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Review

# Indications for permanent pacing in dogs and cats



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## KEYWORDS

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Syncope

**Abstract** Pacemaker implantation is considered as a standard procedure for treatment of symptomatic bradycardia in both dogs and cats. Advanced second-degree and third-degree atrioventricular blocks, sick sinus syndrome, persistent atrial standstill, and vasovagal syncope are the most common rhythm disturbances that require pacing to either alleviate clinical signs or prolong survival. Most pacemakers are implanted transvenously, using endocardial leads, but rarely epicardial leads may be necessary. To decide whether a patient is a candidate for pacing, as well as which pacing modality should be used, the clinician must have a clear understanding of the etiology, the pathophysiology, and the natural history of the most common bradyarrhythmias, as well as what result can be achieved by pacing patients with different rhythm disturbances. The goal of this review was, therefore, to describe the indications for pacing by evaluating the available evidence in both human and veterinary medicine. We described the etiology of bradyarrhythmias, clinical signs and electrocardiographic abnormalities, and the choice of pacing modality, taking into account how different choices may have different physiological consequences to selected patients. It is expected that this review will assist veterinarians in recognizing arrhythmias that may require permanent pacing and the risk-benefit of each pacing modality and its impact on outcome.

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### Abbreviations

AAI (R)	atrium-paced, atrium-sensed inhibition of pacemaker in case of sensed intrinsic activity rate modulation
AF	atrial fibrillation
AV	atrioventricular
AVB	atrioventricular block
cTnl	cardiac troponin I
ECG	electrocardiogram
DDD(R)	dual-paced, dual-sensed, dual mode of response rate modulation
PAS	persistent atrial standstill
PM	pacemaker
SA	sinoatrial
SND	sinus node dysfunction
SSS	sick sinus syndrome
VDD	ventricle-paced, dual-sensed, dual mode of response
VVS	vasovagal syncope
VVI (R)	ventricle-paced, ventricle-sensed inhibition of pacemaker in case of sensed intrinsic activity rate modulation

## Introduction

In recent years, implantation of artificial cardiac pacemakers (PMs) has become a standard procedure for dogs with symptomatic bradycardia, such as advanced second-degree and third-degree atrioventricular block (AVB), sinus node disease, persistent atrial standstill (PAS), and vasovagal syncope (VVS) [1–15]. In human medicine, the first reported PM implantation dates from 1952 [16], whereas, in veterinary medicine, the first case was reported in 1967 [17]. In dogs, most PMs are implanted transvenously using endocardial leads, whereas, in cats and in particular circumstances also in dogs, the use of epicardial leads via thoracotomy or laparotomy may be necessary [7,8]. Modern PMs consist of a sealed pulse generator with a lithium–iodine battery that generates electrical impulses and senses intrinsic cardiac rhythm via a unipolar or a bipolar lead attached to the endocardial or epicardial surface of the heart [7]. Artificial pacing rate, voltage, current, pulse width, and sensitivity can be programmed by a telemetry system, allowing intraoperative and postoperative adjusting [7].

This review describes the indications for pacing and evaluates the available evidence with the aim of assisting veterinarians in selecting the best

management strategy for individual patients, taking into account the impact on outcome and the risk–benefit ratio of particular diagnostic or therapeutic methods.

## Etiology, natural history, and role of pacing

### Atrioventricular conduction disturbances

AVB is a disturbance of impulse conduction through the atrioventricular (AV) node and/or the His–Purkinje system that can be permanent or transient [18]. Atrial impulses can be conducted with delay or be completely blocked depending on anatomical or functional impairment along the conduction system [18]. Atrioventricular disturbances can occur as a result of a primary disorder or secondary to acute or chronic myocardial abnormalities [19]. In human medicine, two degenerative diseases (Lev and Lenegre diseases) have been described as idiopathic degeneration with fibrosis replacement of the intraventricular conduction system, with or without changes in the cardiac skeleton [19]. Similar degenerative changes have been reported in veterinary medicine in dogs with chronic mitral valve disease [20]. Any primary or secondary cardiac disease that affects the AV conduction system (congenital, acquired, or secondary to traumatic, neoplastic, infiltrative, inflammatory, and systemic disorders) may result in complete AVB. More rarely, congenital forms or functional disorders (hyperkalemia, toxicity, antiarrhythmic drugs, high vagal tone, and hyperthyroidism) have also been described [21–31]. In human beings, the most common cause of transient AVB is acute myocarditis [32,33]. The pathogenesis of transient AVB secondary to acute myocarditis implies the presence of myocardial interstitial edema, and a correlation between increased thickness of the edematous cardiac walls and severity of AVB has been described [34]. The same mechanism has been suspected in dogs, with unknown prevalence, as it has been documented that 13% of dogs presented with transient AV conduction disturbances [35]. Both experimental models and human patients with spontaneously occurring acute lymphocytic myocarditis very often present AVB that lasts a few days or, less frequently, 2–3 weeks, and then regresses completely during the convalescent stage of 2–4 weeks in 67%–96% of the patients [32–34,36,37]. In addition, one study reported regression of AVB with improvement recorded within one month from PM implantation in 13% of dogs [35]. In human beings, it has been reported that the prevalence of persistent AVB

after acute myocarditis is of approximately 4% [34] and permanent PM implantation is required in these patients. In children, the occurrence of persistent AVB after resolution of acute myocarditis is higher (28%) [33]. Chronic myocarditis as a cause of longstanding AVB in human beings is considered somewhat uncommon [38]. In dogs, the prevalence of myocarditis-related AVB is unknown, and a few studies have described acute myocarditis in dogs with AVB based on postmortem examination [22,23,30] or using endomyocardial biopsy [39]. This latter study defined enteric *coronavirus* as the pathogen that most commonly causes acute myocarditis and AVB in dogs. In one of these case reports, a very high serum concentration of cardiac troponin I (cTnI) was documented and the authors suggested that this biomarker might help detect dogs with AVB secondary to active myocarditis [22]. Another study proved that cTnI is high at the time of presentation in dogs with permanent AVB but showed a significant reduction over time after PM implantation [40,41]. Lead type and arrhythmia severity did not show significant correlation with cTnI [40]. In human medicine, endomyocardial biopsy is the gold standard for in vivo diagnosis of myocarditis and increased serum concentrations of cTnI and cardiac troponin T are considered reliable to confirm the diagnosis [42–44].

In cats, transient AV conduction disturbances (trifascicular block) have been reported associated with concurrent elevations of cTnI concentrations [45]; therefore, acute myocarditis may be suspected as a cause of the AV node conduction disturbances based on elevated cTnI concentrations [45]. The prevalence of myocarditis-related conduction block is unknown in cats [45,46], although cases of myocarditis secondary to *Toxoplasma gondii* [47], *Bartonella henselae* [46,48], *Streptococcus canis* [49], and *Borrelia burgdorferi* [50] have been reported.

