It was documented by Holter monitoring in 2 older, small breed dogs with stage B2 and C mitral valve disease. In both cases, severe bradycardia was followed by an episode of paroxysmal supraventricular tachycardia, and ultimately led to pulseless electrical activity as the terminal rhythm. It is suspected that the bradycardia resulted from an inappropriate vagal reflex.[19] In some larger breed dogs with mitral valve disease and preexisting left ventricular systolic dysfunction, sudden

death secondary to myocardial ischemia from intramural arteriosclerosis should be a consideration.[20] It is less likely in small breeds.

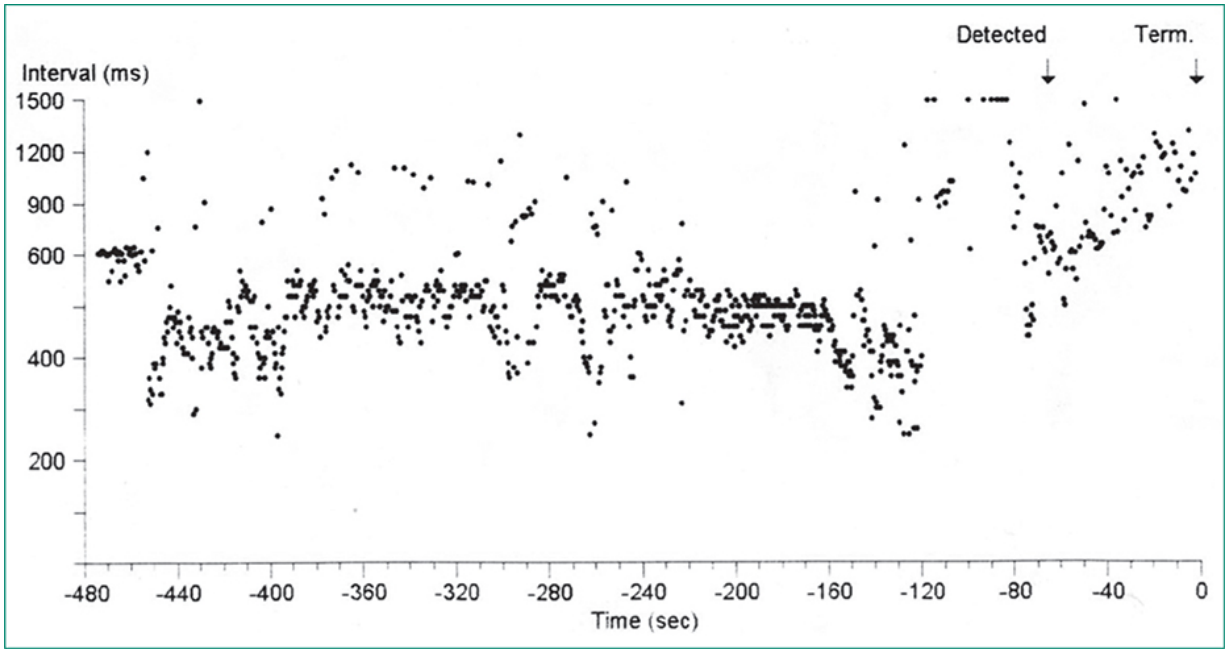


FIGURE 30.3. Implantable loop recorder data from a 10-year-old dog with stage C degenerative mitral valve disease and experiencing syncope. Heart rate tachogram saved during a syncopal event. Initially, the heart rate is stable with a heart rate of approximately 120 bpm. Fifty to 60 seconds before the label "detected", which corresponds to the activation of the recording by the owner, there is a rapid increase in heart rate with a peak of approximately 250 bpm. It is abruptly terminated with a marked reduction in heart rate which is simultaneous with the syncopal event. The heart rate returns to normal soon after with a resolution of the clinical signs. This pattern is highly suggestive of reflex syncope. Y axis, RR intervals in ms; X axis, time in seconds.

THERAPY

Atrial premature beats and ventricular premature beats in dogs with mitral valve disease usually do not require the initiation of therapy. When present, atrial fibrillation should be managed with adequate rate control therapy.[1] A complete workup should be performed in dogs with mitral valve disease and syncope to rule out cardiac syncope and pulmonary hypertension. In most cases, the owner should be reassured that these episodes are usually benign and can be partially avoided by controlling the triggering event. Anecdotally, the author has noted that suspected neurally mediated syncopal events in dogs with mitral valve disease and a severely enlarged

left atrium frequently improve at least temporarily after initiation or optimization of heart failure medications.

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CHAPTER 31

Arrhythmias in systemic disorders

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ELECTROLYTE DISTURBANCES

Several electrolytes play a major role in the genesis of the action potential. The electrolyte composition of serum normally remains within well-defined ranges; deviation from the normal concentrations of one or more electrolytes occurs in a variety of systemic diseases. Alterations in serum electrolyte concentrations may have a marked effect on impulse formation and conduction through the specialized conduction system and working atrial and ventricular myocardium.[1] In the clinical veterinary setting, abnormal serum potassium concentrations are responsible for the vast majority of electrolyte-induced cardiac rhythm disturbances. Although sodium, hydrogen, and calcium imbalances may also induce alterations of the action potential and correlated arrhythmias,[1] in the authors' clinical experience, only potassium and magnesium abnormalities are common enough to warrant discussion.

HYPOKALEMIA

A decreased extracellular potassium concentration is associated with different pathological conditions; the most frequent causes of hypokalemia include loss of potassium from the gastrointestinal tract and urinary loss. This condition is rarely associated with excessive administration of corticosteroids, Cushing's syndrome, or the development of alkalosis. In diabetic patients, it can be present after the administration of insulin.[1]

Electrocardiographic abnormalities are usually recorded with a serum potassium concentration ranging from 2.5 to 3 mEq/L and consist in a progressive depression of the ST segment associated with a decreased T wave amplitude. In some patients, a second repolarization wave, called U wave, can appear after the T wave. In advanced hypokalemia, an increased duration of the QRS complex can be noted secondary to a generalized decrease in conduction velocity at the level of the Purkinje fibers or working ventricular myocardium. An increase in the amplitude and duration of the P wave associated with a slightly increased duration of the PQ interval can also be recorded. In rats, prolongation of the PQ interval and QT interval and widening of the P wave and QRS complexes have been described during furosemide-induced hypokalemia.[2] In experimental settings, chronic hypokalemia in dogs has been shown to increase ventricular vulnerability. This effect depends on the severity of hypokalemia and is more marked in individuals with concomitant myocardial ischemia.[3] Sympathetic nerve activity may also play an important role in the increased ventricular arrhythmogenicity associated with chronic hypokalemia. The increase in ventricular vulnerability is associated with the development of malignant ventricular rhythm disturbances.[3]

Animals receiving digoxin that present concomitant hypokalemia are prone to develop focal atrial tachycardia associated with atrioventricular block and ventricular rhythm disturbances. Treatment is directed towards correcting the main clinical problem and slowly correcting serum potassium concentrations with potassium supplementation.[1]

HYPERKALEMIA

Hyperkalemia is often present in association with adrenal insufficiency, ketoacidotic diabetes, oliguric or anuric renal failure, acidosis, and postsystemic thromboembolic events.[1,4] The clinical importance of hyperkalemia is mainly related to its severe and potentially life-threatening cardiotoxic effects. The clinical manifestations of hyperkalemia include generalized muscle weakness, listlessness, peripheral vascular collapse, and bradycardia. Its effects on the heart muscle consist in decreased excitability, an increased refractory period of the atrial and ventricular myocytes, and slowing of conduction. Potassium, both intra- and extracellular, is the most

important contributor to the membrane resting potential, and hyperkalemia causes the resting membrane potential to shift to less negative values, which leads to a decrease in the slope of phase 0 of the action potential.

The earliest electrocardiographic finding associated with hyperkalemia is peaking of the T wave, which displays symmetric branches. This electrocardiographic abnormality occurs when serum potassium concentrations exceed 5.5 mEq/L, and it is usually seen with shortening of the QT interval. Serum potassium concentrations exceeding 6.5 mEq/L are associated with widening of the QRS complexes, with a rough correlation between QRS complex duration and the degree of hyperkalemia.[4–6] As serum potassium levels exceed 7 mEq/L, the P wave amplitude decreases, while its duration increases due to the slowing of conduction in the atrial myocytes. An increased atrioventricular conduction time (PQ interval prolongation) can be noted in association with P wave changes. When the serum potassium concentration exceeds 8.5 mEq/L, P waves are no longer visible, and a sinoventricular rhythm becomes evident (Fig. 31.1). A further increase in the serum potassium concentration is associated with elevation or depression of the ST segment, and with a concentration of 11–14 mEq/L, ventricular asystole or ventricular fibrillation may occur.[1,5,6]

Hyperkalemia decreases the slope of phase 4 of the action potential with decreased automaticity by increasing membrane permeability to potassium. However, since spontaneous depolarization of the sinus node is mainly associated with calcium currents, automaticity of the sinus node may be highly resistant to hyperkalemia.[7,8]

Local myocardial hyperkalemia has been shown to be associated with the development of ventricular arrhythmias in experimental models. Different authors have suggested that potassium release from ischemic cardiomyocytes during early ischemia may play a role in the development of ventricular rhythm disturbances.[6,8] The administration of procainamide reduces local potassium concentrations at the injured area, with a decrease in the correlated arrhythmic events.[6,8]

Treatment is aimed at correcting the hyperkalemic state and the main systemic disease. Therapy is not needed when the potassium concentration is below 6.6 mEq/L, while intensive care should be provided when the patient’s serum potassium concentration is greater than 8–8.5 mEq/L. Serum potassium concentrations can be lowered with intravenous infusion

of 10% glucose solution because glucose causes potassium to shift from the serum into the intracellular space by altering membrane characteristics and promoting the deposition of glycogen. Subcutaneous or intravenous administration of insulin enhances the cellular uptake of glucose. Another option is sodium bicarbonate, which causes potassium to shift from the extracellular space into the intracellular space due to serum alkalinization. Sodium and calcium antagonize the cardiotoxic effects of potassium, and the administration of sodium gluconate under electrocardiographic monitoring limits the clinical signs of cardiotoxicity without affecting the serum potassium concentration. This effect is considered to be transient and must be associated with other means of lowering the serum potassium concentration.[1]

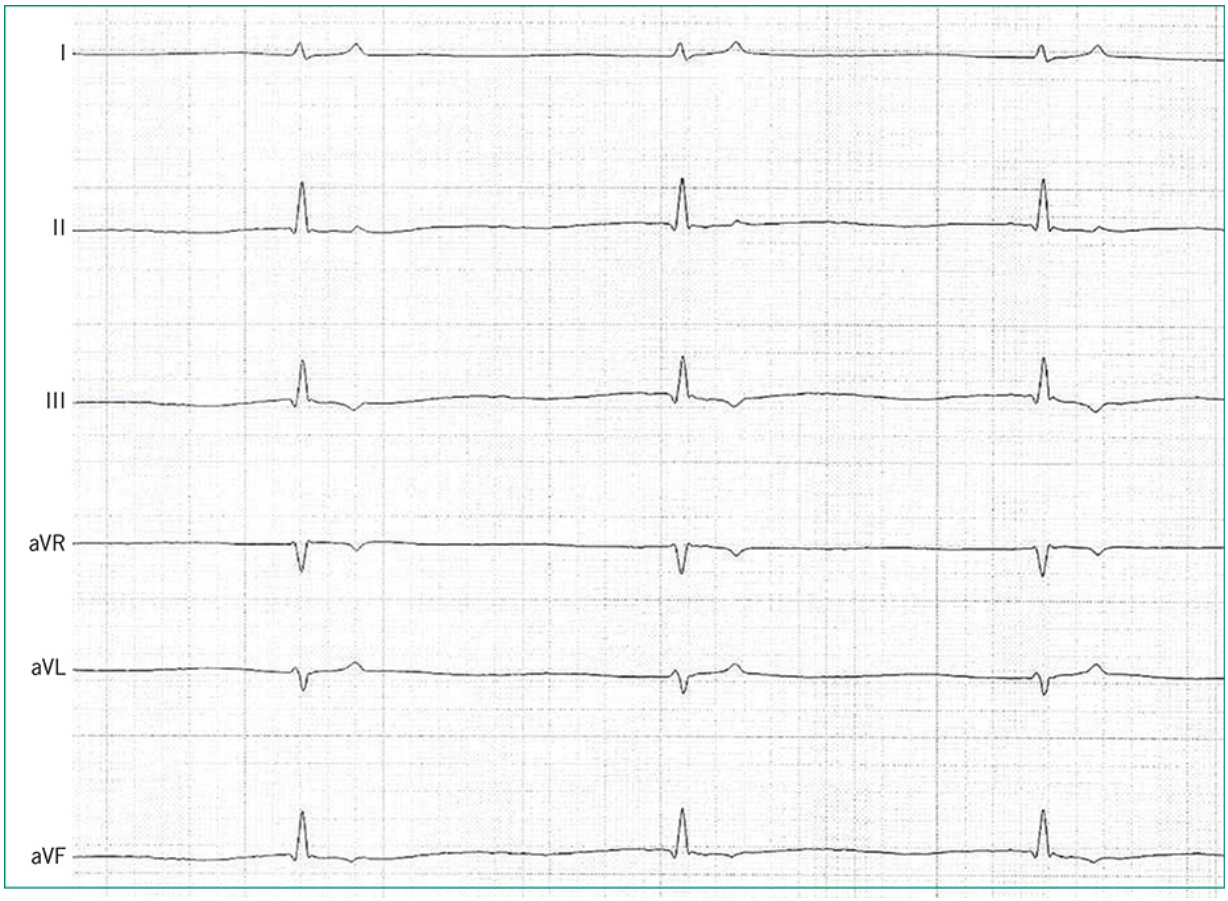


FIGURE 31.1. Sinoventricular rhythm due to hyperkalemia (adrenal insufficiency) in a 4-year-old female German Shepherd. Notice the presence of a narrow QRS complex bradycardia (46 bpm) in the absence of atrial deflections and the prolongation of the QT interval (280 ms). Six limb leads (I, II, III, aVR, aVL, aVF); speed, 50 mm/s; calibration, 10 mm/1 mV.

HYPOMAGNESEMIA

The role of magnesium, a micronutrient involved in maintaining and establishing a normal heart rhythm, is still controversial. Hypomagnesemia is defined as a total serum concentration <0.65 mmol/L (1.58 mg/dL) and is often symptomatic. The range for normal magnesemia is set at 0.85–0.95 mmol/L (2.07–2.3 mg/dL). An important limitation to magnesium measurement methods is that serum magnesium concentrations can be kept within normal limits through intracellular depletion, and there are currently no rapid and effective tests to assess the concentration of intracellular magnesium, which plays an essential role in the heart and whole body. Hypomagnesemia can be a consequence of an insufficient intake, redistribution from the extracellular to the intracellular space, or increased loss through the renal or gastrointestinal system (e.g., prolonged diuretic therapy). Hypomagnesemia can be linked to many factors and causes disturbances in energy metabolism, ion channel exchanges, action potential alteration and myocardial cell instability, all mostly leading to ventricular arrhythmia.[9]

The clinical implications of hypomagnesemia are varied: at the level of the vessels, it increases vulnerability to oxygen-derived free radicals, thus altering the endothelial function and contributing to the genesis of atherosclerotic plaque formation; at the level of the heart, it causes a large variety of arrhythmias and can apparently affect the course of heart failure.[9]

Electrocardiographic findings associated with hypomagnesemia have been reported to include: ST segment depression; peaked, tall, and symmetric T waves; shortening of the PQ and QT intervals; increased QRS duration; and presence of U waves. Hypomagnesemia has also been associated with increased dispersion of ventricular repolarization, which predisposes to polymorphic ventricular tachycardias and lowers the threshold for development of ventricular fibrillation (Fig. 31.2).[9]

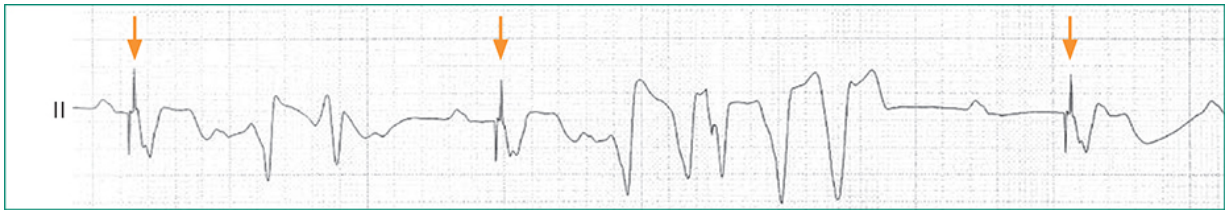


FIGURE 31.2. Polymorphic nonsustained ventricular tachycardia due to hypomagnesemia in a 12-year-old male German Pointer with third-degree atrioventricular block and a pacemaker in VVI

modality. Notice the artificial paced beats (arrows) dissociated from the P waves followed by a wide QRS complex couplet and a run of nonsustained wide QRS complex tachycardia. Note the change in the QRS morphology on a beat-to-beat basis and the presence of irregular RR intervals. Lead II; speed, 50 mm/s; calibration, 20 mm/1 mV.

