ELSEVIER

Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

ELSEVIER

Review

Indications for permanent pacing in dogs and cats

R.A. Santilli, Dr Med Vet, PhD [a,b,*], F. Giacomazzi, Dr Med Vet [a], D.M. Porteiro Vázquez, DVM Dr Med Vet [a], M. Perego, Dr Med Vet [a]

[a] Clinica Veterinaria Malpensa, Viale Marconi 27, 21017 Samarate, Varese, Italy
[b] Department of Clinical Sciences, Cornell University, Ithaca, NY, USA

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.
© 2019 Elsevier B.V. All rights reserved.

* Corresponding author.
    E-mail address: r.santilli@ecgontheweb.com (R.A. Santilli).

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
cTnI	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 ganglias 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 overrepresented, 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 affects 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 noncardiac 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.
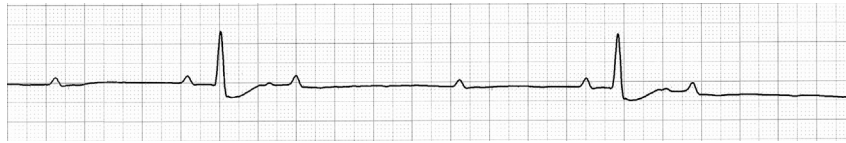

Fig. 3   Electrocardiographic tracing of an 8-year-old, male, Italian hunting dog with advanced or high-grade second-degree atrioventricular block. Two consecutive P waves are blocked and conducted beats have a prolonged PQ interval (150 ms). Lead II, paper speed 50 mm/s, calibration 10 mm/1 mV.

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 shown any correlation [40].

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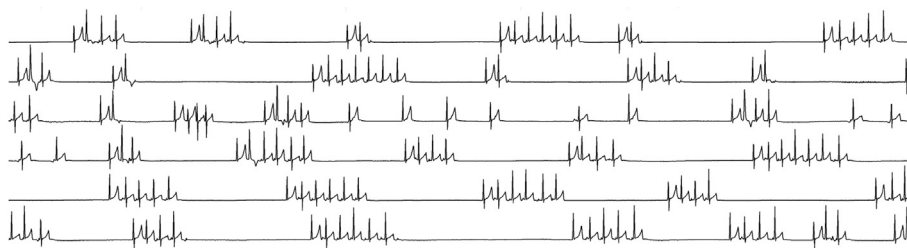
Fig. 5 Holter recording of an 11-year-old, female, West Highland white terrier with frequent syncopal episodes. Note the runs of sinus tachycardia followed by sinus and ventricular arrest interrupted by either junctional escape beats or junctional escape rhythm. Lead Y, paper speed 7.5 mm/s, calibration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

on the Holter monitoring, the mean longest duration of sinus arrest was 7.3 ± 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-
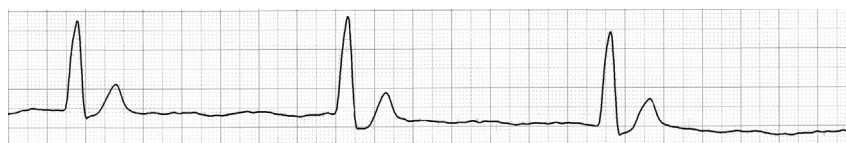

Fig. 6 Electrocardiographic tracing of a 13-year-old, female, Labrador retriever with atrial standstill. Note the absence of P waves with a flat isoelectric line and a wide QRS complex escape ventricular rhythm with a rate of 42 beats per minute. Analysis of endocardial electrograms is needed to differentiate 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,
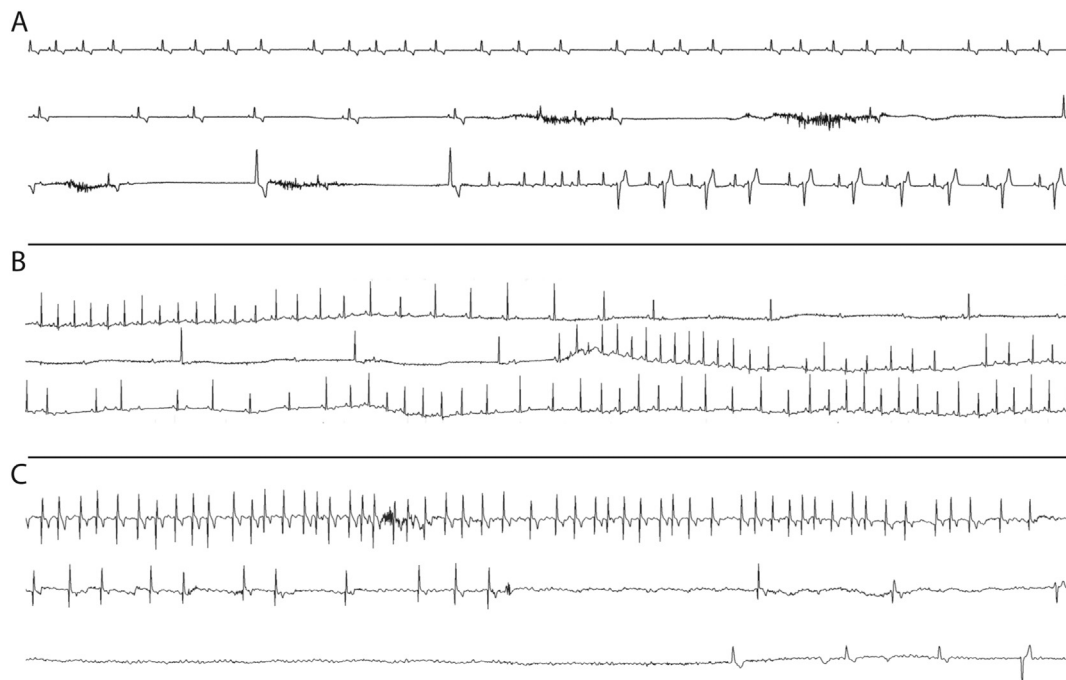