AVB may occur at the approaches to the AV node, at the level of the compact AV node itself, at the level of the penetrating and branching portions of the AV bundle, or at the level of the bundle branches. It has been reported in two dogs that the approaches to the AV node and the AV node itself usually show no significant changes and abnormalities of the AV conduction system are observed in the AV bundle and in the upper portion of the left and right bundle branches [30].

In contrast, in cats, complete AVB can be isolated or associated with hypertrophic cardiomyopathy [51]. In cats with and without hypertrophic cardiomyopathy, marked degeneration and fibrous replacement of the AV conduction system has been

reported and consistently observed in the branching portions of the left and right bundle branches in association with extensive fibrosis of the central fibrous body and endocardial and myocardial fibrosis at the upper border of the ventricular septum [51]. It would seem possible that the pathological process is fundamentally related to the normal aging phenomenon and is probably exaggerated or accelerated by the abnormal mechanical forces created by myocardial hypertrophy [52]. Interestingly, in human beings with hypertrophic cardiomyopathy and subvalvular aortic stenosis, the AV conduction system is extensively impaired by mechanical factors caused by hypertrophy of the ventricular septum [52].

Previously published data have demonstrated that dogs affected by advanced second-degree and third-degree AVB are larger, older, and more frequently intact female [9] and breeds such as Labrador retrievers, Cocker spaniels, German shepherd, Dachshund, and English bulldogs are predisposed [2,7–13].

Cats affected by third-degree AVB are usually middle-aged to older and have concurrent systemic diseases that might account for many of the clinical signs. In one case series, the presence of congestive heart failure or identifiable structural heart disease at diagnosis did not affect median survival times [50].

Survival data suggest that high grade AVB is associated with a guarded prognosis in dogs, with a high mortality rate early in the natural history of the disease. The occurrence of sudden cardiac death among the population of dogs with AVB is 42.7%, and the occurrence of sudden death is reported to be similar in dogs with second and third-degree AVB (40.6% and 32.8%, respectively). From the diagnosis, 24% of dogs die within 30 days and 40% of dogs die within six months [9]. These data confirmed previous findings in human medicine that suggested a high sudden death rate in the first year with a mortality rate of approximately 24% in the first month and 40% in the first 6 months [9]. In veterinary medicine, age does not seem to be associated with sudden death [9], in contrast with human medicine, in which older age has been negatively associated with survival times [53]. The presence of clinical signs also does not seem to be correlated with survival, although high ventricular escape rates and narrower QRS complexes have been negatively associated with survival times [9]. Studies evaluating the association between escape rhythm QRS complex width and survival times have not been performed in humans. Usually, in dogs with AVB, the site of origin of the escape rhythm is

just distal to the site of block [9]. Generally, nodal AVB would result in a narrower QRS complex escape rhythm, generated in the proximal tissues, whereas infranodal AVB would likely result in a wider QRS complex escape rhythm, originating in the Purkinje fibers. Findings in veterinary medicine suggest that dogs with third-degree AVB and wide QRS complex escape rhythms have better survival times than those with narrow QRS complex escape rhythms [9]. This might suggest that the QRS width of the escape rhythms may not be accurate for assessing the site of AVB in dogs and dogs with escape rhythms generated in more proximal junctional tissues have a poorer prognosis [9].

As per different studies performed on dogs, PM implantation is associated with longer survival times and likely prevents the detrimental effects of chronic bradycardia [9,12]. On the other hand, a negative association between terbutaline or methylxanthine administration (or both) and duration of survival has been reported [9].

### Sinus node disease

Sinus node disease is the term generally applied to sinus node dysfunction (SND) that may be manifested electrocardiographically by severe sinus bradycardia and sinoatrial (SA) block/arrest. Such electrocardiographic abnormalities are frequently accompanied by recurrent episodes of focal atrial tachycardia, atrial fibrillation (AF), or atrial flutter, resulting in alternation between paroxysmal supraventricular tachycardia and slow atrial and ventricular rates [54]. Some authors consider that the diagnosis of sick sinus syndrome (SSS) in human beings requires the presence of clinical signs compatible with syncope and similar electrocardiographic findings in an asymptomatic patient warrant a diagnosis of SND rather than SSS [55,56]. In human beings, involvement of the right atrial wall has been proven when conspicuous alterations of the SA node and its approaches have been documented. These changes include total or subtotal destruction of the SA node, areas of nodal-atrial discontinuity, inflammatory or degenerative changes in the nerves and ganglia surrounding the SA node, and pathological changes in the atrial wall [18,57–61]. It has also been proven that, although frequently associated with underlying heart disease and seen most often in the elderly, SSS may occur in the fetus, infant, and child without apparent cause [62]. In this setting, SSS is presumed to be congenital and correlated with a mutation of the alpha SCN5A. In fact, biophysical characterization of the mutants demonstrates loss of function or significant impairments in channel gating (inactivation) that predict reduced

myocardial excitability [62]. These findings reveal a molecular basis for some forms of congenital SSS and define a recessive disorder of a human heart voltage-gated sodium channel [62].

The cardiopathologic findings observed in elderly dogs with myxomatous mitral valve disease are substantially similar to those of human beings and include significant changes, such as extensive damage of the SA node with depletion of the nodal cells and increase of fibrous or fibro-fatty tissue, interrupted contiguity between the SA node and the surrounding atrial myocardium, and interstitial fibrosis of the left and right atrial walls [54]. Previously published data demonstrated that dogs affected by SSS/SND are older, females are over-represented, and Miniature schnauzers, West Highland white terriers, and Cocker spaniels are considered predisposed breeds [54,63–66].

In agreement with human medicine data, there is no evidence that cardiac pacing prolongs survival in dogs with sinus node disease. In one study, survival times did not differ between symptomatic and asymptomatic dogs or between dogs that received PM implantation and dogs that were medically treated (theophylline, propantheline, hyoscyamine, terbutaline) [63]. In dogs, the most common cause of death in the SSS population is euthanasia for non-cardiac-related disease, even though several reported non-cardiac-related causes could have been exacerbated by low cardiac output, causing poor peripheral perfusion [63]. In fact, it has been reported that total survival time and risk of sudden cardiac death in human beings with SND, irrespective of symptoms, are similar to that of the general population [67]. Dogs with SND do not require treatment, whereas dogs with SSS often require PM implantation to reduce the frequency of syncope. The prognosis of SSS in dogs is usually good, although development of congestive heart failure does not appear to be mitigated by PM implantation [63].