CHAGAS' DISEASE

Infection with the protozoan parasite *Trypanosoma cruzi* causes Chagas' disease, which induces a myocardial disorder that affects about 10–20 million people and is responsible for an estimated 50,000 deaths per year in Latin America.[10–16] Sporting and working breeds and medium and large breed dogs from urban and rural areas are most commonly affected by the disease.[11] The infection usually manifests as cardiac disease and rarely neurological disease. However, many infected dogs remain asymptomatic for life.[10] The mechanism for cardiotoxicity is not completely understood, but the main proposed mechanisms include direct cardiotoxic effects of the parasites, the relative immune response, and cellular dysfunction following the parasite invasion. In humans and dogs, there are three distinctive phases of myocarditis: acute, intermediate (or latent), and chronic. Signs in the acute phase are associated with marked parasitemia, while chronic manifestations of the disease may be present over many years in the absence of parasitemia.

Histopathological findings in the acute phase include severe diffuse lymphoplasmacytic and histiocytic necrotizing myocarditis affecting both the atria and ventricles, a large number of parasitic pseudocysts, and minimal signs of fibrosis.[11]

Electrocardiographic findings in patients affected by Chagas' disease in the acute phase include a variety of rhythm disturbances (e.g., sinus tachycardia, sinus node dysfunction, prolonged PQ intervals) and conduction abnormalities (e.g., atrioventricular blocks and intraventricular conduction blocks, supraventricular and ventricular arrhythmias) (Fig. 31.3). The infection by *Trypanosoma cruzi* has been reported to be more severe in dogs presenting with ventricular rhythm disturbances than in those with supraventricular rhythm disturbances or atrioventricular block.[14] In both humans and dogs, the association between ventricular rhythm disturbances and atrioventricular conduction disturbances is considered not

rare. Usually, arrhythmias recorded in the acute phase are associated with high levels of cardiac troponin I.[10,11]

In the chronic phase, histopathological findings include interstitial mononuclear cellular infiltrates, perivasculitis, marked fibrosis, and the rare presence of pseudocysts.[11,17]

During the chronic phase, the electrocardiogram is reported to be usually normal, although ventricular arrhythmias have been observed. Ventricular arrhythmias in this phase are described to be associated with myocardial scars as a sequela of the acute infection.[17]

While the echocardiographic examination may be normal in acutely or mildly affected dogs, findings during the chronic phase include decreased right ventricular systolic function and left ventricular dilation with progressive left ventricular systolic dysfunction. Even if echocardiographic abnormalities can involve both ventricles, the right ventricle is described to be predominantly affected.[11–13] The pathogenesis of biventricular involvement is still unknown, but possible mechanisms include immune-mediated mechanisms and toxic parasitic products affecting the myocytes. The association between myocardial damage and ventricular arrhythmias increases the risk of sudden cardiac death in diseased patients.[11]

Cardiac magnetic resonance imaging has been shown to be useful in the detection of cardiac abnormalities during the chronic phase. In this phase, abnormalities include increased fibrosis, abnormal wall motion of the heart, and decreased global ventricular function.[18]

In human medicine, antiparasitic medications are recommended in the acute phase of the disease as well as in immunosuppressed patients, patients with transplacental infection, and women of childbearing age. They are also recommended in pediatric patients in the chronic phase and in patients with reactivation of the *Trypanosoma cruzi* infection. However, antitrypanosomal treatment in humans during the chronic phase has limited ability to change the clinical outcome, despite evidence of a reduced parasite load. In an experimental model in dogs, a reduction in parasitemia has been documented within 1 month of treatment with benznidazole.[17]

Itraconazole in association with antiarrhythmic treatment (amiodarone) has been described in dogs.[19] In experimental models, it has been proven that effective antiparasitic treatment in the early stage of Chagas's disease can lead to a significant reduction in the frequency and severity of the

parasite-induced cardiac disease, even if parasites are not completely eliminated.[17]

Pacemaker implantation is required when third-degree atrioventricular block is diagnosed. Pacemakers are often required in dogs with Chagas' disease. Ventricular arrhythmias require pharmacological antiarrhythmic treatment; the use of amiodarone at a dose of 10 mg/kg/day has been described.[19] The combination of amiodarone use with implantation of a cardioverter defibrillator has been reported for the management of ventricular arrhythmias associated with atrioventricular blocks.[19]

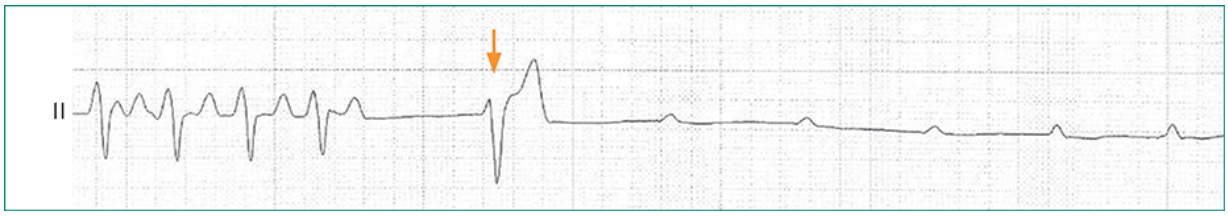


FIGURE 31.3. Monomorphic ventricular tachycardia followed by high-grade atrioventricular block in an 8-year-old male Golden Retriever affected by Chagas' disease. Note the presence of a wide QRS complex tachycardia (250 bpm) followed by a short ventricular arrest interrupted by a ventricular escape beat (arrow). Note, in the second part of the tracing, the presence of blocked P waves with an increasing discharge rate due to an intrinsic high-grade atrioventricular block. Lead II; speed, 50 mm/s; calibration, 20 mm/1 mV.

Those dogs diagnosed at an older age (mean of 9 years) survived between 30 and 60 months, whereas dogs diagnosed at younger age (mean of 4.5 years) survived only up to 65 months after the diagnosis. Dogs requiring pacemaker implantation present a poorer prognosis, with sudden death occurring in 7–13% of patients.[11] The cause of sudden cardiac death remains unknown, even if atrioventricular rhythm disturbances associated with malignant ventricular tachycardias have been proposed as an option.

VIPER ENVENOMATION

Snakes of the *Viperidae* family, which has a worldwide distribution, cause a significant number of envenomations in dogs every year.[20–23]

A viper's venom contains about 30 components, 16 of which have been identified, including proteases, hemorrhagins, amino acid esterases, phospholipases, and neurotoxins. To date, no specific cardiotoxin has been

found in viper venom. The clinical manifestations of viper envenomation in dogs are mainly local and include swelling edema and hematoma formation, mostly attributed to hemorragins in the venom. Systemic signs such as tachypnea and rhythm disturbances with a reported mortality rate of 3.7% can however occur. In dogs and other animals, the causes of death are still unknown, and the importance of myocardial injuries is still unclear, although myocardial necrosis has been described. The increase in cardiac troponin I and the occurrence of ventricular arrhythmias in patients with viper envenomation reflects some degree of myocardial lesions.[20–23] Rhythm disturbances are identified in about 30–57% of dogs with viper envenomation. The most commonly observed arrhythmia is sinus tachycardia, followed by ventricular tachycardia or accelerated idioventricular rhythm, ventricular premature ectopic beats, and atrial premature ectopic beats. Atrioventricular conduction disorders may also be seen (e.g., first- or second-degree atrioventricular block).[20–23] In most cases, the detected arrhythmias have been described to resolve spontaneously with no antiarrhythmic treatment, although dogs with ventricular arrythmias secondary to viper envenomation warrant prolonged electrocardiographic monitoring to evaluate the risk of sudden cardiac death.[20–23]

OBSTRUCTIVE SLEEP APNEA

Obstructive sleep apnea consists of repetitive episodes of complete or partial cessation of breathing, defined respectively as apneas and hypopneas. Obstructive sleep apnea is a common condition in both human and veterinary medicine, and its prevalence is progressively increasing. This may be explained by the increasing age of the population and incidence of obesity.[24–27] The clinical presentation of obstructive sleep apnea is reported to be different to that of brachycephalic obstructive airway syndrome, a common condition in brachycephalic dogs. Obstructive sleep apnea has also been reported in Cavalier King Charles Spaniels in association with intranasal abnormalities.[28]

Obstructive sleep apnea may enhance a variety of electrophysiological mechanisms and lead to rhythm disturbances such as abnormal

automaticity, triggered activities, shortening of the atrial refractory period, prolongation of the repolarization time, and reentrant mechanisms. Abnormal automaticity can result in abnormal impulse formation in the sinus node. This finding is usually related to potassium dysregulation, which is observed during sleep apnea as a result of hypokalemia secondary to transcellular ion shift and reduced renal absorption, hypocapnia, and β-adrenergic stimulation.[24–27]

Sinus node dysfunction findings consisting in bradycardia with chronotropic incompetence, sinus pauses caused by sinus arrest or sinoatrial blocks, and tachycardia-bradycardia syndrome have been described.[29]

Triggered activities involve early or delayed oscillations of the transmembrane action potential, which reaches the action potential threshold resulting in impulse formation. Triggered activities can be the origin of premature atrial or ventricular ectopic beats or can precipitate atrial or ventricular tachycardias. Hypoxia, acidosis, and increased catecholamine levels are considered precipitating factors for the development of triggered activities. In human beings, obstructive sleep apnea is associated with an increased dispersion during the ventricular repolarization phase. This condition represents a predisposing factor for nocturnal sudden cardiac death.[24] Furthermore, the hypoxia and hypercapnia observed during obstructive sleep apnea are described to be responsible for the shortening of the effective refractory period of atrial myocytes. The shortening of the effective refractory period may predispose to the development of atrial fibrillation. In addition, in an experimental animal model, obstructive sleep apnea has been shown to be correlated with an increased expression of genes encoding for the potassium channels I_{K1}, I_{Kr}, I_{Ks}, I_{to}, I_{Kur}, and I_{Kach} and decreased expression of genes encoding for I_{CaL}.[29–31]

A sympathovagal imbalance has been shown in obstructive sleep apnea, with a decrease in heart rate variability associated with cardiovascular mortality.[32] This condition may be the main trigger for the development of rhythm disturbances. The increased respiratory efforts to achieve restoration of airway patency are intrinsic to the physiology of obstructive respiratory events. The vagal influence correlated with these events leads to the sinus bradycardia and sinus arrest observed during apneic events (Fig. 31.4). After upper airway patency restoration, a strong sympathetic drive is

elicited secondary to hypoxia, hypercapnia, and the absence of sympathoinhibition from normal lung reflexes. Obstructive sleep apnea is also associated with intermittent hypoxemic bouts responsible for recurrent sympathetic discharges, thereby favoring arrhythmia development. These sequential alterations of the autonomic nervous system related to the respiratory system lead to enhanced susceptibility to rhythm disturbances. Although electrophysiological changes are demonstrated to favor the development of atrial fibrillation, slowing of conduction due to cardiac structural remodeling caused by obstructive sleep apnea (e.g., fibrosis and connexin dysregulation) is considered a second important mechanism contributing to arrhythmia induction and maintenance.[24,33] The important role of the autonomic nervous system in obstructive sleep apnea and arrhythmogenesis has been further supported by studies in experimental models, in which ablation of the right ganglionated plexus in dogs resulted in inhibition of atrial fibrillation induced by apnea.[24] Obstructive sleep apnea is also reported to be associated with enhanced left stellate ganglion activity and augmented neural remodeling in the atrial tissue, leading to increased vulnerability to atrial fibrillation.[34] Furthermore, obstructive sleep apnea has been shown to upregulate protein levels encoding for β_1 and β_2 receptors in experimental models. Cholinergic M2 receptors are the primary mediators of parasympathetic control of the heart function. In obstructive sleep apnea, M2 and acetylcholine-dependent potassium current have been found to be upregulated (I_{KAch}).[31]

Hypoxia and hypercapnia are the consequence of impaired gas exchange during apneas and hypopneas and are considered to lead to oxygen desaturation, in particular in patients with concomitant pulmonary or cardiovascular diseases. Termination of the upper airway obstruction after a respiratory event may lead to reoxygenation and subsequent formation of reactive oxygen species. These substances are implicated in structural myocardial remodeling leading to myocardial injuries, myocyte apoptosis, activation of fibroblasts to myofibroblasts, and perivascular and interstitial fibrosis. Hypoxia also causes peripheral vasoconstriction with a consequent increase in preload and afterload and therefore in cardiac workload.[24] Obstructive sleep apnea has been described to promote aortic remodeling in a canine experimental model by inducing inflammation of the aortic tissue and subsequent aortic fibrosis, apoptosis, and sympathetic nerve

sprouting.[33] These alterations in the arterial tree correlate with hypertension in patients with obstructive sleep apnea. In normal conditions, activation of the arterial baroreflex reduces sympathetic activity and inhibits the chemoreflex. However, in patients with chronic hypertension, the baroreflex is impaired and chronically reset. Baroreflex impairment may be due to decreased sensitivity and/or an increased set point. A study in a canine model with repeated obstruction of the upper airways showed that baroreceptors reset to a higher pressure with no changes in baroreflex sensitivity.[25,35]



FIGURE 31.4. Ambulatory electrocardiographic recording of a sinus arrest due to obstructive sleep apnea in a 12-year-old female Cavalier King Charles Spaniel. Notice the presence of an initial sinus arrhythmia, followed by progressive sinus bradycardia and a prolonged sinus arrest, interrupted by three escape ventricular ectopic beats. Sinus rhythm is restored in the last line. Y lead; each line corresponds to 10 seconds. Speed, 28 mm/s; calibration, 5 mm/1 mV.

From the mechanical point of view, the upper airway occlusion generates negative intrathoracic pressures that result in an augmented cardiac transmural pressure. These significant changes in pressure related to the respiratory phases lead to an increase in left ventricular afterload and are correlated with acute distension of the atrial walls. Atrial myocyte distension contributes to the acute shortening of the atrial effective refractory period via vagal activation. In addition, these acute changes are correlated with an increased central venous volume. These mechanical alterations lead to the activation of the stretch-mediated ion channels and are correlated with myocardial remodeling, which enhances arrhythmogenic

susceptibility. Moreover, the described changes in intrathoracic pressure during obstructive sleep apneas have been shown to be sufficient to cause ventricular remodeling correlated with right and left ventricular muscle deformation during the systolic phase. The repeated insults due to the negative intrathoracic pressure lead to fluctuations in the afterload burden, left ventricular hypertrophy, and an increased risk of ventricular arrhythmias.[24,29]

The arrhythmia propensity is also increased by the activation of the proinflammatory cascade, cellular 5'-triphosphate depletion, xanthine oxidase activation, and formation of reactive oxygen species typically associated with the repetitive hypoxia/reoxygenation process that occurs during obstructive sleep apnea. The inflammatory state in these patients is correlated with the development and persistence of atrial fibrillation.[24,30,45]

The large shift in transmural pressure, intermittent hypoxia, and upregulation of the systemic inflammation cascade seen in obstructive sleep apnea are important factors in cardiac remodeling. In humans with moderate to severe obstructive sleep disorders, electrocardiographic evidence of a delay in interatrial conduction has been reported and was consistent with different degrees of interatrial blocks and increased P wave dispersion.[24]

Since obstructive sleep apnea is often associated with prolonged sinus arrest, permanent endocardial pacemaker is generally accepted for human and veterinary patients with prolonged symptomatic asystolic pauses.[36]

The administration of trazodone with L-tryptophane, despite possible severe side effects, has been reported to be effective in treating obstructive sleep apnea in an animal model. The drug's effectiveness may be related to increased upper airway dilator activity in sleep and/or enhanced slow-wave sleep.[37] Ondasetron has also been described for the treatment of obstructive sleep apnea and led to a rapid near-complete resolution of the clinical signs, although the follow-up period in this study was short.[38,39]

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CHAPTER 32

Syncope

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Syncope is defined as a transient loss of consciousness due to cerebral hypoperfusion, characterized by a rapid onset, short duration, and spontaneous and complete recovery.[1] The clinical manifestations of syncope are part of a broader group of disorders that includes states of real or apparent loss of awareness with abnormal motor control, loss of responsiveness, and loss of postural tone, defined as loss of consciousness.[1] Loss of consciousness can be transient in case of rapid onset, short duration, and spontaneous and complete recovery, or nontransient if the event lasts for a prolonged period of time, as occurs in coma, severe hypoxia, or hypoglycemia. Transient loss of consciousness can be caused by head trauma (i.e., concussion) or be nontraumatic (i.e., syncope, epileptic seizure, and sleep disorders) (Fig. 32.1).[1,2]

The clinical features of transient loss of consciousness are usually derived from the information taken from witnesses, and it can very often be difficult to differentiate syncope due to global cerebral hypoperfusion from epileptic seizures due excessive brain activity.