Fig. 7 Holter tracings of three dogs with reflex or neurally mediated syncope. (A) Twelve-year-old, female, Cavalier King Charles spaniel with situational syncope occurring during coughing episodes. The first part of the tracing reveals sinus rhythm with an average ventricular rate of 90 beats per minute, 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 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,
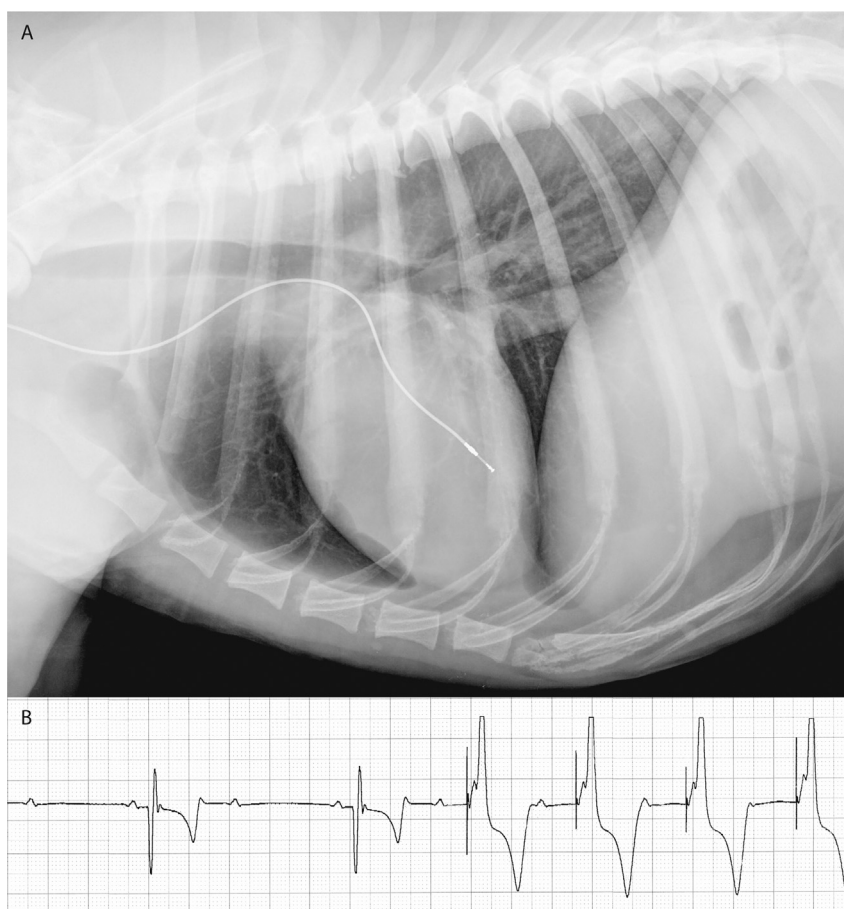
Fig. 8 Thoracic radiograph and electrocardiographic tracing of a 9-year-old, male, Cocker spaniel with 2:1 second-degree atrioventricular block and a permanent pacemaker programmed in VVI modality. (A) Right lateral thoracic radiograph with a single passive ventricular electrode positioned at the level 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 hat 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.

Acknowledgements

References

[1] Sisson D, Thomas WP, Woodfield J, Pion PD, Luethy M, DeLellis LA. Permanent transvenous pacemaker implantation in forty dogs. J Vet Intern Med 1991;5:322–31.

[2] Oyama MA, Sisson DD, Lehmkuhl LB. Practices and outcome of artificial cardiac pacing in 154 dogs. J Vet Intern Med 2001;15:229–39.