### Persistent atrial standstill

Persistent atrial standstill is a rare arrhythmia in both human and veterinary medicine [1,2,7,68–78]. In human beings, PAS has been described to occur in conjunction with a number of muscular dystrophy disorders and with amyloidosis and myocarditis [70,71,73–79]. In dogs, although neuromuscular disease, long-standing cardiac disease, and myocarditis have been proposed as cause of PAS, this rhythm disturbance is generally attributed to atrial myopathy [80,81]. Atrial myopathy is characterized by progressive loss of atrial myocardium, with loss of the ability to conduct impulses, histological findings of myocardial

necrosis, infiltration of inflammatory cells, and replacement fibrosis. Both the atrial myocardium and the conduction system are affected [74,75,79,80,82,83]. In humans, atrial pacing with an output as high as 25 mA is used to confirm the presence or absence of atrial depolarizations [79]. Persistent atrial standstill has to be differentiated from temporary atrial standstill, which can be secondary to digitalis toxicity, quinidine toxicity, myocardial infarction, hyperkalemia, hypoxia, and hypothermia [74–76,83].

One form of atrial standstill called partial atrial standstill has been described in human beings and suspected in a dog [82,84]. This term indicates that certain regions of the atria, sometimes limited to one atrium, are still electrically active, even when no atrial deflections are evident on the surface electrocardiogram (ECG). Endocardial mapping in these cases reveals spontaneous depolarization in these regions, which also respond to pacing.

Electrocardiographically, differential diagnosis for PAS would include third-degree AVB with AF or sinus arrest or block. In dogs presenting wide QRS bradycardia associated with absence of atrial activity, complete differentiation between PAS and third-degree AVB associated with AF cannot be made without endocardial mapping of the right atrium. The presence of fibrillatory potentials (f waves) on the endocavitary atrial ECG confirms AF as a component of the rhythm disturbance. On the other hand, the lack of atrial activity rules out AF and a nodal or ventricular rhythm with retrograde atrial activation [85].

Another cause of wide QRS bradycardia associated with absence of atrial deflections is consistent with failure of impulse formation within the SA node (sinus arrest) or impulse propagation from the SA node to the surrounding atrial myocardium (sinoatrial block), compatible with SND. If this finding is associated with third-degree AVB with a ventricular escape rhythm, as reported in a dog, this arrhythmia cannot be differentiated on the surface ECG from PAS or AF with third-degree AVB [86]. Sinus node disease associated with third-degree AVB cannot be diagnosed on standard endocardial mapping and atrial pacing is required to evaluate atrial capture.

Persistent atrial standstill has been also described in cats, and the definitive diagnosis was made using electrophysiological study and histological examination. The histopathological findings were consistent with loss of atrial cardiomyocytes, in which remaining cells were separated by

residual atrial collagenous connective tissue and fat [87].

Although documented in several breeds of dogs and cats [69,71,73–75,81,82,87], PAS has most commonly been reported in English springer spaniels and Labrador retrievers [69,74]. Prognosis in human beings with PAS is variable and rapid disease progression is noted in individuals affected by underlying cardiac disease, such as myocarditis. Congestive heart failure is frequently reported as the cause of death in people with this finding [88]. It has been initially suggested that dogs with PAS have a poor prognosis, despite PM implantation, although some studies showed that the survival times are similar to other bradyarrhythmias [2,7,71,74,75,89]. The median survival time of PAS dogs was reported to be approximately 28 months after pacing, indicating that these animals can be expected to survive a similar amount of time to dogs affected by other bradyarrhythmias [74]. However, of the dogs with PAS that died, 64% suffered a cardiac-related death [74], which appears to be a relatively high incidence compared with other bradyarrhythmias, where it varies from 22% to 60% [2,7,12]. Despite the high incidence of cardiac-related death in PAS dogs, no difference in survival times was noted between cardiac and non-cardiac causes of death [74].

#### **Disturbances of the autonomic nervous system**

Disturbances of the autonomic nervous system can induce either slow heart rate or depressed vascular tone (or both), causing transient cerebral hypoperfusion and, ultimately, transient self-limited episodes of loss of consciousness [90]. Traditionally, reflex syncope refers to a heterogeneous group of conditions in which cardiovascular reflexes that are normally useful in controlling the circulation become intermittently inappropriate in response to a trigger [91]. Triggering situations vary considerably in and between individual patients, and, in most cases, the efferent pathway does not strongly depend on the nature of the trigger. Based on the trigger, reflex syncope can be classified as VVS (mediated by emotion or by orthostatic stress), situational syncope (traditionally associated with specific circumstances, such as cough, swallowing, post-exercise, vomiting, micturition, and defecation), carotid sinus syncope (mechanical manipulation of the carotid sinuses), and 'atypical form' with uncertain or even apparently absent triggers [92]. Swallowing and cough syncope have been reported in the dog [93,94]. In human medicine, it has been proposed

that frequent vasovagal-mediated cardiac asystole may be a potential cause of sudden cardiac death [95]. In addition, in human medicine, PM therapy has gained new impetus in the light of the most recent studies and it has been suggested that, considering the not insignificant complications associated with pacing, PM implantation should only be considered in patients aged >40 years, with severe recurrent syncope, in whom long asystole periods have been documented with an implantable loop recorder [96]. In veterinary medicine, PM implantation has been described in dogs with VVS that presented transient loss of consciousness after excitement or cough [12]. Syncope markedly reduced in frequency after pacing, whereas pre-syncope was unaffected. This is likely due to the coexistence of hypotension and bradycardia as a cause of VVS. Pacing can ameliorate bradycardia but not hypotension at the time of collapse [12,97].

### Pathophysiology of symptomatic bradyarrhythmias

Bradyarrhythmias requiring cardiac pacing can be caused by a variety of etiologies, and early identification of a potentially reversible cause is the first step towards treatment. In general, when a transient or reversible cause is excluded, indication for cardiac pacing is determined by the severity of the bradycardia and the clinical signs, rather than its etiology [67]. The main physiological effect of bradycardia is increased stroke volume and decreased cardiac output. As long as the increase in stroke volume is able to compensate for the decrease in heart rate, patients with profound bradycardia can remain completely asymptomatic.

Although permanent forms of bradyarrhythmias are caused by an intrinsic disease, such as SND, AVB, or PAS, the etiology of intermittent symptomatic bradyarrhythmias can be difficult to diagnose. Possible causes of intermittent symptomatic bradyarrhythmias include intermittent/paroxysmal AVB, some forms of SND, such as tachycardia–bradycardia syndrome, and disturbance of

the autonomic nervous system, such as vasovagal sinus arrest or AVB.