Syncopal episodes can sometimes be preceded by presyncope, a corollary of clinical signs often due to autonomic activation, such as nausea, vomiting, weakness, and alteration of sight and hearing.[1]

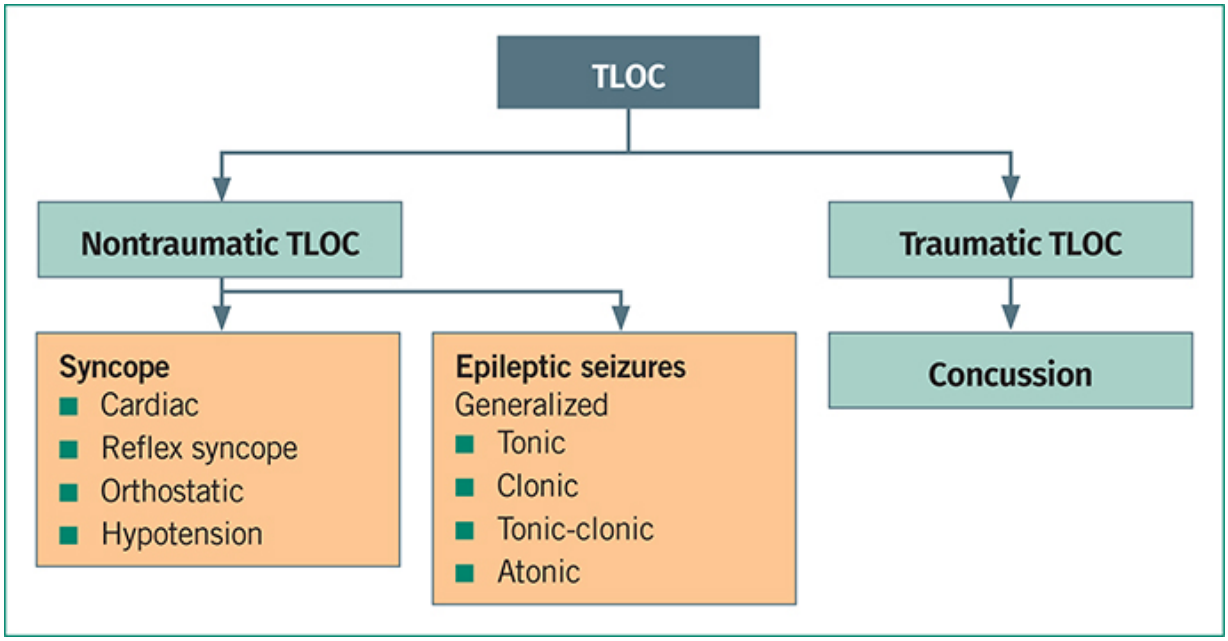


FIGURE 32.1. Schematic view of syncope in the context of transient loss of consciousness (TLOC). Nontraumatic transient loss of consciousness is classified into two groups: syncope and epileptic seizures. Combinations occur, for example, anoxic-epileptic or anoxic seizures.

PATHOPHYSIOLOGY AND CLASSIFICATION

In a normal dog, regional cerebral blood flow values range from 50 to 100 mL/100 g/minute,[3] which represents 3–5% of the stroke volume at rest. This amount of flow satisfies the minimal need to maintain consciousness. These values differ from those reported in humans, in which the average cerebral blood flow at rest is around 15–20% of the stroke volume.[1] In addition to the higher cerebral blood flow, the biped position makes human beings more susceptible to loss of consciousness. In this species, a sudden cessation of cerebral blood flow for 6 to 8 seconds or, in upright position, a drop in systolic blood pressure of 50–60 mmHg at heart level, which corresponds to 30–45 mmHg at brain level, can both induce loss of consciousness. In veterinary medicine, no data are available regarding cerebral blood flow cessation times or drops in blood pressure required to induce loss of consciousness. However, Holter findings reported in dogs during transient loss of consciousness showed that the ventricular arrest that induced syncope always lasted more than 6 seconds, regardless of the underlying nature of the episode.[4–6]

The ultimate mechanism of syncope is a fall in systemic blood pressure with a decrease in global cerebral blood perfusion, and since systemic blood pressure is the product of cardiac output and total peripheral resistance, a fall in either can cause loss of consciousness.

Syncope can therefore be classified according to the underlying pathophysiological mechanism, that is, a fall in total peripheral resistance, in cardiac output, or both (Fig. 32.2; Table 32.1).[1]

The main causes of a fall in total peripheral vascular resistance include sympathetic withdrawal due to an inappropriate reflex inducing vasodilation (vasodepressive reflex syncope),[1,7] and functional and structural impairment of the autonomic nervous system leading to orthostatic hypotension.[1] The main causes of a drop in cardiac output include reflex bradycardia (i.e., cardioinhibitory reflex syncope),[1,7] cardiovascular disorders (i.e., intrinsic sinus nodal, atrial, or atrioventricular nodal arrhythmias; congenital valvular stenosis; pulmonary hypertension; and pulmonary thromboembolism) and finally inadequate venous return either due to volume depletion or pooling.[1]

Epileptic seizures can also cause transient loss of consciousness when motor control is lost and concomitant loss of postural tone occurs, as in tonic, clonic, tonic-clonic, and atonic generalized seizures (see Fig. 32.1).[1] Severe cerebral hypoxia, usually caused by a drop in cardiac output secondary to prolonged ventricular arrest, can promote anoxic-epileptic or anoxic seizures if true seizure activity or characteristics of seizure activity are present, respectively, as reported in cats.[8] Anoxic seizures are defined as nonepileptic events due to an abrupt interruption of the energy supply to the metabolically active cerebral neurons, and can be misinterpreted as epileptic seizures.[8]

One last possible cause of syncope reported in English Bulldogs and Cavalier King Charles Spaniels is sleep-disordered breathing induced by obstructive upper airway syndrome or by intranasal abnormalities, respectively.[2,9]

Table 32.1 shows the recent classification of syncope based on the underlying pathophysiological mechanism and modified for dogs and cats, which includes:

- Cardiac syncope

- Reflex or neurally mediated syncope
- Orthostatic hypotension syncope

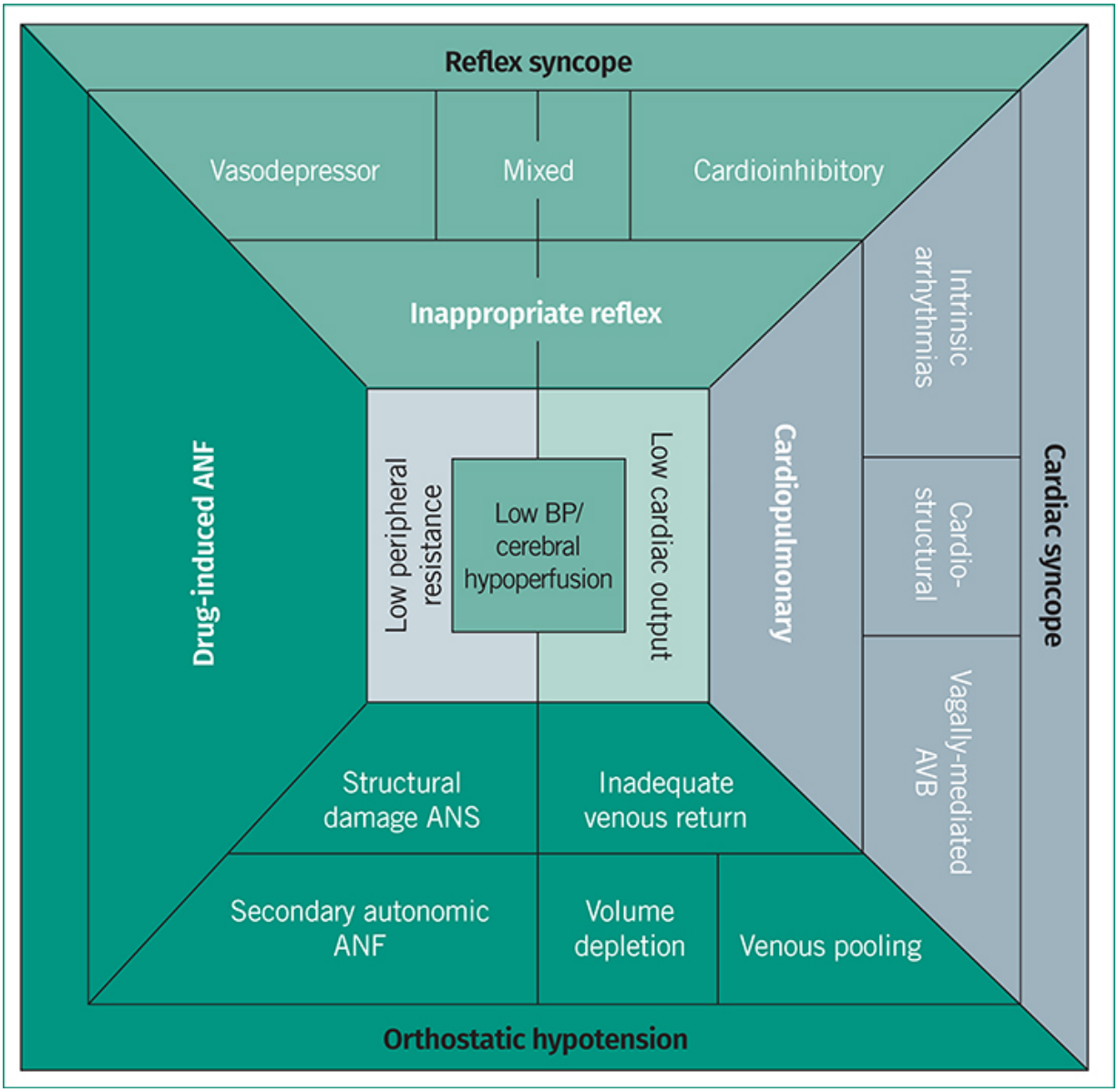


FIGURE 32.2. Classification of syncope according to the underlying pathophysiology. AVB, atrioventricular block; BP, blood pressure; ANF, autonomic nervous failure; ANS, autonomic nervous system.

TABLE 32.1. Classification of syncope.

Cardiac syncope	Reflex syncope	Orthostatic hypotension syncope
1. **Intrinsic arrhythmias**	1. **Vasovagal**	1. **Drug-induced**

a. *Bradycardias*
   i. Sinus node dysfunction (sick sinus syndrome)
   ii. Atrioventricular conduction disorders
   ii. Atrial standstill
b. *Tachycardias*
   i. Supraventricular tachycardias
   ii. Ventricular tachycardias

2. **Functional vagally mediated paroxysmal atrioventricular block**
   a. *Paroxysmal atrioventricular block due to vagal overactivity*
3. **Cardiostructural heart diseases**
   a. *Congenital heart disease*
      i. Right ventricular outflow tract obstructions
         - Pulmonic stenosis (valvular, subvalvular, supravalvular)
         - Double-chamber right ventricle

   a. *Emotional*
   b. *Sleep-disordered breathing*
   c. *Orthostatic*
2. **Situational**
   a. *Cough*
   b. *Gastrointestinal (swallowing, defecation)*
   c. *Postexercise*
3. **Carotid sinus**
   a. *Neck tightening*

   a. *Vasodilators*
   b. *Diuretics*
2. **Venous pooling**
   a. *Exercise-induced*
   b. *Postprandial*
   c. *Prolonged rest*
3. **Volume depletion**
   a. *Hemorrhage*
   b. *Diarrhea*
   c. *Vomiting*
4. **Secondary autonomic failure (neurogenic orthostatic hypotension)**
   a. *Diabetes*
   b. *Kidney failure*
   c. *Spinal cord injuries*

■ Tetralogy of Fallot ■ Double-outlet right ventricle ii. Aortic and subaortic stenosis **b.** *Hypertrophic cardiomyopathy* **c.** *Cardiac tamponade* **d.** *Intracardiac tumors* **4. Pulmonary diseases** **a.** *Pulmonary hypertension* **b.** *Pulmonary thromboembolism*		

CARDIAC SYNCOPE

Cardiac syncope is a transient loss of consciousness induced by a sudden drop in cardiac output secondary to intrinsic arrhythmias, cardiostructural diseases, or respiratory diseases (see Table 32.1).

Intrinsic arrhythmias are the most common causes of cardiac syncope in dogs and cats. Severe bradycardias or tachycardias can induce a drop in cardiac output and cerebral perfusion. Drops in cerebral perfusion occur more commonly when other cofactors are present (e.g., alteration of left ventricular systolic function, blood volume, or vasomotor reflex).[10]

Bradycardia due to sinus node, atrial, or atrioventricular node disorders is the most common cause of pacemaker implantation in dogs since it induces syncope in 62–78% of the cases.[11–18] In cats, high-grade atrioventricular block is also a common cause of syncope, which has been documented in 21–57% of cases.[6,8,19,20] Sudden ventricular arrest due to sinus arrest, atrial standstill, and atrioventricular block without subsidiary escape rhythms are the causes of syncope in this cohort of patients. The changes in ventricular refractoriness that characterize dogs with prolonged chronic bradycardia, such as those seen during complete atrioventricular block and atrial

standstill, can predispose them to torsades de pointes and sudden cardiac death.[18,21] In a study, sudden cardiac death occurred in 42.7% of the dogs with advanced or complete atrioventricular block; 24% died within 30 days of the diagnosis, and 40% within 6 months.[13] Cardiac death occurs in a minority of cats with advanced and complete atrioventricular block, and none of the published studies showed an increase in survival time after pacemaker implantation, although an improvement in the patients' clinical condition was observed.[6,8,19,20,22]

Sinus arrest and atrioventricular block can also be secondary to vagal overactivity.[23] Vagal overactivity can occur at the level of the sinus node, inducing prolonged sinus arrest, or at the level of atrioventricular node, inducing third-degree atrioventricular block associated with sinus bradycardia without structural disease of the nodal structures. This condition is associated with an enhanced density of M2 and M3 muscarinic receptors at the level of nodal structures.[24,25] This conduction disturbance can induce transient loss of consciousness and is caused by vagal overactivity in the absence of any intrinsic atrioventricular nodal disorder or inappropriate vagal reflex. Its electrocardiographic features are similar to those of reflex cardioinhibition or of nocturnal atrioventricular blocks secondary to sleep disorders, such as obstructive or central sleep apnea (see p. 415). These latter bradyarrhythmias involve, however, different mechanisms from the pathophysiological and therapeutic points of view.[2,4,9]

Supraventricular and ventricular arrhythmias are very rarely responsible for syncopal events. The occurrence of such events will depend on the ventricular rate, the position of the animal at the onset of the arrhythmia, and the presence of underlying cardiostructural or pulmonary diseases impacting the activation of vasomotor reflexes.[4,10,26,27]

Structural heart diseases and pulmonary diseases can induce transient loss of consciousness as a result of their direct effect on stroke volume, mainly during exercise when cardiac output can no longer satisfy metabolic requests due to mechanical obstruction or systolic failure. In these disorders, however, possible changes in systemic blood pressure and reflex cardioinhibition have been also described.[2,9,28–30]

Syncope has been reported in 52% of Boxers and 48% of English Bulldogs with arrhythmogenic cardiomyopathy,[31–33] in 7% of Dobermans

with dilated cardiomyopathy,[34] in 21% of dogs with pulmonic stenosis,[35] in 6% of dogs with subaortic stenosis,[36] in 28% of dogs with cardiac tamponade,[37] in 61% of dogs with pulmonary hypertension of any cause,[38,39] and in 0.28% of cats with hypertrophic cardiomyopathy.[40]

REFLEX SYNCOPE

The term reflex or neurally mediated syncope refers to a complex group of conditions in which the cardiovascular reflexes that maintain circulatory homeostasis are suddenly and abnormally activated, thereby inducing bradycardia and/or vasodilation. This in turn leads to systemic hypotension and cerebral hypoperfusion, which is ultimately responsible for transient loss of consciousness.[1,7] A necessary requirement to the development of reflex syncope is the integrity of the autonomic nervous system during these episodes, which distinguishes them from dysautonomic syncopal syndromes.[1]

Reflex syncope may result from a vasodepressor effect (i.e., vasodilation predominates), a cardioinhibitory effect (i.e., bradycardia or asystole predominates), or it may be mixed if both effects are present (Fig. 32.3).[1,7] The rapidity of onset and the degree of bradycardia and hypotension do not depend only on a reflex as such, but also on external or environmental factors, such as effort, or different stimuli (i.e., cough, swallowing, defecation, exercise, neck tightening).[1,41–44]

According to triggering factors, reflex syncope can be further subdivided into:

- Vasovagal syncope
- Situational syncope
- Carotid sinus syncope

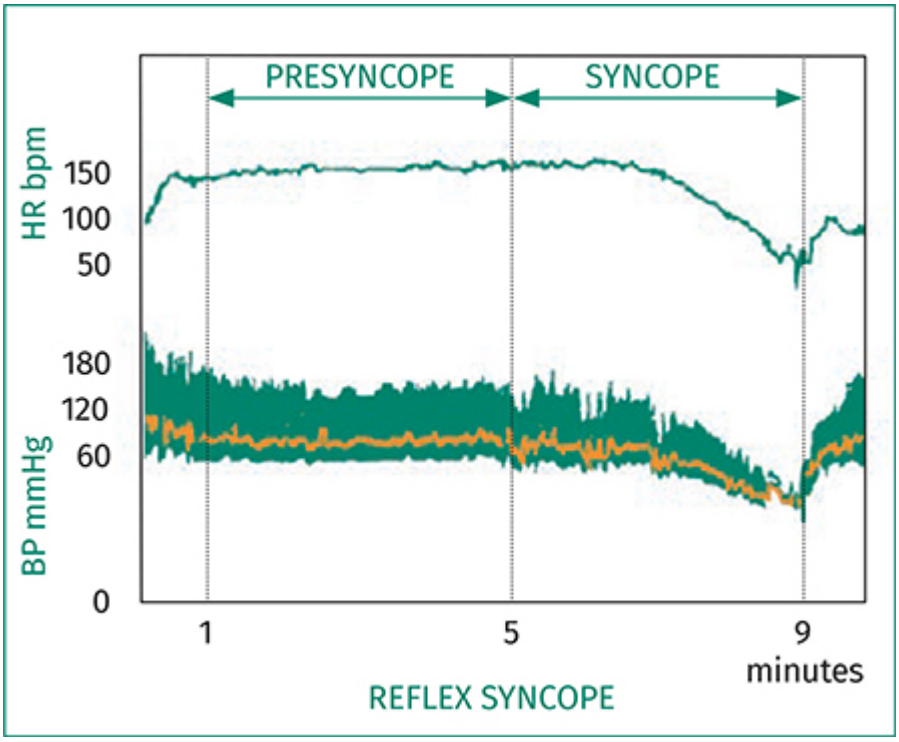


FIGURE 32.3. Heart rate and systolic, diastolic, and mean (orange line) systemic pressure tracings during reflex syncope. The recording started 9 minutes before the occurrence of transient loss of consciousness and ended 1 minute after to record presyncope, syncope, and postsyncope. Notice the initial increase in heart rate just before the loss of consciousness, the ventricular arrest causing a drop in blood pressure, and the rapid recovery of heart rate and blood pressure, which reach a normal value within 2 minutes. HR, heart rate; BP, blood pressure.