[3] Bulmer BJ, Oyama MA, Lamont LA, Sisson DD. Implantation of a single-lead atrioventricular synchronous (VDD) pacemaker in a dog with naturally occurring 3rd-degree atrioventricular block. J Vet Intern Med 2002;16:197–200.

[4] Roberts DH, Tennant B, Brockman D, Bellchambers S, Charles RG. Successful use of a QT-sensing rate-adaptive pacemaker in a dog. Vet Rec 1992;130:471–2.

[5] Flanders JA, Moïse NS, Gelzer AR, Waskiewicz JC, MacGregor JM. Introduction of an endocardial pacing lead through the costocervical vein in six dogs. J Am Vet Med Assoc 1999;215:46–8.

[6] Darke P. Clinical teaching. Vet Rec 1992;130:562.

[7] Wess G, Thomas WP, Berger DM, Kittleson MD. Applications, complications, and outcomes of transvenous pacemaker implantation in 105 dogs (1997–2002). J Vet Intern Med 2006;20:877–84.

[8] Visser LC, Keene BW, Mathews KG, Browne WJ, Chanoit G. Outcomes and complications associated with epicardial pacemakers in 28 dogs and 5 cats. Vet Surg 2013;42:544–50.

[9] Schrope DP, Kelch WJ. Signalment, clinical signs, and prognostic indicators associated with high-grade second- or third-degree atrioventricular block in dogs: 124 cases (January 1, 1997-December 31, 1997). J Am Vet Med Assoc 2006;228:1710–7.

[10] Hildebrandt N, Stertmann WA, Wehner M, Schneider I, Neu H, Schneider M. Dual chamber pacemaker implantation in dogs with atrioventricular block. J Vet Intern Med 2009;23:31–8.

[11] Domenech O, Santilli R, Pradelli D, Bussadori C. The implantation of a permanent transvenous endocardial pacemaker in 42 dogs: a retrospective study. Med Sci Monit 2005;11:168–75.

[12] Johnson MS, Martin MW, Henley W. Results of pacemaker implantation in 104 dogs. J Small Anim Pract 2007;48:4–11.

[13] Lichtenberger J, Scollan KF, Bulmer BJ, Sisson DD. Long-term outcome of physiologic VDD pacing versus non-physiologic VVI pacing in dogs with high-grade atrioventricular block. J Vet Cardiol 2015;17:42–53.

[14] Penning A, Connolly DJ, Gajanayake I, McMahon LA, Luis Fuentes V, Chandler KE, Volk HA. Seizure-like episodes in 3 cats with intermittent high-grade atrioventricular dysfunction. J Vet Intern Med 2009;23:200–5.

[15] Ferasin L, van de Stad M, Rudorf H, Langford K, Hotston MA. Syncope associated with paroxysmal atrioventricular block an ventricular standstill in a cat. J Small Anim Pract 2002;43:124–8.

[16] Zoll PM. Resuscitation of the heart in ventricular standstill by external electric stimulation. N Engl J Med 1952;247:768–71.

[17] Buchanan JW, Dear MG, Pyle RL, Berg P. Medical and pacemaker therapy of complete heart block and congestive heart failure in a dog. J Am Vet Med Assoc 1968;15:1099–109.

[18] Olgin JE, Zipes DP. Specific arrhythmias: diagnosis and treatment. In: Braunwald E, editor. Heart Disease: A Textbook of Cardiovascular Medicine. 10th ed. Philadelphia: WB Saunders Co; 2015. p. 792–7.

[19] Waller BF, Gering LE, Branyas NA, Slack JD. Anatomy, histology, and pathology of the cardiac conduction system. Part V. Clin Cardiol 1993;16:565–9.

[20] Kaneshige T, Machida N, Yamamoto S, Nakao S, Yamane Y. A histological study of the cardiac conduction system in canine cases of mitral valve endocardiosis with complete atrioventricular block. J Comp Pathol 2007;136:120–6.

[21] Liu SK, Tilley LP, Tashijan RJ. Lesions of the conduction system in the cat with cardiomyopathy. Recent Adv Stud Cardiac Struct Metab 1975;10:681–93.

[22] Church WM, Sisson DD, Oyama MA, Zachary JF. Third degree atrioventricular block and sudden death secondary to acute myocarditis in a dog. J Vet Cardiol 2007;9:53–7.

[23] Atwell RB, Sutton RH. Focal lymphocytic non-suppurative myocarditis and 3 degrees heart block in a 2-year-old dog. Aust Vet J 1990;67:265.

[24] Sykes JE, Kittleson MD, Chomel BB, MacDonald KA, Pesavento PA. Clinicopathologic findings and outcome in dogs with infective endocarditis: 71 cases (1992–2005). J Am Vet Med Assoc 2006;228:1735–47.