### Clinical presentation and diagnosis

#### AV conduction disturbances

Clinical signs depend on the severity of the heart block, the rate of the escape rhythm, and the presence or absence of concomitant cardiovascular disease [98]. The most commonly reported clinical sign is transient loss of consciousness, which occurs in 23%–77% of dogs, followed by weakness and exercise intolerance (14%–48%), lethargy (23%–26%), vomiting and diarrhea (11%–23%), and signs of congestive heart failure (3%–10%). In about 4% of cases, no clinical signs are reported [1–3,7–13]. Congestive heart failure signs, such as ascites or pulmonary edema, can be present due to several myocardial changes induced during sustained abnormal AV activation and decreased heart rate [99].

Clinical signs are present in the majority of cats with third-degree AVB, although around one-third of cats with third-degree AVB had their arrhythmia diagnosed as an incidental finding [50]. If present, clinical signs are consistent with transient loss of consciousness [14] or related to congestive heart failure [15,50].

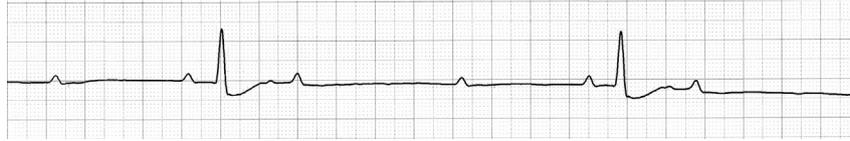
First-degree AVB is diagnosed when a prolongation of the PQ interval is documented (Fig. 1), whereas second-degree AVB is diagnosed when some of the atrial impulses are not conducted to the ventricles. In human medicine, second-degree AVB with normal QRS duration is defined as type A and it is assumed that the site of conduction failure is above the bifurcation of the bundle of His. On the other hand, type B is a second-degree AVB with a wide QRS complex and the site of block is assumed to be below the bundle branch bifurcation [100]. Second-degree AVB can show different AV conduction ratios. If one out of every two P waves is conducted to the ventricles, the second-degree AVB is named 2:1 AVB (Fig. 2), and if more than one P waves are consecutively blocked, the second-degree AVB is named advanced (Fig. 3).



**Fig. 1** Electrocardiographic tracing of a 16-year-old, female, mix-breed dog with severe first-degree atrioventricular block (PQ interval 200 ms). Lead II, paper speed 50 mm/s, calibration 10 mm/1 mV.



**Fig. 2** Electrocardiographic tracing of a 12-year-old, female, Lhasa apso with 2:1 second-degree atrioventricular block. Every other P wave is blocked and conducted beats have a prolonged PQ interval (220 ms). Lead II, paper speed 50 mm/s, calibration 10 mm/1 mV.



**Fig. 3** Electrocardiographic tracing of an 8-year-old, male, Italian hunting dog with advanced or high-grade second-degree atrioventricular block. Two consecutive P waves are blocked and conducted beats have a prolonged PQ interval (150 ms). Lead II, paper speed 50 mm/s, calibration 10 mm/1 mV.

Third-degree AVB is characterized by absence of conduction along the AV node. Electrocardiographic findings are consistent with the presence of normal P waves and idioventricular rhythm with AV dissociation (Fig. 4). Trifascicular block occurs when the right and left bundle branches are alternately interrupted due to infranodal disease or when a bifascicular block accompanies a nodal block with evidence of AV conduction disturbance [45].

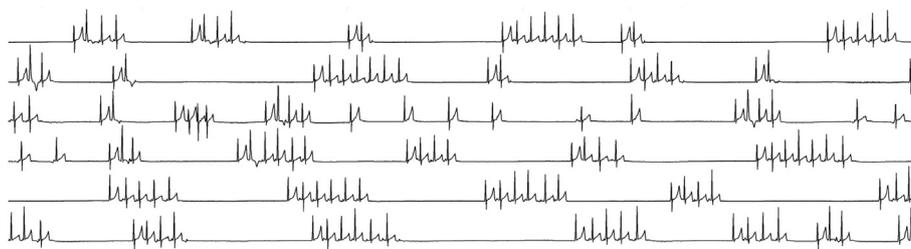
From the diagnostic point of view, one study tried to determine if serum cTnI concentration in dogs could distinguish between cardiogenic syncope and collapse due to either generalized epileptic seizures (both with and without cardiac disease) or VVS, but due to the overlap in cTnI concentrations between groups, measurement in an individual patient is not optimally discriminatory to differentiate them [101]. In other studies, it has been proven that serum cTnI concentration is high on presentation and shows significant reduction after PM implantation [40,41,69] although lead type and severity of the arrhythmia did not show any correlation [40].

### Sinus node dysfunction

As per the largest retrospective study performed in veterinary medicine, which included 93 dogs with SSS or SND, 66% of dogs presented with clinical signs due to cardiac disease at the time of presentation. Syncope represented the most common clinical sign, occurring in 95% of cases. The median frequency of syncope at the time of presentation was one episode per day with some dogs experiencing as few as one single episode in their lifespan and others experiencing up to 15 episodes a day. Less commonly, the clinical presentation was consistent with lethargy. The remaining 34% of dogs were asymptomatic for the bradycardia and were, therefore, diagnosed with SND [63]. Electrocardiographic findings were consistent with sinus arrest in 48%–80% of patients and sinus bradycardia in 33% of patients. The mean duration of the pauses reported on the ECG was  $2.5 \pm 1.3$  s long [63,64]. Concomitant conduction disturbances of the AV node were present in about 33% of patients [64]. On Holter monitoring (24 and 48 h ambulatory ECG), bradycardia-tachycardia syndrome was detected in 21% of dogs (Fig. 5). Also,



**Fig. 4** Electrocardiographic tracing of a 12-year-old, male, Golden retriever with third-degree atrioventricular block. Note the presence of atrioventricular dissociation (sinus rate 100 beats per minute, ventricular escape rate 50 beats per minute). Lead II, paper speed 50 mm/s, calibration 10 mm/1 mV.



**Fig. 5** Holter recording of an 11-year-old, female, West Highland white terrier with frequent syncopal episodes. Note the runs of sinus tachycardia followed by sinus and ventricular arrest interrupted by either junctional escape beats or junctional escape rhythm. Lead Y, paper speed 7.5 mm/s, calibration 2 mm/mV.

on the Holter monitoring, the mean longest duration of sinus arrest was  $7.3 \pm 3.2$  s. No statistically significant differences were reported between symptomatic and asymptomatic patients on ECG or Holter monitor findings.