VASOVAGAL SYNCOPE

Classic vasovagal syncope is mediated by fear, emotion, pain, or orthostatic stress, and is usually preceded by prodromal signs due to autonomic activation (e.g., pallor of the mucous membranes, nausea, vomiting).[1] However, vasovagal syncope does not always manifest in a typical manner, that is, it may occur in the absence of prodromal signs or typical triggering-precipitating factors. This is mainly seen in elderly animals and is attributed to age-related changes in autonomic tone, particularly in those animals with cardiac failure, in which an increase in sympathetic modulation of the heart rate and a decrease in heart rate variability have been observed.[45]

Clinical signs of sleep-disordered breathing include interrupted sleeping, open-mouth breathing, choking, and apneic episodes, which, in severe cases, provoke hypoxia and sinus arrest and/or paroxysmal atrioventricular block with loss of consciousness. The combined effect of carotid body

stimulation by hypoxemia without lung inflation due to cessation of breathing results in a high degree of vagal tone and eventual bradycardia.[2,9]

If a vasovagal genesis of syncope is suspected, but the history and exclusion of a cardiac and respiratory cause are not sufficient to establish a diagnosis, the test of choice is the tilt test, which unfortunately cannot be performed in domestic animals.[1,7] The tilt test reproduces syncope in the laboratory by means of prolonged orthostatic stress which, combined with immobilization, causes in humans susceptible to vasovagal reaction a redistribution of blood in the lower limbs. This induces vasoconstriction and reflex tachycardia, with contraction of an empty left ventricle, which promotes tension of the C fibers of cardiopulmonary mechanoreceptors. This triggers an inhibitory reflex directed to the cardiovascular center of the medulla oblongata, which in turn triggers an excitatory efferent vagal response (bradycardia and asystole) and an inhibitory efferent adrenergic response (vasodilation and hypotension), thereby resulting in arterial hypotension and transient loss of consciousness. This reflex is called the Bezold–Jarish reflex (Fig. 32.4) and can also be activated by chemical stimulation of the same cardiopulmonary receptors with serotonin.[46,47] The Bezold–Jarish reflex has been also proposed with increased intraventricular pressure secondary to pulmonic stenosis, aortic and subaortic stenosis, and pulmonary hypertension.[30,35,36,38]

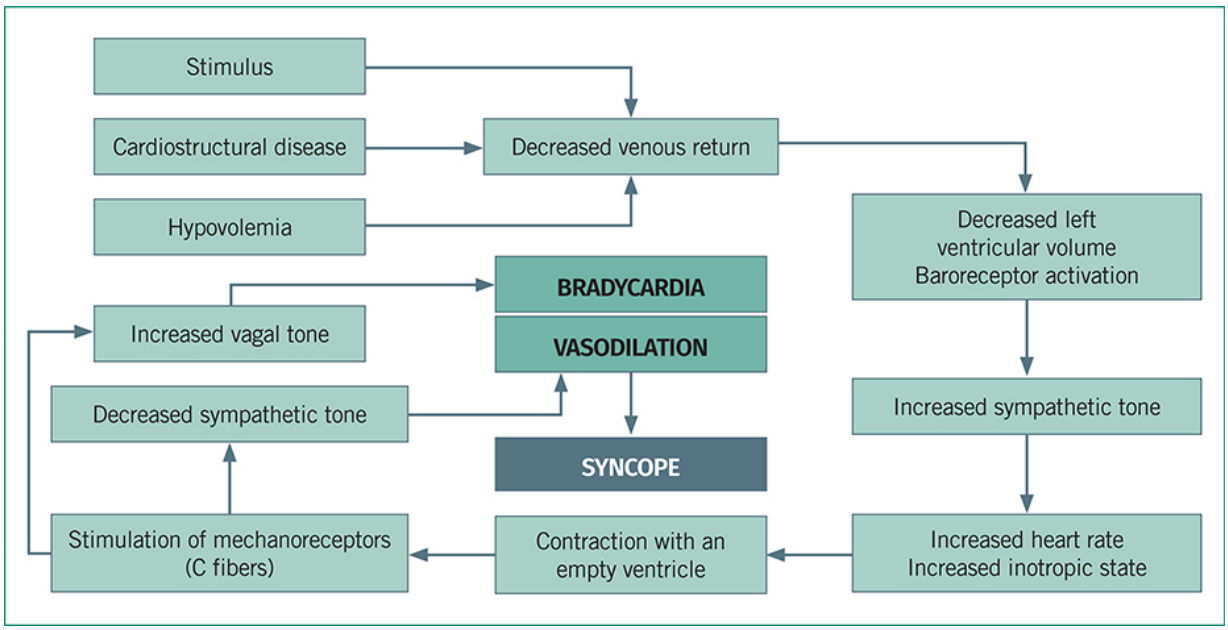


FIGURE 32.4. Sequence of events occurring in case of Bezold–Jarisch reflex activation. The circulatory response changes from normal maintenance of arterial pressure to parasympathetic activation and sympathetic inhibition, which causes hypotension. These alterations are triggered by reduced cardiac venous return, fear, pain, or increased intraventricular pressure. This mechanism is probably mediated via afferent nerves from the heart and by various noncardiac receptors, which may become paradoxically active. This response can occur during regional anesthesia, hemorrhage, or compression of the caudal vena cava. Afferent pathways are characterized by unmyelinated fibers, which are activated via mechanoreceptors that are usually sensitive to left ventricular distension but may also respond to hypovolemia. The arterial baroceptors and cardiac afferents enter the brain via the glossopharyngeal and vagus nerves and synapse in the nucleus tractus solitarius and the ventrolateral medulla. The efferent response increases vagal activity and decreases sympathetic activity. The result in combination is bradycardia and vasodilation that causes significant hypotension and syncope.

SITUATIONAL SYNCOPE

This term refers to all those forms of reflex neurally mediated syncope associated with particular situations (e.g., cough, defecation, swallowing, after exercise) that act as triggering events.[1,41–44] Sometimes (e.g., syncope after cough), the activation of a reflex originating from peripheral afferents causes bradycardia and/or hypotension resulting in transient loss of consciousness, while in other cases the predominant mechanism is mechanical and determined by sudden hemodynamic changes.

The most common situational syncope in dogs is tussive syncope, which is usually associated with a collapsed trachea, chronic obstructive pulmonary disease, or valvular heart disease leading to atrial enlargement. Chronic cough induces a reversible reduction in perfusion to the cerebral reticular activating system, following a cascade of hemodynamic changes. During a coughing episode, the thoracic and abdominal pressures increase; these increases are transmitted via the great veins to the cranial cavity, in a similar way to the Valsalva maneuver. The abrupt increase in the intrathoracic pressure decreases venous blood return and cardiac filling, which reduces cardiac output. This results in decreased systemic blood flow, causing arterial baroreflex-mediated vasodilation.[1,44]

Defecation also induces an increase in the intrathoracic and intra-abdominal pressures that tends to reduce venous return, cardiac output, and peripheral blood flow (Valsalva maneuver). Defecation syncope is associated with pulmonary embolism and sudden cardiac death in cats.[43] Release of the Valsalva maneuver on completion of defecation and the resultant sudden increase in cardiac output promotes a vacuum effect due to

sudden reduction in intra-abdominal pressure that may dislodge intravascular clots with subsequent pulmonary embolisation.[1]

Swallowing syncope has been reported in dogs and cats[41,42] and is caused by stimulation of the esophageal receptors; signals from these receptors are then transmitted to the nucleus tractus solitarius of the medulla oblongata, which in turn stimulates the nucleus of the vagus nerve in this area and/or suppresses the vasomotor center, thereby causing situational syncope.

One last form of situational syncope happens postexercise when, secondary to muscular vasodilation, a reduction in venous return takes place together with the efferent vagal stimulation mediated by the Bezold–Jarisch reflex.[1,28,29,46,47]

The diagnosis of situational syncope is mainly based on a history of transient loss of consciousness occurring during or shortly after urinating, coughing, defecating, swallowing, or doing exercise.

CAROTID SINUS SYNCOPE

Carotid sinus syncope, also called “carotid sinus syndrome”, is triggered by vagal hyperactivation secondary to accidental stimulation of the carotid glomus, which causes hypotension and bradycardia.[1] It is induced by pressure on the carotid sinus baroreceptors located above the bifurcation of the common carotid artery. Spontaneous carotid sinus syndrome can be defined as syncope which, based on anamnesis, occurs as a result of an accidental mechanical compression of the carotid sinuses, for example, by accidental compression of the collar. The relationship between carotid sinus compression and syncope has not been determined. In humans, it represents 26–60% of syncope of an undetermined nature. To confirm the diagnosis, it is necessary to resort to carotid sinus massage, which aims to reproduce spontaneous syncope. This form of syncope has never been described in dogs or cats.

ORTHOSTATIC HYPOTENSION SYNCOPE

Circulatory alterations that occur in standing position produce signs defined as orthostatic hypotension. Syncope is one of these signs, although there

can also be many others such as loss of balance, disorientation, visual disturbances, hearing disturbances, and asthenia.[1,48]

Three forms of orthostatic hypotension have been described in humans:

1. Classical orthostatic hypotension: reduction in systolic blood pressure by a value greater than or equal to 20 mmHg within 3 minutes of active standing.
2. Initial orthostatic hypotension: immediate decrease in blood pressure following standing, which resolves within 30 seconds with the disappearance of symptoms and the return of blood pressure values to normal.
3. Progressive orthostatic hypotension: slow and progressive fall in blood pressure values when standing, with symptoms that appear a few minutes after assuming the orthostatic position. It is linked to impaired mechanisms of adaptation to the upright position, with dysautonomia. The characteristics of progressive orthostatic hypotension are similar to those of vasovagal syncope, which could suggest a similar pathophysiological basis.

In a healthy animal, due to the gravitational stimulus and the hydrostatic pressure, the assumption of the orthostatic position determines a sequestration of blood in the high-capacitance veins located below the heart (plane of hydrostatic indifference), with a consequent reduction in the central venous pressure, cardiac output, and systemic blood pressure. The deactivation of arterial and cardiopulmonary baroreceptive inhibitory mechanisms produces a reduction in vagal activity and a reflex increase in sympathetic nervous activity, which leads to arterial and venous vasoconstriction and to an increase in peripheral vascular resistance, heart rate, and inotropism so as to maintain the cerebral pressure and perfusion values.[48]

Hypovolemia or drugs that induce hypovolemia or vasodilation, secondary dysautonomia, or diastolic alteration with reduced left ventricular filling can cause transient or chronic alteration of the nervous mechanisms of cardiovascular regulation during orthostatic hypotension.

This form of syncope, although it is suspected in dogs when it happens after a rapid change in position, has not yet been described in small animals.

DIAGNOSIS OF SYNCOPE

The initial evaluation of an animal that has experienced transient loss of consciousness must include a history, physical examination, blood pressure measurement, and 12-lead electrocardiogram. Echocardiography and 24-hour Holter monitoring are usually also considered in case of suspicion of cardiac or reflex syncope, while external and implantable loop recorders are used only in case of rare episodes.[4–6,26,49–52] Laboratory tests should be performed if a reduction in the circulating volume due to internal bleeding or dehydration is suspected, and in some cases cardiac troponin I (CTnI) levels can also be measured in an attempt to differentiate between the possible causes of transient loss of consciousness.[53]

HISTORY AND CLINICAL PRESENTATION

The medical history must define all the circumstances in which the transient loss of consciousness occurred: position and activity of the animal, any predisposing and precipitating factors (e.g., hot environments, pain, cough, defecation, swallowing, postexercise), and prodromal signs (e.g., nausea, vomiting). It is necessary to know the characteristics of the transient loss of consciousness: how the loss of posture occurred, the color of the mucous membranes (pallor, cyanosis), the duration of the transient loss of consciousness, as well as any accompanying movements (tonic, clonic, tonic-clonic, myoclonus, automatisms) and their duration. The period after a transient loss of consciousness should also be described to highlight any clinical signs such as vomiting, confusion, mucosal color, trauma, urinary and fecal incontinence, or focal neurological signs.[1,8,41–43,54]

The presence of previous diseases (including those of a familial nature) and the possible use of drugs (e.g., vasodilators, antiarrhythmics, diuretics) should be investigated. It is important to determine the time interval between the first and last episode of transient loss of consciousness in the case of recurring episodes. However, it should be noted that in most cases, the owners are unable to provide the requested information due to the confusion experienced during the transient loss of consciousness of their pet.

The first step is to exclude nonsyncopal causes of transient loss of consciousness such as epileptic seizures. Syncope rarely has prodromes,

while these are usually present in case of epileptic seizures. Loss of consciousness is typical of syncope, although common in epileptic seizures. The most common signs of epileptic seizures are involuntary movements such as tonic-clonic or clonic contractions, automatisms (e.g., chewing, drooling, biting of the tongue), a bluish color of the mucous membranes, prodromal hallucinations sometimes associated with tremors, deviation of the head, and a state of confusion that lasts for a few minutes (>15–30 seconds). In a small percentage of cases of reflex or cardiac syncope, contractions may be found, but these are short in duration (<15 seconds) and happen later (after the fall), while in epileptic seizures they can appear when the animal is still in a standing position. A protracted state of confusion usually characterizes epileptic seizures, while weakness can appear in case of vasodepressive reflex syncope. During syncopal episodes, mucous membranes are usually pale, while they are cyanotic during epileptic seizures, and arrhythmias are very common during syncope, while quite rare during epilepsy. Finally, syncope does not respond or usually worsens with antiepileptic drugs, while patients with epilepsy respond to these drugs.[1,55]

Rarely, syncope due to prolonged asystole can take the form of an anoxic seizure,[8] or manifest with focal neurological signs due to impaired cerebral autoregulation with focal neuronal hibernation.[56]

Once nonsyncopal causes of transient loss of consciousness have been excluded, syncope should be classified into cardiac, reflex, or orthostatic syncope (see Table 32.1). The initial evaluation may reveal signs or electrocardiographic findings of high diagnostic value. Vasovagal syncope is easily diagnosed if precipitating events such as fear, pain, manipulation, or prolonged standing were associated with prodromal signs. Situational syncope is diagnosed if it occurred during or immediately after defecation, coughing or swallowing, or exercise.[41–44] Syncope due to orthostatic hypotension is diagnosed when there is evidence that the episode occurred after a rapid change of position, for example, from supine to quadrupedal position.[48] Arrhythmic syncope is diagnosed by surface or ambulatory electrocardiogram when there is ventricular arrest due to sinus arrest for >6 seconds, third-degree or paroxysmal atrioventricular block, or paroxysmal supraventricular or ventricular tachycardia during the episode of transient loss of consciousness.[4,5,8,22,26,50]

DIAGNOSTIC TESTS

Establishing a correct diagnosis of syncope is difficult but fundamental to differentiate benign from malignant forms. All diagnostic procedures currently used in veterinary clinical practice to identify the etiology of syncope have limited sensitivity, specificity, and diagnostic power.