#### Persistent atrial standstill

Reported clinical signs are consistent with syncope in 60% of PAS cases. Exercise intolerance, lethargy, and depression are noted in 50% of cases, and signs potentially related to congestive heart failure, such as abdominal distension, are noted in 40% of the cases [74].

Electrocardiographic findings of PAS are absent P waves and idioventricular escape rhythm with normal serum potassium concentration (Fig. 6) [74].

#### Disturbances of the autonomic nervous system

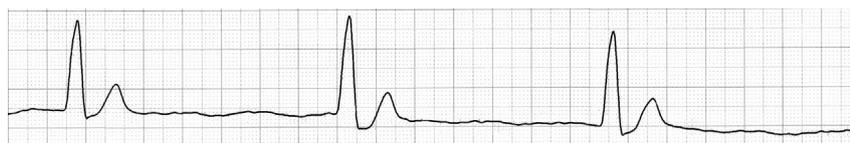
In human medicine, after the introduction of the head-up tilt test in clinical practice, the clinical presentation of VVS has been classified as typical (or classical) and atypical (or non-classical) [102]. A few clinical features and recent data suggest that even unexplained falls and syncope during sleeping hours may possibly be clinical presentations of VVS. Overall, tilt testing and carotid sinus massage display a high positivity rate in patients with unexplained falls (about 60%). These data seem to indicate that some unexplained falls could be cases of atypical VVS/carotid sinus syncope with retrograde amnesia. Some clinical

features suggest that syncope during sleeping hours is a form of VVS with a different clinical presentation: high prevalence of autonomic prodromes, diurnal episodes of typical VVS and specific phobias, and positive tilt testing with severe cardioinhibition [102].

Since the standard ECG is usually normal, tilt testing is used in human medicine because it enables the reproduction of a neurally mediated reflex in laboratory settings [92]. Blood pooling and decrease in venous return due to orthostatic stress and immobilization trigger the reflex. The final effect, hypotension, and, usually, concomitant slowing of the heart rate, are related to impaired vasoconstriction capability followed by sympathetic withdrawal and vagal over activity [88]. The clinical scenario that corresponds to the tilt test is reflex syncope triggered by prolonged standing. However, the test can also be positive in patients with other forms of reflex syncope [103] and in patients with SSS [104].

Also, in human medicine, it has been proven that N-terminal pro-b-type natriuretic peptide can be useful in differentiating patients with cardiac and reflex syncope. In fact, a value that exceeds 200 pg/mL seems to be more rational in determining cardiac syncope [105].

Few data are available regarding the diagnosis of VVS syncope in dogs [12,93,94,106]. The diagnosis can be performed with the ambulatory electrocardiography, which can document the presence of prolonged vagal-induced cardio-



**Fig. 6** Electrocardiographic tracing of a 13-year-old, female, Labrador retriever with atrial standstill. Note the absence of P waves with a flat isoelectric line and a wide QRS complex escape ventricular rhythm with a rate of 42 beats per minute. Analysis of endocardial electrograms is needed to differentiate this rhythm from atrial fibrillation with third-degree atrioventricular block and sinus standstill with third-degree atrioventricular block. Lead II, paper speed 50 mm/s, calibration 10 mm/1 mV.

inhibition inducing ventricular arrest because of either sinus arrest or paroxysmal AVB [106]. In some dogs, VVS can be followed by paroxysmal vagal AF [107]. As previously stated, when persistent, bradyarrhythmia is usually diagnosed using the standard ECG. Both in human and veterinary medicine, correlation between the clinical signs and the bradyarrhythmia with Holter, implantable or external loop recorder is essential to decide if cardiac pacing therapy is necessary (Fig. 7A–C) [67,108–121].

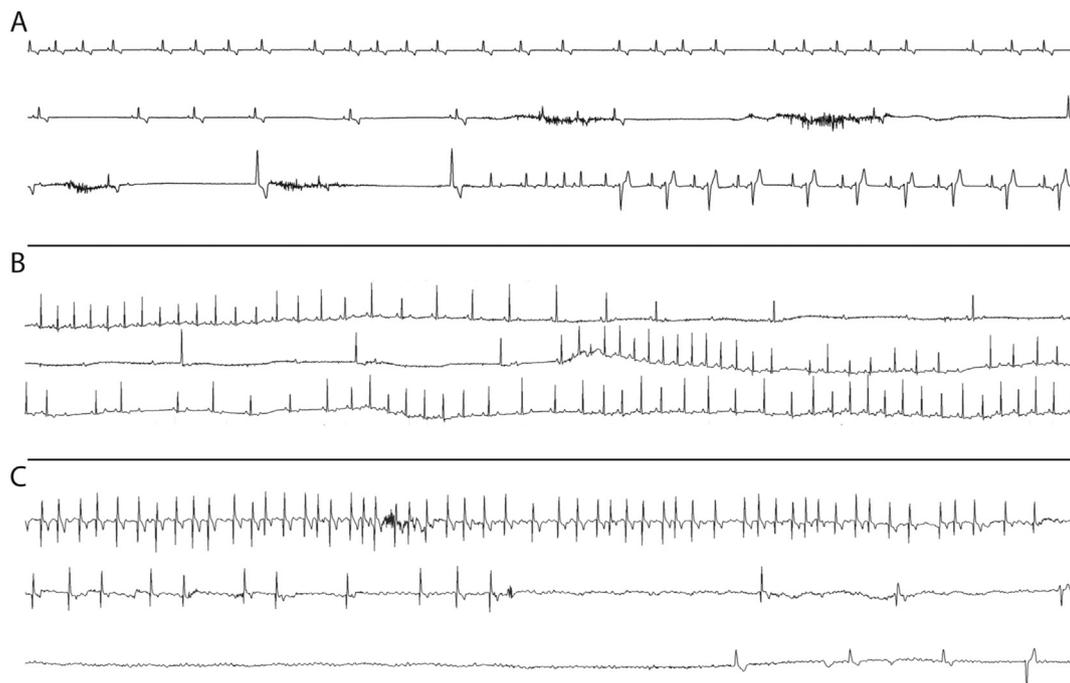
The strategy of prolonged monitoring provides a good diagnostic accuracy. However, both the diagnosis and the related therapy are delayed, often for a long time, until an event can be documented and the recurrent event may cause harm or even death [67].

## Indications for pacing and choice of pacing mode

### Persistent bradycardia

Data reported in veterinary medicine showed that indications for PM implantation in dogs consist of third-degree AVB in 53%–64% of patients, SSS in 14.8%–29%, second-degree AVB in 3.8%–9%, PAS in 3.2%–5.5%, and VVS in 3.8%. In this section, we provide an overview of indications for pacing relative to the previously described cardiac rhythm disorders.