Standard surface electrocardiogram

A surface electrocardiogram is usually performed in syncopal dogs and cats for 5 consecutive minutes. This recording time represents 0.3% of the 24 hours; therefore, in case of chronic arrhythmias such as sinus node dysfunction, atrioventricular conduction block, or atrial standstill, a possible relationship between the recorded arrhythmias and transient loss of consciousness can be established, while paroxysmal arrhythmias can be missed. A 5-minute electrocardiogram with no abnormalities or with supraventricular or ventricular arrhythmias cannot indeed rule out reflex syncope or paroxysmal intrinsic rhythm disturbances.[15,26,28,29,57]

Prolonged electrocardiographic monitoring

Prolonged electrocardiographic monitoring is a procedure used to diagnose paroxysmal bradyarrhythmias and paroxysmal tachyarrhythmias. Several monitoring systems are available: Holter monitoring, external loop recorder, and implantable loop recorder.[4–6,26,49–52] Regardless of the monitoring system used, the current reference standard for the diagnosis of syncope is considered to demonstrate a correlation between the signs and the recorded arrhythmia. A recording showing asystole lasting >6 seconds due to sinus arrest, paroxysmal atrioventricular block, or paroxysmal supraventricular or ventricular tachycardia during the episode of transient loss of consciousness can generally be considered sufficient for the diagnosis of cardiac syncope. In contrast, the absence of arrhythmias at the time of the syncopal episode makes it possible to exclude an arrhythmic cause. Characterization of electrocardiographic findings during a transient loss of consciousness episode can further define the etiology, by allowing classification of the syncope as reflex, due to intrinsic arrhythmias, or functional vagally mediated (Table 32.2).[1,4,5,,26,58]

TABLE 32.2. Classification of syncope according to heart rhythm during episodes of transient loss of consciousness (TLOC), rates of occurrence, and number of episodes per dog.

Type	Subtype	Description	% TLOCs [a]	% Dogs [b]	Episodes/dog
Type 1. Ventricular arrest (R-R pause ≥6 s)	Type 1A. Sinus arrest	Progressive sinus bradycardia or initial sinus tachycardia followed by progressive sinus bradycardia until sinus arrest	32.6	29.3	1–14
	Type 1B. Advanced AVB with sinus bradycardia	Advanced AVB with a concomitant and progressive decrease of sinus rate	4.8	5.5	1–4
	Type 1C. Slow ventricular response atrial fibrillation	Atrial fibrillation followed by progressive slowing of the ventricular response until ventricular arrest	3	3.3	1–2
	Type 1D. Sudden onset sinus arrest	Sinus arrest with sudden onset during sinus rhythm, persistent sinus bradycardia, or after a supraventricular tachycardia	18.7	18.5	1–7
	Type 1E. Advanced AVB with sinus tachycardia	Sudden onset of AVB with a concomitant increase of sinus rate	13	13.0	1–12
Type 2. Sinus bradycardia (<60 bpm)		Constant sinus bradycardia	6.1	8.7	1–2
Type 3. No or slight rhythm variations		Sinus rhythm, sinus arrhythmia, or sinus tachycardia	20.9	19.5	1–4
Type 4. Tachycardia (≥180 bpm)	Type 4A	Atrial fibrillation with high ventricular response	0	0	
	Type 4B	Supraventricular tachycardia (except sinus tachycardia)	0.45	1.1	1
	Type 4C	Ventricular tachycardia	0.45	1.1	1

AVB, atrioventricular block; bpm, beats per min. [a] Total number of TLOCs = 230. [b] Total number of dogs = 92.
Source: Perego M. et al.[4]

The electrocardiographic findings during syncope can be classified as reported in Table 32.2[4] into:

- Type 1: Ventricular arrest (R-R pause ≥6 seconds)
- Type 2: Sinus bradycardia (≤60 bpm)
- Type 3: No or slight rhythm variation
- Type 4: Tachycardia (≥180 bpm)

Type 1 can be further classified into:

- 1A: Progressive sinus bradycardia or initial sinus tachycardia followed by progressive sinus bradycardia until sinus arrest (Fig. 32.5).
- 1B: Advanced atrioventricular block with a concomitant and progressive decrease in the sinus rate. (Fig. 32.6).

- 1C: Atrial fibrillation followed by progressive slowing of the ventricular response until ventricular arrest (Fig. 32.7).
- 1D: Sinus arrest with a sudden onset during sinus rhythm, persistent sinus bradycardia or after an episode of supraventricular tachycardia (Fig. 32.8).
- 1E: Sudden onset of atrioventricular block with a concomitant increase in the sinus rate (Fig. 32.9).

Type 4 can also be further classified into 4A (fast atrial fibrillation), 4B (supraventricular tachycardia except sinus tachycardia), and 4C (ventricular tachycardia) (Fig. 32.10).[4]

The electrocardiographic abnormalities recorded during 24-hour Holter monitoring in dogs are attributable to an inappropriate vagal reflex (1A, 1B, 1C, or 2) in 10–47% of cases, to intrinsic arrhythmias such as sinus node dysfunction (1D) in 18.5% of cases, to atrioventricular conduction block (1E) in 13% of cases, and to supraventricular (4B) or ventricular (4C) tachycardia in 1% of cases. In 18–19.5% of cases, a sinus rhythm was recorded during the transient loss of consciousness episode and therefore no diagnosis could be established.[4,26,49]

A similar distribution of electrocardiographic findings was documented in dogs during syncope using an external loop recorder[4,6] and an implantable loop recorder.[5,51,52] A few case reports have documented supraventricular tachycardia and junctional rhythm during transient loss of consciousness in cats monitored with an implantable loop recorder.[50,57]

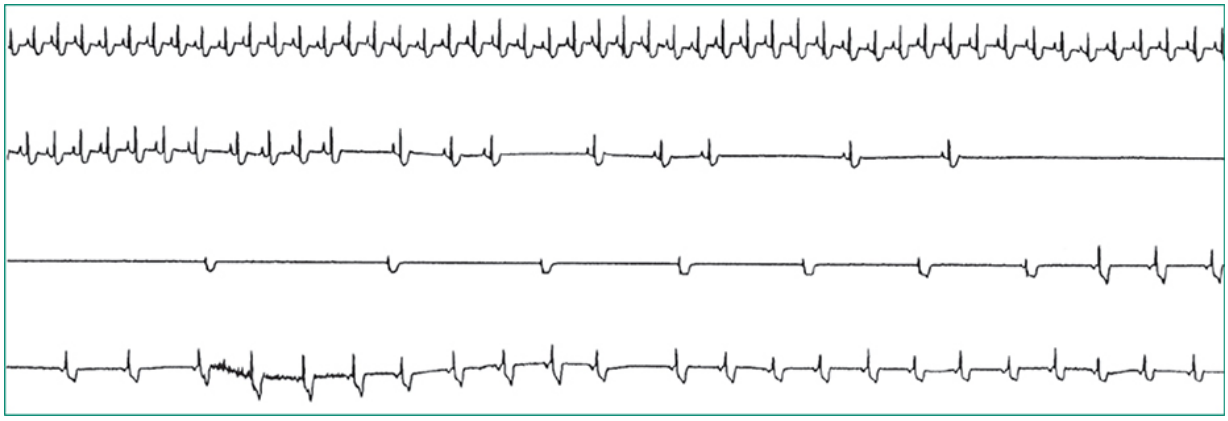


FIGURE 32.5. Ambulatory electrocardiographic recording of a type 1A reflex syncope in a 14-year-old male Poodle with myxomatous mitral valve disease and severe pulmonary hypertension. Before the syncopal episode, the dominant rhythm is a sinus rhythm with an average heart rate of 145 bpm

with progressive ST depression. The tracing then shows a progressive decrease in the heart rate down to 45 bpm, followed by a ventricular arrest lasting 7.8 seconds due to a prolonged sinus arrest. After the pause, a junctional escape rhythm appears with a ventricular rate from 20 to 35 bpm, followed by an increase in the heart rate with an average of 65 bpm and preceded by a negative P' wave and a progressive normalization of the ST segment. ST depression can be either secondary to the hypoxia due to the drop in the stroke volume or to simultaneous vasodepression with a fall in the systemic arterial pressure. Y lead; each line corresponds to 30 seconds. Speed, 7.5 mm/s; calibration, 2 mm/1 mV.

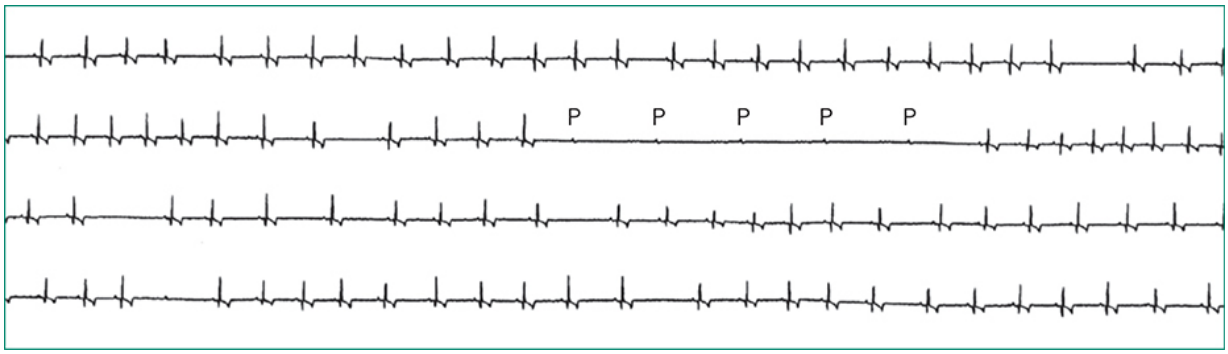


FIGURE 32.6. Ambulatory electrocardiographic recording of a type 1B reflex syncope in a 12-year-old female mixed-breed dog without structural heart disease. Before the syncopal episode, the dominant rhythm is a sinus rhythm with an average heart rate of 90 bpm. The tracing then shows a progressive decrease in the heart rate down to 55 bpm, followed by a ventricular arrest lasting 7.6 seconds due to a paroxysmal atrioventricular block. During the ventricular arrest, the sinus rate is 40 bpm. After the pause, sinus rhythm with an average rate of 100 bpm is observed. Y lead; each line corresponds to 30 seconds. Speed, 7.5 mm/s; calibration, 2 mm/1 mV.

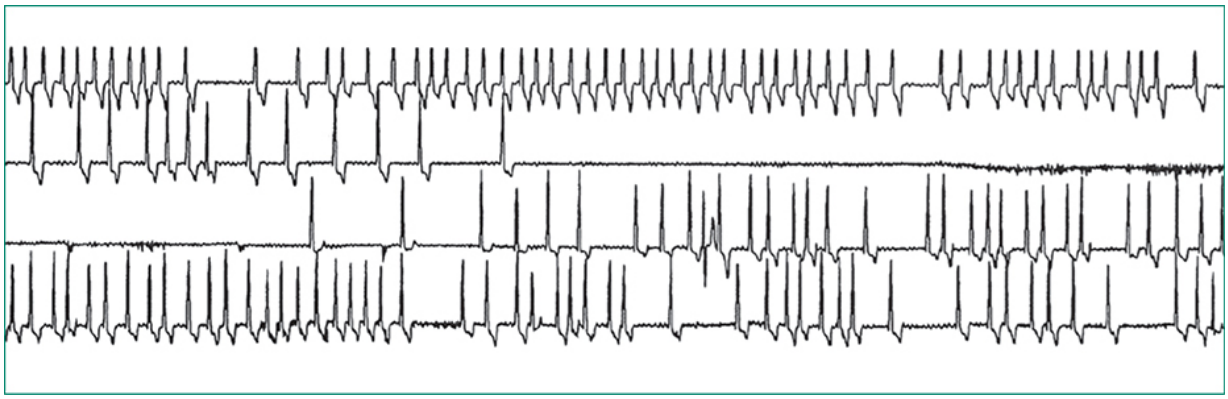


FIGURE 32.7. Ambulatory electrocardiographic recording of a type 1C reflex syncope in an 11-year-old female Cavalier King Charles Spaniel with advanced myxomatous mitral valve disease. Before the syncopal episode, the dominant rhythm is persistent atrial fibrillation with an average ventricular rate of 220 bpm. The tracing then shows a progressive decrease in the heart rate down to 85 bpm, followed by a ventricular arrest lasting 17 seconds due to a paroxysmal atrioventricular block. After the pause, the ventricular rate progressively increases up to 165–190 bpm. Y lead; each line corresponds to 30 seconds. Speed, 7.5 mm/s; calibration, 2 mm/1 mV).

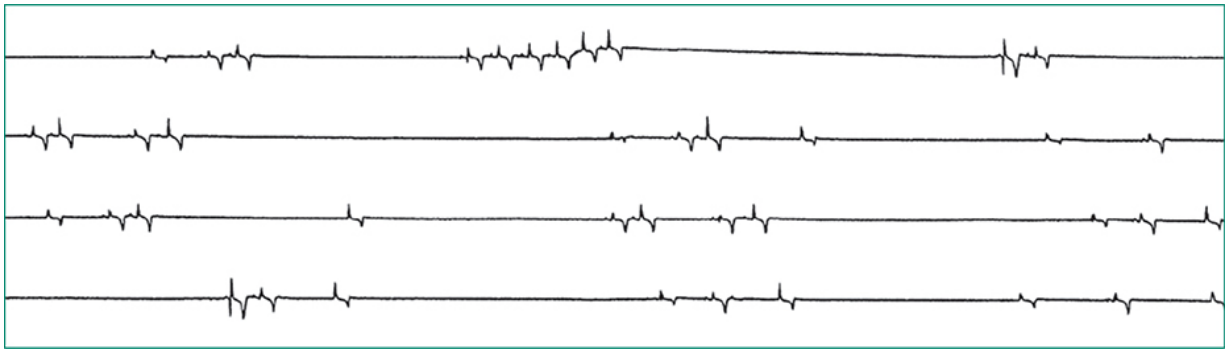


FIGURE 32.8. Ambulatory electrocardiographic recording of a type 1D cardiac syncope in a 14-year-old female West Highland White Terrier with sick sinus syndrome. The tracing shows frequent and sudden ventricular arrests (with the longest lasting 9 seconds) due to sinus arrest, preceded by sinus beats with an average heart of 120 bpm. Y lead; each line correspond to 30 seconds. Speed, 7.5 mm/s; calibration, 2 mm/1 mV.

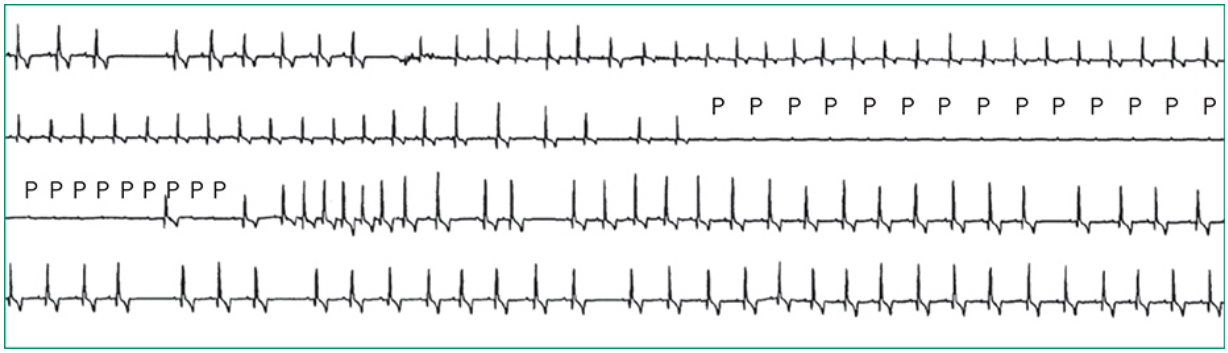


FIGURE 32.9. Ambulatory electrocardiographic recording of a type 1E cardiac syncope in a 2-year-old female Rottweiler with intrinsic atrioventricular nodal conduction disease. Before the syncopal episode, the dominant rhythm is a sinus rhythm with an average rate of 115 bpm. The tracing then shows a progressive decrease in the heart rate down to 80 bpm, followed by a ventricular arrest lasting 10 seconds due to a paroxysmal atrioventricular block. During the ventricular arrest, the sinus rate ranges from 95 to 160 bpm. After the pause, focal atrial tachycardia is observed with a rate of 170 bpm, followed by recovery of normal sinus rhythm. Y lead; each line correspond to 30 seconds. Speed, 7.5 mm/s; calibration, 2 mm/1 mV.

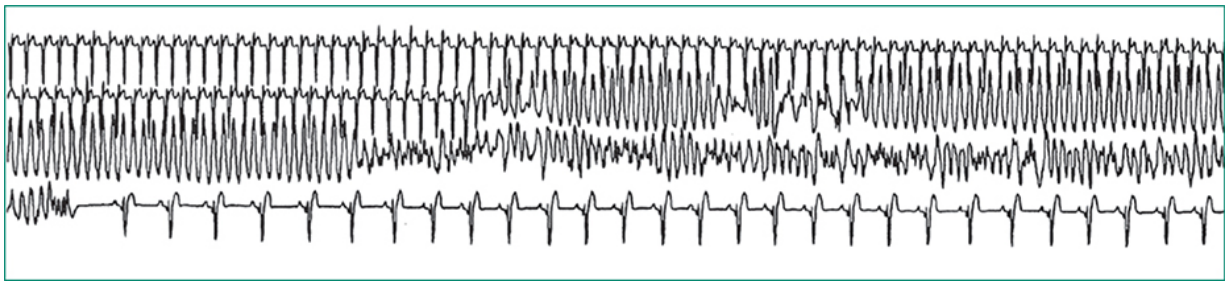


FIGURE 32.10. Ambulatory electrocardiographic recording of a type 4C cardiac syncope in a 5-year-old male American Staffordshire Terrier with inflammatory cardiomyopathy due to viral persistence. Before the syncopal episode, the dominant rhythm is a supraventricular tachycardia conducted with complete right bundle branch block and a rate of 230 bpm. The tracing then shows

sudden and repetitive runs of polymorphic ventricular tachycardia with a rate ranging from 330 to 380 bpm, which lasts 33 seconds and induce a transient loss of consciousness or, given the severity of the rhythm disturbance, aborted sudden cardiac death. Polymorphic ventricular tachycardia stops suddenly and sinus rhythm resumes, with an average heart rate of 80 bpm. Y lead; each line corresponds to 30 seconds. Speed, 7.5 mm/s; calibration, 2 mm/1 mV.

24-Hour Holter monitoring

The time interval between one syncopal episode and the next in most animals is measurable in weeks or months. Therefore, Holter monitoring has a low diagnostic yield when attempting to establish a relationship between clinical signs and electrocardiographic findings in animals with syncope (range, 1.1–15%).[4,26,49] Furthermore, it is necessary to consider the daily variability of the heart rhythm in the dog, with a window ranging from 40 bpm during vagal hypertonia to over 250 bpm during moments of sympathetic hypertonia, and the possibility of sinus pauses of up to 5 seconds and second-degree atrioventricular blocks during physiological vagal hypertonia. Therefore, Holter monitoring is especially indicated in animals that have frequent syncope or presyncope and in those with clinical findings that suggest arrhythmic syncope, to guide subsequent investigations (e.g., electrophysiological study) or therapeutic decisions (e.g., implantation of a pacemaker).[15,26]

Stress tests can be performed during Holter monitoring. Syncope during exertion in the presence of a structural heart disease suggests a probable cardiac cause. In the presence of an intraventricular conduction disorder, the increase in the heart rate during the ergometer test may lead to second- and third-degree atrioventricular block, usually infra-Hisian, suggesting the possible occurrence of complete atrioventricular block, which needs to be treated with pacemaker implantation. In the absence of structural heart disease, syncope during or just after exertion can be an expression of vagal reflex vasodilation.[1]

External loop recorders

External loop recorders are useful in the diagnosis of syncope in animals with frequent syncopal episodes and in which it is difficult to obtain information using a standard electrocardiogram and Holter monitoring. These devices have an owner activation function that allows the recording of an electrocardiogram as the signs are observed, but they can also activate

automatically based on the parameters set by the operator. Their retrospective memory feature is particularly useful to correlate clinical signs to arrhythmias in case of cardiac or reflex syncope. The difficulty in using this recorder lies in the owner's ability to record the arrhythmic event during the transient loss of consciousness due to the emotional stress of the moment. In dogs, the diagnostic yield in cases of syncope is around 35%.[4,6]

Implantable loop recorders

The implantable loop recorder is by far the prolonged monitoring system with the highest diagnostic value. It is the diagnostic gold standard for patients suffering from recurrent syncope with a long interval between one episode and another. In fact, its monitoring capacity is 36 times greater than that of an external loop recorder and 1,000 times greater than that of a Holter device. Implantable loop recorders are small electrocardiographic devices (volume, 7 mL; weight, 15 grams) that are implanted under the skin for up to 36 months. They possess a cyclical memory and, once activated by the owner at the time of the signs using an external activator, they record an electrocardiographic tracing for a few minutes, both before and after activation. Thanks to specific recognition algorithms similar to those used in pacemakers and implantable defibrillators, the latest generation loop recorders are also able to automatically record, without the need for any intervention by the owner, any significant arrhythmic event previously defined by the operator. The recorded data can then be analyzed in the clinic by interrogating the device remotely using telemetry. Once a diagnosis has been obtained, or when the battery is exhausted, the device can be removed. In dogs, implantable loop recorders have a diagnostic yield ranging from 56% to 65%.[5,51,52] These devices have also been successfully used in cats.[50,57]

Echocardiography

Echocardiography is recommended in animals with syncope with a known heart disease or when a heart disease is suspected from the initial evaluation (i.e., history and physical examination findings, presence of electrocardiographic abnormalities). It is useful to identify the presence of cardiac and cardiopulmonary structural diseases that can cause syncope such as aortic or pulmonic stenosis, hypertrophic and dilated

cardiomyopathy, pericardial diseases, pulmonary hypertension, arrhythmogenic cardiomyopathy, and intracardiac tumors.[28–30, 32–40,54]

PROGNOSIS OF SYNCOPE

In human beings, cardiac syncope has a poor prognosis, in particular in cases with a low left ventricular ejection fraction and/or cardiac arrhythmias, while reflex syncope usually has an excellent prognosis.[1]

A study following dogs with syncope, collapse, and exercise intolerance over time revealed the episodes were self-limiting in 42% of cases and continued in the long term in 23% of dogs. Sudden cardiac death was related to the events in 16.2% of cases and in 36% of cases when the Boxer breed was analyzed separately.[54]

In Dobermans with dilated cardiomyopathy, sudden cardiac death was related to the presence of ventricular tachycardia, ventricular ectopic beats with a short coupling interval (>260 bpm), and CTnI >0,34 ng/mL. However, no relationship between syncope and death was found.[34] Similarly, a relationship between syncopal episodes and death could not be found in cats with hypertrophic cardiomyopathy[40] or in Boxers with arrhythmogenic cardiomyopathy.[33] A weak correlation between syncope and a shorter survival time was documented in English Bulldogs with suspected arrhythmogenic cardiomyopathy.[32]

In dogs, recurrent reflex syncope can impact on ventricular perfusion, thereby inducing pulseless electrical activity and sudden cardiac death.[59]

THERAPY

The treatment of animals with syncope is aimed at preventing sudden cardiac death, syncopal recurrences, and improving quality of life. Cardiac syncope should be treated by correcting the underlying disorder and may involve: implanting a pacemaker in case of intrinsic arrhythmias secondary to sinus node dysfunction, atrial standstill, atrioventricular block, and functional vagally mediated atrioventricular block;[11,12,14,15,17,18,23,60] performing balloon valvuloplasty for pulmonic and aortic stenosis;[35,36]

treating supraventricular or ventricular arrhythmias;[31,33,34,61] performing pericardiocentesis;[37] reducing pulmonary pressure using phosphodiesterase V inhibitors;[38] or correcting upper airway obstruction.[2,9]

The duration of reflex and orthostatic syncope can be reduced using the antishock position, i.e., by elevating the back of the animal's body to increase blood flow to the brain. Situational and carotid sinus syncope can be corrected by treating the trigger with a cough suppressor, limiting exercise, or avoiding collars. In case the cardioinhibitory component is substantial, a permanent pacemaker can be used to limit ventricular arrests, although concomitant vasodepression can still usually induce presyncope.[14]

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CHAPTER 33

Sudden cardiac death

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DEFINITION

Sudden cardiac death is defined as death following a sudden cardiac arrest in a patient with either known or previously undetected cardiac abnormalities, in whom the mode and time of death are unexpected. The generally accepted temporal definition is bracketed by an interval of up to 1 hour between the onset of an abrupt change in clinical status and loss of consciousness.[1]

Sudden cardiac death can be characterized by four temporal elements. *Prodromes*, which occur weeks or months before the event, are generally predictors of an impending cardiac event, but not specific for sudden cardiac arrest itself. In veterinary patients, owners can note dyspnea, weakness, paroxysmal tachycardia based on observation of the chest, and syncope. Whether dogs and cats also suffer from angina is still unknown. A sudden onset of these clinical signs often marks the *onset of the terminal event,* which can last up to one hour before the actual onset of *cardiac arrest*. Lastly, *biological death* is defined as an absolute and irreversible event involving cessation of all biological functions.[2]

CAUSES OF SUDDEN CARDIAC DEATH AND ASSOCIATED DISEASES

In people, diseases of the coronary arteries and their consequences have been estimated to account for at least 80% of sudden cardiac deaths in Western countries.[3] The second most important cause of sudden cardiac death in people are cardiomyopathies, such as dilated cardiomyopathy, hypertrophic cardiomyopathy, and arrhythmogenic cardiomyopathy. Electrical cardiac diseases with no structural abnormalities, and more particularly Brugada syndrome, long and short QT syndrome, and catecholaminergic polymorphic ventricular tachycardia constitute another important cause of sudden cardiac death.[4]

In companion animals, myocardial infarctions are considered to be uncommon, although they have been suspected to play a role in acute and severe heart failure.[5,6]

Arrhythmic sudden cardiac death in dogs and cats has been primarily related to ventricular arrhythmia secondary to myocardial diseases, primarily dilated cardiomyopathy, arrhythmogenic cardiomyopathy, myocardial hypertrophy, and myocarditis, with the myocardial changes caused by these diseases acting as anatomical substrates.[7–11] Primary electrical diseases are also reported in dogs, but there is considerably less information in the veterinary literature than in the human literature. No studies investigating pure electrical diseases in cats have been published to date. Other causes of sudden cardiac death are related to bradyarrhythmias, tachycardia-induced cardiomyopathy, and acute heart failure.

MECHANISM OF SUDDEN CARDIAC DEATH

RELATIONSHIP BETWEEN STRUCTURE AND FUNCTION

The occurrence of potentially lethal arrhythmias is the end of a cascade of pathophysiological abnormalities that result from complex interactions between coronary vascular events, myocardial injury, variations in autonomic tone, and the metabolic and electrolytic status of the myocardium.[12]

The interaction of the three main factors is traditionally represented by Coumel's triangle, which relates the substrate, the trigger, and the autonomic nervous system (Fig. 33.1).[13]

The substrate is strictly related to the underlying structural heart disease and the consequent presence of remodeling, ventricular dilation, hypertrophy, scars, fibrosis, and conduction abnormalities.

The two components of the autonomic nervous system, the sympathetic and parasympathetic systems, act in concert to modulate the electrical and mechanical properties of the heart, and evidence in human medicine suggests that enhanced sympathetic activity and impaired cardiac parasympathetic responsiveness are negative prognostic indicators for morbidity and mortality associated with sudden cardiac death. The effect of sympathetic stimulation on the heart has also been linked to the concept of nerve sprouting through experimental studies in dogs. The nerve sprouting hypothesis of sudden cardiac death states that myocardial infarction results in nerve injury, which is followed by sympathetic nerve sprouting and regional myocardial hyperinnervation. The combination of augmented sympathetic nerve sprouting with an electrically remodeled myocardium results in ventricular tachycardia, ventricular fibrillation, and sudden cardiac death. This hypothesis has been demonstrated through the increase of sympathetic nerve sprouting by nerve growth factor infusion to the left stellate ganglion in dogs with complete atrioventricular block and myocardial infarction, which consequently increased the frequency of ventricular arrhythmias and sudden cardiac death.[14] However, the parasympathetic system can also play a predominant role in the pathogenesis of sudden cardiac death. For example, vasovagal reflexes in people can cause loss of consciousness due to prolonged asystole and hypotension and thereby lead to a serious outcome such as sudden cardiac death.[15] In a 2021 study describing the different rhythm patterns in a heterogeneous population of dogs that had experienced sudden cardiac death during Holter monitoring, inappropriate vagal reflexes were suspected to be a trigger of asystole/suspected pulseless electrical activity. Furthermore, this reflex seemed to work as a modulating factor for fatal ventricular tachycardia in this population.[16]

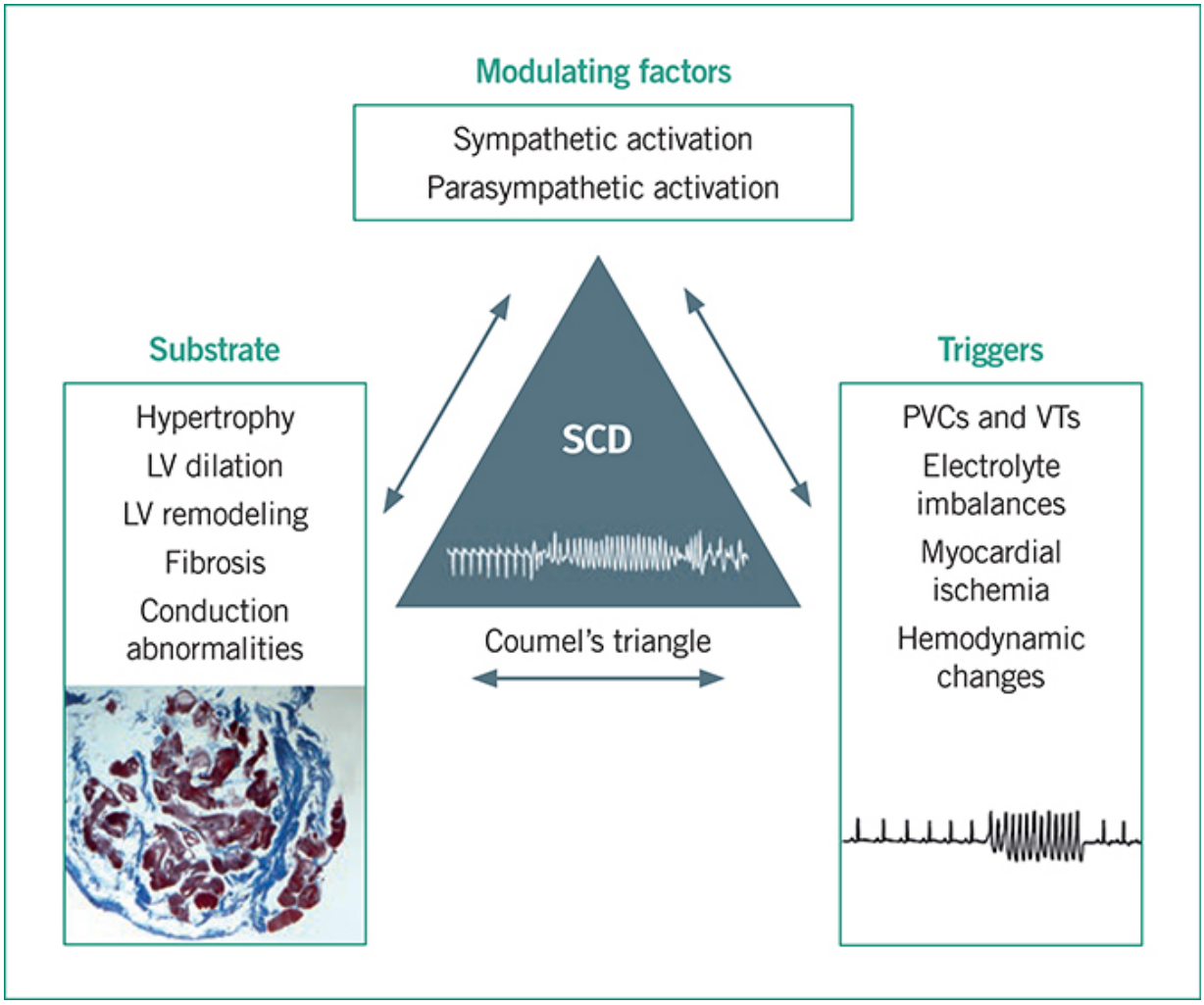


FIGURE 33.1. The arrhythmogenesis triangle proposed by Coumel is useful to describe the main pathophysiological mechanisms involved in sudden cardiac death (SCD).[78] LV, left ventricle; PVC, premature ventricular complex; VT, ventricular tachycardia.

Regarding the trigger, R-on-T phenomenon has been described as an electrical event preceding sudden cardiac death in about 70% of human patients that experienced sudden onset primary ventricular fibrillation.[17] This mechanism has been classically considered, anecdotally or on the basis of single case reports, as the most common arrhythmic event leading to sudden cardiac death in dogs as well.[18] The risk of R-on-T phenomenon is related to the prematurity of the ventricular arrhythmias and to the duration of the QT interval. The assessment of QT/TQ restitution evaluates the ability of the heart to recover from one beat to the next by examining the relationship between the QT interval (action potential duration) and the TQ interval (diastolic interval). The restitution on a beat-to-beat basis is

measured from the QT interval and the TQ interval as a ratio. When the QT/TQ ratio increases, the arrhythmic risk increases, in particular the vulnerability to reentrant arrhythmias.[19]

TACHYARRHYTHMIA VS. BRADYARRHYTHMIA DURING SUDDEN CARDIAC DEATH

The electrical mechanisms of cardiac arrest can be divided into tachyarrhythmic and bradyarrhythmic-asystolic events or into shockable vs. nonshockable arrests (Figs. 33.2–33.4).

Tachyarrhythmic events include ventricular fibrillation and pulseless sustained ventricular tachycardia, in which a perceptible pulse may not be present and adequate blood flow is not maintained.

Bradyarrhythmic-asystolic events include severe bradyarrhythmias, pulseless electrical activity, and the inability to generate a mechanical event because of complete absence of electrical activity (asystole). To qualify as a mechanism of cardiac arrest, severe bradyarrhythmias must be slow enough to result in an inability to perfuse adequately and maintain consciousness. However, no exact values have been established for dogs and cats, as vasomotor tone is also involved in the ability to maintain perfusion. In pulseless electrical activity, the electrical rate can be considerably faster but is in general much slower than in true pulseless ventricular tachycardia.