In contrast to sinus node disease, AVB may require PM implantation for prognostic reasons and pacing may be indicated in symptomatic and asymptomatic patients [67]. Several observational studies, performed at the beginning of the PM era,



**Fig. 7** Holter tracings of three dogs with reflex or neurally mediated syncope. (A) Twelve-year-old, female, Cavalier King Charles spaniel with situational syncope occurring during coughing episodes. The first part of the tracing reveals sinus rhythm with an average ventricular rate of 90 beats per minute, followed by progressive sinus bradycardia that is interrupted by sinus and ventricular arrest of 9 s and is followed by a ventricular escape beat and a sinus beat. An additional episode occurred with shorter sinus and ventricular arrests with duration of 3.4 s followed by a ventricular escape beat and finally sinus rhythm with ventricular bigeminy. Lead Y, paper speed 7.5 mm/s, calibration 2 mm/mV. (B) Eight-year-old, female, beagle with situational syncope occurring during coughing episodes. The first part of the tracing reveals sinus rhythm with an average ventricular rate of 130 beats per minute, followed by progressive sinus bradycardia and paroxysmal or intermittent atrioventricular block with junctional escape rhythm (average ventricular rate 20 bpm). After 26 s, sinus rhythm recovered. Note that the sinus rate was very slow (30–40 beats per minute) during the period of atrioventricular block. Lead Y—paper speed 7.5 mm/s—calibration 2 mm/mV. (C) Nine-year-old, female, boxer with severe subaortic stenosis, persistent atrial fibrillation, and a history of syncopal episodes. The first part of the tracing reveals atrial fibrillation with an average ventricular rate of 250 beats per minute followed by progressive reduction of the ventricular rate, ventricular arrest (duration of 5 s) that is interrupted by a ventricular escape rhythm (average ventricular rate of 31 beats per minute), and a second prolonged ventricular arrest (13 s) that induced syncope. Lead Y, paper speed 7.5 mm/s, calibration 2 mm/mV.

suggest that pacing prevents recurrence of syncope and improves survival in people [92]. In veterinary medicine, different studies proved that PM implantation should be strongly considered in all dogs with third-degree AVB and advanced second-degree AVB, regardless of clinical signs [1,2,7–9,12–15,35,122].

In human medicine, in case of second-degree AVB Wenckebach type (progressive prolongation of the AV conduction time until block occurs), indication for permanent pacing is controversial, unless the AVB causes symptoms or the conduction delay occurs at intra- or infra-His levels [67]. It has been proven that, in patients with first-degree AVB, cardiac pacing is not recommended unless the PQ interval fails to adapt to the heart rate during exercise and is long enough (usually > 300 ms) to cause symptoms due to inadequate left ventricular filling or to an increase in wedge pressure, as the left atrial systole occurs close to or simultaneous with the previous left ventricular systole [67]. In such cases, small, uncontrolled studies have shown an improvement in symptoms with normalization of the PQ interval with dual-chamber pacing (AV resynchronization therapy) [67]. In veterinary medicine, one study that analyzed long-term intrinsic rhythm in dogs with AV nodal conduction disturbances had proven that the majority of cases showed persistent or progressive AVB [35]. In particular, paroxysmal third-degree AVB progressed to permanent third-degree AVB and most cases of 2:1 second degree AVB also progressed to third-degree AVB [35]. These findings are not in agreement with human medicine, in which 2:1 second degree AVB is considered to be stable [123], but support the need for PM implantation in dogs affected by paroxysmal third-degree AVB and 2:1 s degree AVB [35].

In cats, ventricular escape depolarization rates vary between 100 and 140 bpm [50] and clinical signs are often absent or minimal, suggesting that the presence of severe clinical signs, rather than heart rate, might be an important indicator for PM implantation in this species [50]. In agreement with data in dogs [35], a small percentage of cats are reported to have experienced a regression of third-degree AVB that converted into second-degree AVB or sinus rhythm [50] and/or a regression of trifascicular block into sinus rhythm [45].

In general, both in human and veterinary medicine, sinus node disease is only an indication for pacing if the bradycardia is symptomatic [1,2,7–12,35,63,67]. As previously reported in both human and veterinary medicine, because cardiac pacing is not known to prolong survival in patients with SSS, permanent pacing is currently

used to relieve symptoms attributed to bradycardia in these patients [63,67]. Although the quality of evidence in human studies is modest, there is a strong consensus that human and dogs with SSS will benefit from cardiac pacing for symptom relief [63,67]. In human medicine, the usefulness of cardiac pacing in patients showing chronotropic incompetence is uncertain, and the decision should be made on a case-by-case basis [67]. In agreement with human medicine [67], dogs affected by sinus node disease are generally old and frequently have concomitant structural heart disease. It has been proven that congestive heart failure is common in dogs affected by sinus node disease and is present in 14% of this population, accounting for 20% of total deaths and 65% of cardiac deaths [63]. In these situations, demonstration of a clear cause–effect relationship between symptoms and sinus node disease is often difficult to achieve [63,67].

Pacemaker implantation is recommended in dogs with PAS. The PM, while relieving clinical signs by increasing heart rate and cardiac output, would not be expected to slow the progression of myocardial degeneration, and this is the rationale for the poor prognosis associated with PAS [7,74]. As a consequence of the historically poor prognosis associated with PAS, it has been suggested that dogs with this disease are less ideal candidates for PM implantation than those affected by other bradyarrhythmias [89]. However, when considering reported data about survival times after PM implantation for other bradyarrhythmias, it appears that dogs with PAS have similar survival times [2,7,71,74,75,124,125].

In human medicine, it has been proved that when compared with single-chamber pacing, dual-chamber pacing results in small but potentially important benefits for patients with AVB and/or sinus node disease, even if a difference in mortality has not been observed [126–130]. More than a quarter of patients with VVI (ventricle-paced, ventricle-sensed inhibition of PM in case of sensed intrinsic activity) pacing develop ‘PM syndrome’, which reduces quality of life [67]. In crossover trials, symptoms of PM syndrome (dyspnea, dizziness, palpitations, pulsations, and chest pain) were reduced by reprogramming the PM to dual-chamber mode [67]. Overall, dual-chamber pacing is associated with better exercise performance compared with fixed-responsive, but not with rate-responsive VVI pacing [67]. In veterinary medicine, one study analyzed atrial single-chamber PM implantation for the treatment of SND [131]. Dogs affected by SND can be paced from the atria, which provides a more physiologic approach to

management. In dogs with no coexisting AVB evaluated by 24-h Holter monitoring, AAI/AAIR (atrium-paced, atrium-sensed inhibition of PM in case of sensed intrinsic activity, R Rate modulation) pacing modality can be considered [131]. In human medicine, during permanent PM implantation, a stepped-up atrial pacing protocol is used to identify the AV nodal Wenckebach blocking point. A Wenckebach point of <120 beats per minute in humans is considered a contraindication for single-chamber atrial pacing [132–134]. The corresponding Wenckebach point limit in dogs anesthetized with a variety of drugs is unknown and would need to be established before recommendations can be made [131]. Nevertheless, in a limited case series of operators with limited experience in the specific implantation procedure, the incidence of complications related to atrial lead stability appeared to be high [131]. In human medicine, it has been proven that AVB develops in 0.6%–1.9% of patients with sinus node disease, which represents a disadvantage of AAIR pacing [67]. These findings support the routine use of dual-paced, dual-sensed, dual mode of response rate modulation, rather than AAIR, pacing in patients with SSS [67]. Also, in human medicine, in patients with sinus standstill, dual-chamber pacing is considered the pacing mode of choice [67], whereas AAIR is not considered for routine use [130]. Unnecessary right ventricular pacing should be systematically avoided in patients with sinus standstill by programming the PM with a long AV interval [135,136]. However, programming an excessively long AV interval to avoid RV pacing in patients with prolonged AV conduction may be disadvantageous from a hemodynamic point of view by causing diastolic mitral regurgitation [135,136].

In human medicine, it has been proven that rate-responsive pacing, when compared with fixed-rate pacing, is associated with better exercise performance; improved daily activity; decrease of symptoms of shortness of breath, chest pain, and palpitations; and improved quality of life [67]. Therefore, rate-responsive pacing is the pacing mode of choice and fixed-rate VVI pacing should be abandoned in patients with permanent AF and AVB (Fig. 8A and B) [67].

There are several rate-responsive technologies available, but the most commonly used in dogs is based on activity-driven sensors [137]. An exercise test of 20–30 min has been proposed to find the correct programming to meet metabolic demands that depends on the size of the animal, level of fitness, and different environmental factors. The best setting to obtain an optimal performance is to

maintain an AV ratio below 1.5 during exercise [137]. In the same study, the QT/activity mode dual sensor failed because it responded very little to exercise [137].

Both in human and veterinary medicine, synchronous AV pacing can be performed with a single lead physiologic pacing with VDD (V Ventricle paced, D Dual sensed, D Dual mode of response) modality or with two leads with DDD modality (Fig. 9A and B). As per the guidelines for human patients [67], the primary indication for single lead physiologic pacing is third-degree AVB with normal SA node function, because VDD PMs are unable to pace the atria during periods of sinus arrest and they are unable to maintain AV synchrony in patients with sinus node disease [3,10,110]. The prevalence of chronotropic incompetence in dogs with third-degree AVB is unknown. The potential for humans to develop sinus node disease after PM implantation is one argument against the utilization of a single lead physiologic PM [138]. In veterinary medicine, it has been described that dogs that present an atrial rate <70 beats per minute and a negative atropine response test (<25% increase of sinus rate 20–30 min post 0.04 mg/kg atropine SQ injection) [63] are excluded from consideration of single lead VDD PM implantation [110]. Other contraindications to physiologic VDD PMs are represented by AVB complicated by AF or supraventricular tachycardia. Although physiologic pacing cannot be achieved in patients with AF, the automatic mode switching in most new generation pulse generators can help preventing inappropriate ventricular stimulation if infrequent paroxysms of non-sustained AF or supraventricular tachycardia occur during VDD pacing [110]. Furthermore, the atrial dipole of the lead has to be placed at the junction of the cranial vena cava and right atrium to avoid inappropriate atrial sensing. The likelihood to achieve this goal is dependent on the size of the dog and on the distance between the atrial array and the ventricular electrode (AV distance) [110]. A strict minimum weight for VDD PM implantation is difficult to establish but, in general, it is easier to appropriately position the pacing lead in larger dogs [110]. In veterinary medicine, no large-scale, long-term studies in dogs with naturally occurring third-degree AVB are available, and the decision of a physiologic PM mode implantation is based on the age of the dog and on its level of physical activity [110]. Younger dogs seem to be good candidates for physiologic pacing because they can potentially live longer and may be more active, although older dogs may also benefit because of concurrent structural heart disease [110]. Working, hunting,



**Fig. 8** Thoracic radiograph and electrocardiographic tracing of a 9-year-old, male, Cocker spaniel with 2:1 second-degree atrioventricular block and a permanent pacemaker programmed in VVI modality. (A) Right lateral thoracic radiograph with a single passive ventricular electrode positioned at the level of right ventricular apex. (B) Electrocardiographic tracing. Note, in the first part of the tracing, 2:1 second-degree atrioventricular block followed by ventricular paced beats that are dissociated from the P waves (VVI modality). Lead II, paper speed 50 mm/s, calibration 10 mm/1 mV.

and agility dogs may benefit from AV synchronous pacing, and a short-term study revealed 44% increase in echocardiographically determined stroke volume and 28% increase cardiac output during VDD pacing compared with fixed-rate VVI pacing [139]. Whether these data are confirmed during exercise is uncertain, although an experimental study suggests a limitation in stroke volume reserve during fixed-rate VVI pacing [140]. In veterinary medicine, it has been described that, perhaps, a sub-population of dogs with third-degree AVB associated with structural heart disease could have the greatest advantage from physiologic VDD pacing stimulation because of the presence of AV synchrony and not-fixed RR interval compared with VVI pacing [110]. In fact, by pacing the ventricle after the atrial contraction, physiologic PMs help avoid atrial contraction against a closed AV mitral valve and may limit mitral valve

insufficiency, thereby decreasing mean left atrial pressures [139–143]. Lower left atrial pressures associated with prolonged diastolic filling time and appropriate AV synchrony may enhance left ventricular filling and improve systolic performance [142]. Although one study in dogs demonstrated that dual-chamber PM implantation resulted in increased procedural and anesthetic times, compared with single-chamber PM implantation, it did not result in higher complication rates [13,144]. Nevertheless, a more recent retrospective study demonstrated no statistically significant benefit in survival times in dogs that received a physiologic VDD PM compared with dogs that received a non-physiologic VVI PM [13]. These data are consistent with prospective studies in human beings comparing single-chamber (VVIR) (R Rate modulation) and dual-chamber (DDD) pacing to analyze the impact of physiologic pacing on mortality.