The important distinction between pulseless electrical activity and pulseless ventricular tachycardia is that the latter is a shockable rhythm.

Defining the initial rhythm can be difficult because of spontaneous changes between ventricular fibrillation-ventricular tachycardia and nontachyarrhythmic mechanisms.

This difficulty can confound attempts to correlate primary electrophysiological mechanisms with the outcome. For example, the time between the onset of a ventricular tachycardia and deterioration to asystole or pulseless electrical activity can be brief, limiting the potential benefit of interventions. Conversely, an initially bradyarrhythmic event can change to ventricular fibrillation/ventricular tachycardia.

In humans, most sudden cardiac deaths have been related to acute ventricular tachyarrhythmias. Ventricular tachycardia, ventricular fibrillation, or torsade de pointes appear to be the most common pathophysiological events involved in fatal arrhythmias in people.

Nontachyarrhythmic mechanisms, which include pulseless electrical activity, asystole, and bradycardia severe enough to result in loss of adequate cerebral and other organ perfusion, are less frequently reported as a cause of sudden cardiac death.[4,12,17,20]

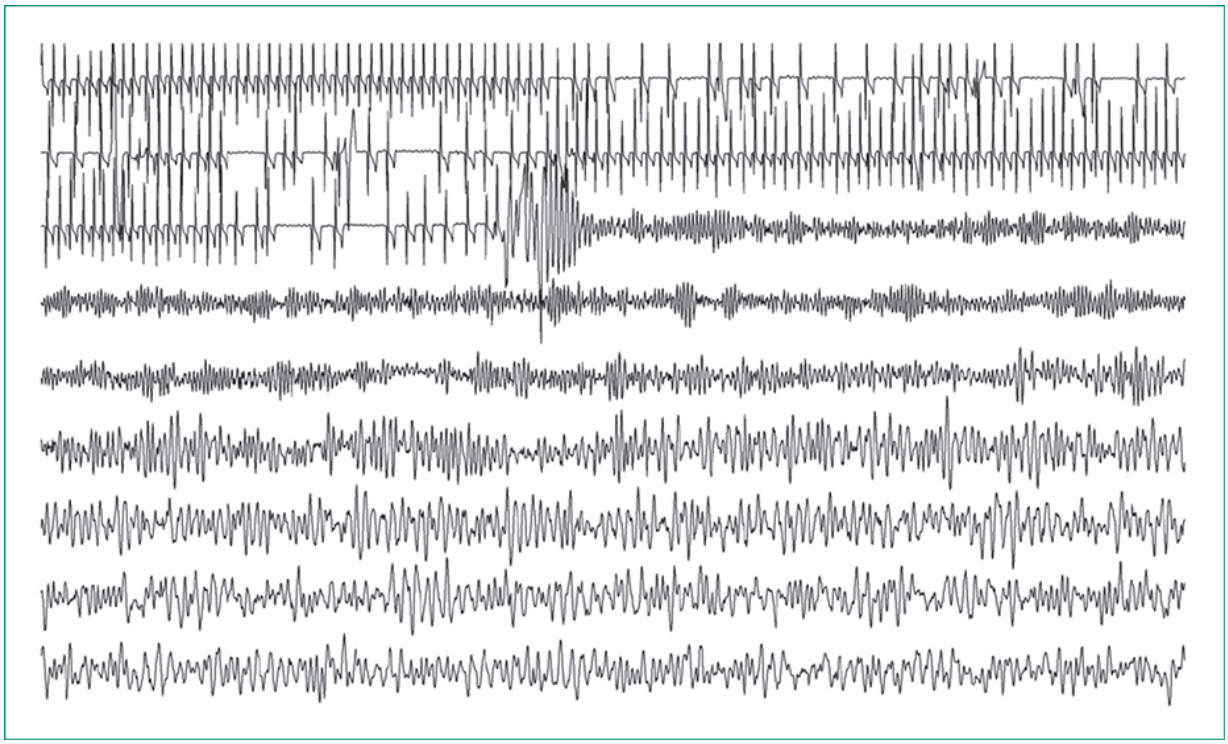


FIGURE 33.2. Ambulatory electrocardiographic recording from a 3-year-old male Golden Retriever affected by persistent atrial fibrillation with fast ventricular response, showing a premature ventricular ectopic beat with a short coupling interval inducing polymorphic ventricular tachycardia (torsades de pointes) that degenerated into ventricular fibrillation. Lead Y; each line corresponds to 30 seconds. Speed, 7.5 mm/s; calibration, 2 mm/mV.

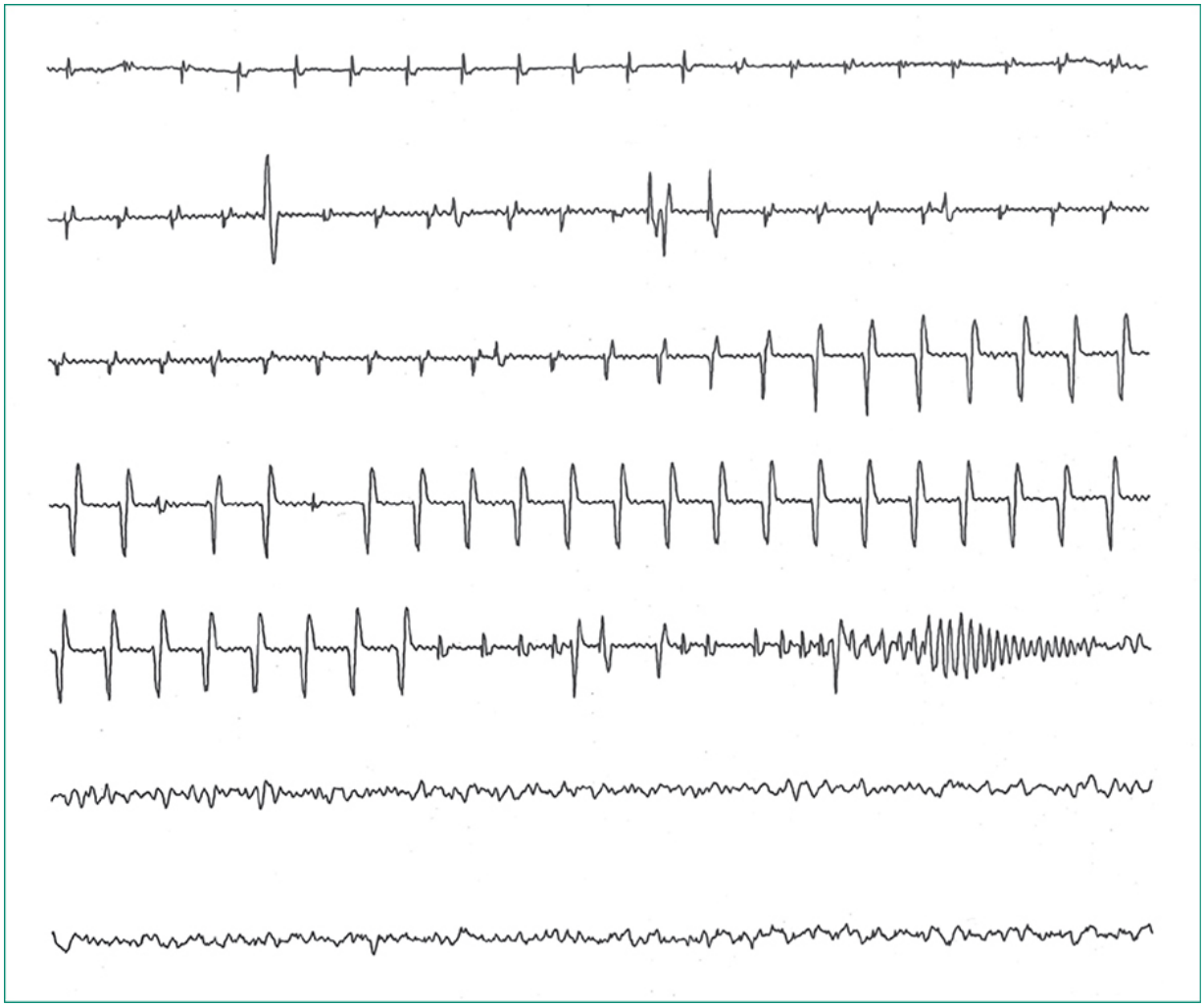


FIGURE 33.3. Ambulatory electrocardiographic recording from a 5-year-old female Pit Bull Terrier with a dilated cardiomyopathy phenotype and persistent atrial fibrillation interrupted by single ventricular ectopic beats, one couplet, and a run of accelerated idioventricular rhythm. Before the fatal event, atrial fibrillation with normal atrioventricular conduction recurred and was interrupted by single ventricular ectopic beats, one couplet, and one final ventricular ectopic beat with R-on-T phenomenon inducing torsade de pointes that degenerated into ventricular fibrillation. Lead Y; each line corresponds to 10 seconds. Speed 7.5 mm/s; calibration 2 mm/mV.

In the previously cited study describing the different rhythm patterns in a population of dogs experiencing sudden cardiac death during Holter monitoring, three different rhythm patterns associated with sudden cardiac death have been described. The most common pattern was ventricular fibrillation triggered by monomorphic ventricular tachycardia or ventricular premature complexes (42% of cases), followed by asystole or bizarre escape complexes suggestive of pulseless electrical activity (37% of cases). The last pattern in order of frequency was ventricular fibrillation triggered

by polymorphic ventricular tachycardia or torsades de pointes (21 % of cases).[16]

A differentiation between monomorphic and polymorphic ventricular tachycardia related to sudden cardiac death was also investigated in this study, and both monomorphic and polymorphic ventricular tachycardia appeared to degenerate into ventricular fibrillation; in some cases, monomorphic ventricular tachycardia progressed to polymorphic ventricular tachycardia before ventricular fibrillation. In humans, monomorphic ventricular tachycardia leads to sudden cardiac death only if other special conditions contribute to insufficient perfusion, or if it degenerates into polymorphic ventricular tachycardia or ventricular fibrillation. However, polymorphic ventricular tachycardia caused up to 40% of sudden cardiac deaths that occurred in hospital during rhythm monitoring.[4] In dogs, monomorphic ventricular tachycardia is traditionally associated with structural cardiac disease, which, due to the presence of an area of fibrosis and slow conduction, is responsible for the generation of the reentry mechanism. Polymorphic ventricular tachycardia, in the absence of QT segment prolongation, can be observed in animals with or without an underlying structural cardiac disease, and can result from reentry and triggered activity, such as in German Shepherds with early afterdepolarizations arising from the Purkinje fibers and possibly maintained by a reentrant mechanism.[21,22]

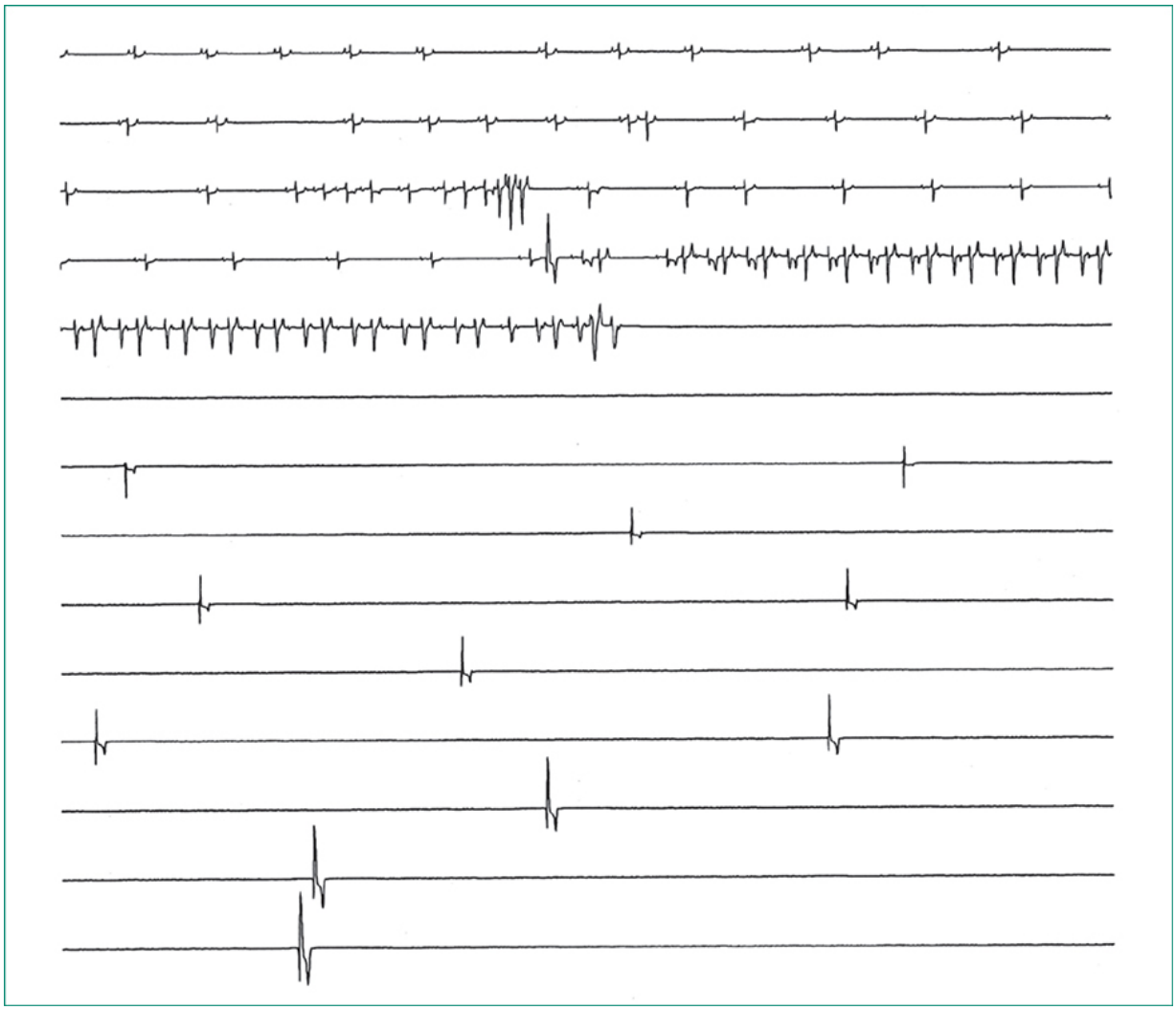


FIGURE 33.4. Ambulatory electrocardiographic recording from a 15-year-old male Chihuahua affected by myxomatous mitral valve disease and unexplained frequent episodes of transient losses of consciousness. ST depression is evident in the first part of the tracing; it is initially interrupted by one triplet and one single ventricular ectopic beat and then by one episode of ventricular bigeminy and one polymorphic triplet. Finally, a prolonged sinus arrest occurs, with a slow ventricular escape rhythm and electromechanical dissociation. Lead Y; each line correspond to 30 seconds. Speed, 7.5 mm/s; calibration, 2 mm/mV.

ARRHYTHMOGENIC MECHANISM OF THE DIFFERENT CAUSES OF SUDDEN CARDIAC DEATH, EPIDEMIOLOGY, AND RISK STRATIFICATION

DILATED CARDIOMYOPATHY

The most important arrhythmogenic mechanism of ventricular tachycardia in human patients suffering from dilated cardiomyopathy, demonstrated through electrophysiological studies, is reentry.[23]

The midmyocardial but also epicardial scar tissue found in patients with dilated cardiomyopathy can result in ectopic foci that start firing signals that may turn into ventricular premature complexes. These can then easily evolve into ventricular tachycardia and/or ventricular fibrillation and sudden death, for example.[24]

Another important contributing factor is myocardial ischemia, which can be explained by defective myocardial perfusion, decreased wall motion, and abnormal cell metabolism; these are often present in patients with dilated cardiomyopathy. Ischemia can be a direct cause of arrhythmias: it can be considered as a structural defect resulting in an electrical defect.[25] In some specific cases, such as the phospholamban gene mutation in Welsh Springer Spaniels, arrhythmogenesis seems to be caused by defective calcium handling.[26]

Most of the epidemiological data available in veterinary medicine regarding sudden cardiac death secondary to dilated cardiomyopathy concern the most common familiar form. Doberman Pinschers, Boxers, and Great Danes are particularly at risk for sudden cardiac death; sudden cardiac death in Dobermans has been reported to occur apparently much more commonly than in people, in approximately one third of animals in the preclinical phase of dilated cardiomyopathy and in an additional 30% of dogs with clinical signs.[27,28] The following points have been related to the risk of sudden cardiac death in Doberman Pinschers:

- Electrocardiographic criteria: a QRS duration of ≥60 ms has been associated with shorter survival times in dogs with dilated cardiomyopathy.[29] The presence of atrial fibrillation at presentation in Doberman Pinschers with dilated cardiomyopathy and congestive heart failure has been also found to increase the risk of cardiac-related death and to reduce survival time.[30]
- Holter criteria: the total number of ventricular premature complexes has not been found to be relevant for risk assessment for sudden cardiac death. This contradicts the previous presumption of many authors that a

high number of ventricular premature complexes represented a malignancy criterion and that antiarrhythmic treatment should be commenced upon occurrence of a critical number of ventricular premature complexes.[8] In human medicine, a ventricular premature complex burden >24% is considered critical mainly for the development of systolic dysfunction, but it is not related to sudden cardiac death risk.[31] In dogs, the prevalence of ventricular tachycardia and ventricular premature complexes with a peak rate >260 bpm, regardless of their type, have been have been instead identified as effective prognostic markers for sudden cardiac death risk assessment.[8] Heart rate variability and heart rate turbulence are important predictive factors for sudden cardiac death in human medicine. In particular, heart rate variability proved to be the most interesting marker, as it is considered a standard noninvasive method for evaluating autonomic nervous system function; a lower heart rate variability is related to poorer autonomic function.[32] Although heart rate variability and turbulence have both been studied in dogs affected by dilated cardiomyopathy, no exact cutoff values for these parameters have yet been established.[33,34]

- Echocardiography: an enlarged heart, represented by a ratio between left ventricular end-diastolic volume and body surface area (LVEDV/BSA) >91.3 mL/m^2, has been found to be the most important variable to identify Doberman Pinschers with dilated cardiomyopathy carrying a high risk of sudden cardiac death. In particular, the probability of sudden cardiac death occurrence increases 8.5-fold for each 50 mL/m^2 unit increment in LVEDV/BSA.[8]
- Biomarkers: in a first study by Oyama et al., a value of cardiac troponin I (cTnI) >0.20 ng/mL was related to a shorter survival time (112 days).[35] In a later study, a value of cTnI >0.34 ng/mL was defined as an additional prognostic marker for sudden cardiac death risk according to conditional inference tree analysis.[8] N-terminal pro–B-type natriuretic peptide (NT-proBNP) has been studied mostly to predict echocardiographic changes in the preclinical stages, but a value > 900 pmol/L has been related to shorter survival times (284 days).[36]

ARRHYTHMOGENIC CARDIOMYOPATHY

Arrhythmogenic cardiomyopathy is an important cause of sudden cardiac death in people and Boxer dogs;[9] this myocardial disorder has also been described in English Bulldogs[37–39] and in isolated case reports of different breeds.[40]

In humans affected by arrhythmogenic cardiomyopathy, almost 97% of ventricular arrhythmias are monomorphic and caused by scar-related reentry. In one third of all patients, these ventricular premature complexes evolve into sustained ventricular tachycardia over 3 years from their diagnosis.[23] Humans and dogs with arrhythmogenic cardiomyopathy are very susceptible to malignant ventricular arrhythmia and thus sudden cardiac death, and both of these species show ventricular premature complexes and monomorphic ventricular tachycardia that classically display a left bundle branch block morphology.[38,39,41]

Sudden death has been reported in 39% of dogs in a group of Boxers with arrhythmogenic cardiomyopathy. Interestingly, myocarditis and myocardial injury and fibrofatty repair were characteristic of these Boxers that died suddenly, and there were no significant difference in demographics, clinical features, or the extent of fatty replacement of the right ventricle between Boxer dogs with arrhythmogenic cardiomyopathy that died of sudden death and those that died of other causes.[9] In humans, it is hypothesized that an infectious component contributes to the onset and progression of this disease because of the frequent finding of myocarditis on histological examination.[42]

Sudden death has been reported in 22% of patients in a group of English Bulldogs with presumed arrhythmogenic cardiomyopathy, and the median survival time of the entire population was 8.3 months.[37]

In cats, sudden death is not a feature of the spontaneous feline model of arrhythmogenic cardiomyopathy.[43]

HYPERTROPHIC CARDIOMYOPATHY

Scar-related reentry is the main mechanism suspected in people affected by hypertrophic cardiomyopathy.[44] In these patients, the major clinical features associated with an increased risk of sudden cardiac death are age (younger patients have an increased risk), the presence of nonsustained ventricular tachycardia, the severity and extent of left ventricular hypertrophy, a family

history of sudden cardiac death at a young age, the presence of non-neurocardiogenic syncopal episodes, the severity of left atrial remodeling, the presence of left ventricular outflow tract obstruction, and an abnormal blood pressure response to exercise.[45]

In cats, sudden cardiac death has been most commonly associated with feline hypertrophic cardiomyopathy, a disease that shows similarities with its human counterpart.[10] The most important observational study of feline hypertrophic cardiomyopathy—the REVEAL study—provided important data regarding cardiovascular morbidity and survival in cats with the preclinical nonobstructive and obstructive forms of the disease. During the study period, cardiovascular death occurred in 27.9% of 1008 cats with hypertrophic cardiomyopathy and, unlike what is reported in humans, the risk for cardiovascular death was not different between cats with the obstructive form and those with the nonobstructive form.[45,46]

A retrospective study evaluating 255 cats with hypertrophic cardiomyopathy showed that even mildly to moderately affected asymptomatic animals have significantly more frequent and severe ventricular and supraventricular arrhythmias than healthy cats, which could lead to an increased risk of sudden cardiac death (hazard ratio, 3.88). In particular, risk stratification in these cats revealed that the presence of syncope, regional wall hypokinesis, increased left atrial size, decreased fractional shortening and ejection fraction, and the presence of spontaneous echo contrast or thrombi significantly increase the risk of sudden cardiac death.[47]

CORONARY ARTERY ABNORMALITIES

The probable mechanisms for ventricular tachycardia or ventricular fibrillation in human patients with coronary artery disease are acute ischemia and reentry via myocardial scar, especially in those with a prior infarct. In human patients with chronic ischemic disease, the most powerful predictor of sudden cardiac death is an ejection fraction below 40%.[2]

Unlike in humans, myocardial infarctions are rarely reported in veterinary literature, although a case review showed intramural arteriosclerosis appeared to be a common finding at necropsy in dogs.[5] In this review, 87% of dogs that experienced sudden cardiac death had hyaline arteriosclerosis, of which half had concurrent myocardial infarctions.

SUBAORTIC STENOSIS

Sudden cardiac death is commonly reported in severe subaortic stenosis, although the underlying mechanisms have not been determined. Nonetheless, myocardial ischemia with secondary fatal ventricular arrhythmias is presumed to be the most likely mechanism.[48] Polymorphic ventricular tachycardia leading to ventricular fibrillation was shown during Holter monitoring in a dog with severe subaortic stenosis and atrial fibrillation.[18] In naturally occurring subaortic stenosis, an altered coronary artery flow and pathological changes to coronary arteries reducing the luminal diameter have been demonstrated,[49,50] whereas in an experimental study an increase in myocardial oxygen demand owing to left ventricular hypertrophy was evident.[51] Other cases of sudden cardiac death secondary to conditions causing left ventricular pressure overload have a similar pathophysiological mechanism.[52]

Sudden death has been reported in 19% of dogs affected by severe forms of subaortic stenosis (defined as a left ventricular outflow tract gradient between 80 and 130 mmHg) and 60% of dogs affected by the very severe form (defined as a gradient >130 mmHg). Sudden death in these groups also occurred in a younger age range than in the group of dogs affected by mild subaortic stenosis.[53] Holter monitoring is therefore highly recommended in patients with the severe and very severe forms of subaortic stenosis. Note that the presence of ST segment changes on the resting electrocardiogram has not been shown to correlate with pressure gradient, age, heart rate or number of ventricular premature complexes on 24-hour Holter monitoring.[54]

MYOCARDITIS

In the acute phase of myocarditis, acute necrosis and edema can cause high grade atrioventricular blocks together with ventricular arrhythmias. The chronic stage, however, corresponds to replacement fibrosis and, typically, to the development of a dilated cardiomyopathy phenotype. Both supraventricular and ventricular arrhythmias, but more particularly the latter, continue to be detected, although atrioventricular block is rare.[55,56]

In some cases of myocarditis, it can be very difficult to control ventricular arrhythmias with drugs, and dogs with non-drug-responsive

ventricular tachycardia can develop easily ventricular fibrillation and die.

ACUTE HEART FAILURE

All causes of acute heart failure can result in sudden cardiac death because of the circulatory failure itself or of secondary arrhythmias. The electrophysiological mechanisms involved may be related to acute stretching of the ventricular myocardial fibers or the His–Purkinje system.[57] However, the roles of neurohumoral mechanisms and acute electrolyte shifts have not been fully evaluated. The causes of acute cardiac failure associated with sudden cardiac death in dogs include acute pulmonary edema in any form of advanced heart disease, acute pulmonary embolism, acute myocardial infarction, acute myocarditis, congenital heart disease, and cardiac tamponade.

BRADYARRHYTHMIAS

Sinus node dysfunction

It has been reported that the total survival time and risk of sudden cardiac death in humans with sinus node dysfunction, irrespective of their symptoms, are similar to that of the general population.[58] Similarly, the most common cause of death in dogs affected by sick sinus syndrome is euthanasia for noncardiac related disease, and treatment is therefore indicated only in order to improve bradycardia-related clinical signs.[59,60]

Atrioventricular conduction disorders

The occurrence of sudden cardiac death in dogs with atrioventricular block is considerably high (42.7%), and it is reported to be similar in dogs with second- and third-degree atrioventricular block (40.6% and 32.8%, respectively). Twenty-four percent of dogs die within 30 days and 40% of dogs die within 6 months of being diagnosed. Age does not seem to be associated with sudden death. Dogs with third-degree atrioventricular block and wide QRS complex escape rhythms have been reported to have better survival times than those with narrow QRS complex escape rhythms, meaning that dogs with escape rhythms generated in more proximal junctional tissues have a poorer prognosis.[61] An experimental study in dogs showed that cardiac electrical remodeling after atrioventricular block is

associated with an increase in beat-to-beat variability of repolarization; therefore, dogs affected by chronic atrioventricular block are also prone to arrhythmia-related sudden cardiac death.[62]

The prognosis for cats affected by third-degree atrioventricular block is more variable, and the median survival time for cats with cardiac-related death has been reported to be 132 days in a 2021 retrospective study.[63]

Disturbances of the autonomic nervous system

In human medicine, it has been proposed that frequent vasovagal-mediated cardiac asystole may be a potential cause of sudden cardiac death.[64] Vagal reflex was considered the most likely trigger of asystole/suspected pulseless electrical activity leading to sudden cardiac death in 7 dogs in a 2021 study, although concomitant factors due to underperfusion could not be completely ruled out.[16]

TACHYCARDIA-INDUCED CARDIOMYOPATHY

In a study conducted in experimental dogs with tachycardia pacing-induced heart failure, tachycardia-induced heart failure exhibited malignant arrhythmia with prolonged heterogeneous repolarization and led to sudden cardiac death.[65]

Deterioration of left ventricular ejection fraction, dilation of the left ventricle, and thus fibrosis and the resulting increase in the risk of sudden cardiac death occur with both sustained ventricular and supraventricular arrhythmias, although they appear to be more marked with the former type of arrhythmia than with the latter.[66]

In addition, a 2021 retrospective case-control study demonstrated that dogs with atrial fibrillation showed a higher prevalence of sudden cardiac death in comparison to dogs in sinus rhythm matched for echocardiographic diagnosis. A younger age at diagnosis, a larger left atrial size, and a history of syncope were all independent predictors of sudden cardiac death in dogs with atrial fibrillation. The median survival time for dogs with atrial fibrillation was 492 days, which is significantly shorter than that in dogs in sinus rhythm (593 days).[67]

PRIMARY ELECTRICAL DISEASE

Data on channelopathies causing primary electrical cardiac disease and possibly sudden cardiac death in dogs and cats are extremely rare but have recently gained more attention.

German Shepherds are known to suffer from sudden cardiac death due to an inherited disease characterized by episodes of ventricular tachycardia that can evolve into ventricular fibrillation and eventually asystole, which typically occurs during sleep or after exercise. Moïse et al. found that all dogs studied died between the ages of 4 and 30 months and polymorphic nonsustained ventricular tachycardia was present in all of them, and no specific histopathological lesions were present at necropsy.[21,22] The higher incidence of ventricular tachycardia after long RR intervals is consistent with the initiation of such tachycardias by early afterdepolarization-induced triggered activity.[68] Abnormal maturation of sympathetic innervation in affected dogs may have promoted the development of prolonged repolarization and early afterdepolarizations by inhibiting the functional expression of repolarizing ionic currents in the ventricle.[68] Jesty et al. found that German Shepherd dogs with these ventricular arrhythmias had lower ATP2A2/SERCA2a expression. The SERCA pump plays a big role in the calcium homeostasis and thus in the normal development of action potentials.[69]

In Rhodesian Ridgebacks, defective myocardial cellular respiration and inadequate ATP synthesis have been suspected to cause electrical instability, conduction disorders, and changes in the action potential, eventually leading to ventricular arrhythmias and sudden cardiac death. A variant in the QIL-1 gene resulting in a mitochondrial cardiomyopathy has been described in these dogs.[70]

Sudden death has also been described in a population of young Leonbergers (<3 years): it occurred at a median age of 12 months, without any previous clinical signs and usually during rest. Findings in this population resemble those in German Shepherds with ventricular arrhythmias (young age of onset, sudden death at rest, and ventricular arrhythmias with features of polymorphic ventricular tachycardias with no evidence of structural cardiac disease).

The English Springer Spaniel is the first canine breed in which an inherited long QT syndrome has been suspected. Gene sequencing revealed

that the puppies in the study had mutations in the *KCNQ1* gene, which seemed to impair cardiac repolarizing currents, similar to *KCNQ1* mutations causing long QT syndrome type 1 in humans.[71]

PREVENTION OF SUDDEN CARDIAC DEATH

In human medicine, patients with ischemic cardiomyopathy and an ejection fraction below 35% should receive an implantable cardioverter defibrillator after optimization of anti-ischemia therapy and after at least 40 days have passed since myocardial infarction or 3 months since revascularization, or both.

ß-Blockers have a favorable effect on prevention of sudden cardiac death; the Metoprolol Controlled-Release Randomized Intervention Trial in Heart Failure showed a 41% decrease in sudden cardiac death in heart failure patients with an ejection fraction below 40% with ß-blocker therapy. The combined post hoc analysis of the European Myocardial Infarction Amiodarone Trial and the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial revealed a 61% decrease in sudden cardiac death in post–myocardial infarction patients treated with both ß-blockers and amiodarone, although no change in overall mortality was noted.[2]

In veterinary medicine, there is no evidence to date that any antiarrhythmic drugs can reduce the risk of sudden cardiac death. In a 2004 study that included Doberman Pinschers with dilated cardiomyopathy that experienced ventricular tachycardia, syncope, or collapse, sudden cardiac death appeared to be delayed through the use of different types of antiarrhythmic drugs.[7] Conversely, in a 2016 study, Doberman Pinschers with dilated cardiomyopathy that received different antiarrhythmic drugs (i.e., sotalol, amiodarone, mexiletine, digoxin, carvedilol) were at a higher risk of dying of sudden cardiac death than Doberman Pinschers not receiving antiarrhythmic treatment. This result could lead to the conclusion that antiarrhythmic treatments are harmful to these patients, but the Doberman Pinschers receiving antiarrhythmic drugs in this study were also at a higher risk of dying of sudden cardiac death, as they were affected by more malignant arrhythmias.[8]

In a randomized controlled clinical study that included 49 Boxers with normal echocardiograms and Holter recordings with more than 500

ventricular premature complexes/24 hours, treatment with sotalol or mexiletine-atenolol was efficacious in reducing the number of ventricular premature complexes, the severity of the arrhythmias, and the maximum and mean heart rates. Treatment with procainamide and atenolol was however not effective.[72]

Results derived from a study performed in a dog model of sudden cardiac death indicated that omega-3 fatty acids have antiarrhythmic properties and could therefore prevent ischemia-induced ventricular fibrillation.[73] A subsequent clinical study showed similar positive results in a population of Boxers affected by arrhythmogenic cardiomyopathy and receiving omega-3 fatty acids for 6 weeks; these dogs had a significant reduction in the number of ventricular premature complexes after this supplementation.[74]

Regarding primary electrical disease, a single prospective, randomized cross-over design study investigated the antiarrhythmic efficacy of three pharmacological protocols (mexiletine or sotalol monotherapy and mexiletine-sotalol combination therapy) in German Shepherds affected by a severe phenotype of inherited ventricular arrhythmias (more than 6000 ventricular premature complexes per 24 hours/more than 5% of ventricular ectopies per 24 hours). The results showed that combination therapy reduced the frequency of ventricular premature complexes and total ventricular ectopies, while sotalol monotherapy increased the number of ventricular tachycardia runs. However, combination therapy was not effective in abolishing runs of ventricular tachycardia, a parameter that could be better related to the risk of sudden cardiac death than the total number of ventricular ectopies.[75]

Two reports of the use of implantable-cardioverter defibrillator in dogs have been published, and the reported complications have prevented the routine use of this technique in veterinary medicine.[76,77] These problems were mainly related to oversensing of the T wave and to the different heart rates during exercise between dogs and humans. These points frequently caused inappropriate shocks after implantation, and to date programming algorithms specifically designed for veterinary patients are lacking.

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