**Fig. 9** Thoracic radiograph and electrocardiographic tracing of a 7-year-old, male, German shepherd with third-degree atrioventricular block and a dual-chamber permanent pacemaker programmed in VDD modality. (A) Right lateral thoracic radiograph with a passive atrial electrode positioned at the level of right atrial appendage and a passive ventricular electrode placed at the level of the right ventricular apex. (B) Electrocardiographic tracing. Note the presence of P waves that are sensed by the pacemaker and then trigger ventricular paced beats after a programmed atrioventricular delay (160 ms) (VDD modality). Lead II, paper speed 50 mm/s, calibration 10 mm/1 mV.

These studies only demonstrated secondary benefits, such as the decrease in AF and improved quality of life, but without any effect on mortality [97,126,145,146]. As previously stated, non-physiologic pacing may be associated with PM syndrome [147]. Although, historically, intolerance to VVI pacing has been considered an infrequent consequence to ventricular pacing, a crossover study identified that 65% of human being experienced moderate to severe clinical signs consistent with PM syndrome [148]. Numerous studies have evaluated and identified significant improvements in cardiovascular symptom scores and self-perceived health between physiologic and non-physiologic pacing (both VVI and VVIR) [149–157]. In veterinary medicine, one retrospective study analyzed the perceived symptomatic improvement in quality of life or exercise tolerance by asking owners to complete a quality of life questionnaire, but no statistically significant

differences were identified between the two pacing modalities. Whether there are no quality of life benefits, the benefits are too subtle to be detected by the owners in otherwise sedentary dogs, or the quality of life questionnaire was inappropriately designed to document clinical benefits is difficult to determine [139].

Dogs affected by third-degree AVB can also benefit from biventricular pacing [158,159]. In human beings, the standard use of biventricular pacing is for cardiac resynchronization therapy in patients with systolic dysfunction, ventricular conduction delay, and heart failure [67]. The use of biventricular pacing in patients with third-degree AVB is aimed to maintain a synchronous ventricular activation pattern. This may preserve ventricular function over a long period and prevent myocardial failure, occasionally noted in veterinary patients [158,159]. Newly developed congestive heart failure after PM implantation not

associated with AV valvular or primary myocardial disease is reported in 3.6%–11.5% of patients [2,7,9,10,12]. Furthermore, patients affected by third-degree AVB associated with chronic degenerative mitral valve disease or dilated cardiomyopathy may be more sensitive to bisynchronous apical right ventricular pacing [158]. Dogs with preexisting congestive heart failure secondary to myxomatous degenerative mitral valve disease or dilated cardiomyopathy presented 1-year mortality rate more than twice when compared with dogs without initial evidence of congestive heart failure [2]. In human medicine, it has been proven that pacing at any ventricular site leads to abnormal ventricular activation and the sequence of ventricular activation is more important for left ventricular function than the temporal synchronization within the left ventricular myocardium [160,161]. In dogs, it has been shown that, at least in the acute phase, biventricular pacing appears to improve some indices of myocardial performance [158,159]. The left ventricular function improvement may be related to the normalization of the ventricular activation sequence, because right and left ventricles are synchronous, and not only to the normalization of the activation of the left ventricle alone [158]. Compared with dual chamber, biventricular pacing systems are more expensive and many patients that need PM implantation are too small for these systems [158].

In cases of permanent or persistent AF associated with third-degree AVB and in cases of PAS, the indication is single-chamber mode with the ventricular lead positioned at the level of the right ventricular apex [2,7,68–75].

In veterinary medicine, implantation of dual-chamber epicardial PMs was described in dogs in which transvenous leads placement is considered unsuitable. Potential limitations of this technique include the possibly increased anesthetic time required for implantation of a dual-chamber when compared with a single-chamber epicardial system and the increased anesthetic time and more invasive nature with required technical expertise associated with implantation of an epicardial pacing system when compared with a transvenous system [161].

Despite the widespread use in dogs, PM implantation is rarely reported in cats [162], as it is limited to cats that present severe symptomatic bradyarrhythmias. Pacemaker implantation in the cat requires an epicardial lead that is positioned by thoracotomy or ventral celiotomy-transdiaphragmatic technique, and the selected pacing modality is VVIR [8,50,162].

### **Intermittent bradycardia**

Both in human and veterinary medicine, there are two clinical features of intermittent bradycardia, in patients affected by intrinsic sinus node disease, in which cardiac pacing is indicated: documented symptomatic intermittent sinus arrest or sinoatrial block and documented prolonged sinus pause following the termination of tachycardia in the tachycardia–bradycardia syndrome. In both, the underlying mechanism is the abnormally prolonged time needed for recovery of automaticity by a diseased SA node. Prolonged pauses typically cause transient loss of consciousness. In these documented cases, PM implantation is indicated [63,67].

In cases of intermittent or paroxysmal AVB, when correlation between symptoms and ECG findings is established, there is general consensus that cardiac pacing is effective and useful for symptom relief [67].

In human medicine, intermittent or paroxysmal AVB that occurs in patients with underlying heart disease and/or bundle branch block is usually regarded as a manifestation of intrinsic disease of the AV conduction system (Stokes–Adams) [67]. In veterinary medicine, it has been proven that both intermittent and paroxysmal AVB can progress into permanent AVB [35].

Indications for permanent pacing with intermittent advanced AVB are similar to those with persistent AVB [35,67].

In general, in patients with reflex syncope, cardiac pacing should be the last choice and should only be considered to highly selected patients (presence of long pauses, history of recurrent syncope). In a large retrospective study in veterinary medicine, PM implantation was successful in eliminating or reducing clinical signs in dogs with frequent VVS [11]. However, clinical signs only completely resolved after pacing in a small percentage of affected dogs. In the majority of dogs, clinical signs reduced markedly but did not cease [12]. This is likely due to the coexistence of hypotension and bradycardia as the cause of syncope. Pacing can ameliorate bradycardia but not hypotension at the time of the transient loss of consciousness [97].

In intermittent bradycardia, pacing may be required only for short periods of time. In these situations, the benefits of bradycardia and pause prevention must be weighed against the detrimental effects of permanent pacing [67]. Patients should not be subjected to permanent ventricular stimulation. Therefore, manual adaptation of AV interval or programming AV hysteresis preventing unnecessary right ventricular pacing plays a

particularly important role in this patient group [135,136].

In case of intermittent bradycardia, particularly in dogs with SSS and no clinical signs, temporary pacing with transvenous or transthoracic technique can be used to perform procedure under general anesthesia [163–165].

In conclusion, permanent pacing should be considered a first line therapy in most of canine and feline bradyarrhythmias, as it improves quality of life and prolongs survival. The etiology of the underlying rhythm disturbance, the clinical signs, and natural history of the disease should be analyzed in detail to better understand prognosis and to choose pacing modalities.

## Conflicts of Interest Statement

The authors do not have any conflicts of interest to disclose.

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