[25] Hackett TB, Van Pelt DR, Willard MD, Martin LG, Shelton GD, Wingfield WE. Third degree atrioventricular block and acquired myasthenia gravis in four dogs. J Am Vet Med Assoc 1995;206:1173–6.

[26] Malik R, Zunino P, Hunt GB. Complete heart block associated with lupus in a dog. Aust Vet J 2003;81:398–401.

[27] Gallay J, Belanger MC, Helie P, Coté E, Johnson TO, Peters ME. Cardiac leiomyoma associated with advanced atrioventricular block in a young dog. J Vet Cardiol 2011;13:71–7.

[28] Stern JA, Tobias JR, Keene BW. Complete atrioventricular block secondary to cardiac lymphoma in a dog. J Vet Cardiol 2012;14:537–9.

[29] Abbott JA, King RR. Third degree atrioventricular block following non-penetrating chest trauma in a dog. J Small Anim Pract 1993;34:377—80.

[30] Kaneshige T, Machida N, Nakao S, Doiguchi O, Katsuda S, Yamane Y. Complete atrioventricular block associated with lymphocytic myocarditis of the atrioventricular node in two young adult dogs. J Comp Pathol 2007;137:146—50.

[31] James TN, Robertson BT, Waldo AL, Branch CE. De subitaneis mortibus. XV. Hereditary stenosis of the His bundle in Pug dogs. Circulation 1975;52:1152—60.

[32] Wang JN, Tsai YC, Lee WL, Lin CS, Wu JM. Complete atrioventricular block following myocarditis in children. Pediatr Cardiol 2002;23:518—21.

[33] Batra AS, Epstein D, Silka MJ. The clinical course of acquired complete heart block in children with acute myocarditis. Pediatr Cardiol 2003;24:495—7.

[34] Morimoto S, Kato S, Hiramitsu S, Uemura A, Ohtsuki M, Kato Y, Sugiura A, Miyagishima K, Yoshida Y, Hishida H. Role of myocardial interstitial edema in conduction disturbances in acute myocarditis. Heart Vessels 2006;21:356—60.

[35] Santilli RA, Porteiro Vázquez DM, Vezzosi T, Perego M. Long-term intrinsic rhythm evaluation in dogs with atrioventricular block. J Vet Intern Med 2016;30:58—62.

[36] Kishimoto C, Matsumori A, Ohmae M, Tomioka N, Kawai C. Electrocardiographic findings in experimental myocarditis in DBA/2 mice: complete atrioventricular block in the acute stage, low voltage of the QRS complex in the subacute stage and arrhythmias in the chronic stage. J Am Coll Cardiol 1984;3:1461—8.

[37] Mahoney LT, Marvin Jr WJ, Atkins DL, Clark EB, Lauer RM. Pacemaker management for acute onset of heart block in childhood. J Pediatr 1985;107:207—11.

[38] Uemura A, Morimoto S, Hiramitsu S, Hishida H. Endomyocardial biopsy findings in 50 patients with idiopathic atrioventricular block: presence of myocarditis. Jpn Heart J 2001;42:691—700.

[39] Santilli RA, Grego E, Battaia S, Gianella P, Tursi M, Di Girolamo N, Biasato I, Perego M. Prevalence of infectious cardiotropic pathogens in the myocardium of adult dogs with unexplained myocardial and rhythm disorders. J Am Vet Med Assoc 2019 (in press).

[40] Wiedemann N, Hildebrandt N, Wurtinger G, Henrich E, Hassdenteufel E, Schneider M. Follow-up of troponin I concentration in dogs with atrioventricular block and dual-chamber pacing in a case-matched study. J Vet Cardiol 2017;19:247—55.

[41] Trafny DJ, Oyama MA, Wormser C, Reynolds CA, Singletary GE, Peddle GD. Cardiac troponin-I concentrations in dogs with bradyarrhythmias before and after artificial pacing. J Vet Cardiol 2010;12:183—90.

[42] Kindermann I, Barth C, Mahfoud F, Ukena C, Lenski M, Yilmaz A, Klingel K, Kandolf R, Sechtem U, Cooper LT, Böhm M. Update on myocarditis. J Am Coll Cardiol 2012;59:779—92.

[43] Smith SC, Ladenson JH, Mason JW, Jaffe AS. Elevations of cardiac troponin I associated with myocarditis. Experimental and clinical correlates. Circulation 1997;95:163—8.

[44] Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined-a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol 2000;36:959—69.

[45] Oxford EM, Giacomazzi FB, Moïse NS, Santilli RA. Clinical and electrocardiographic presentations of transient trifascicular block in three cats. J Vet Cardiol 2018;20:204—12.

[46] Joseph JL, Oxford EM, Santilli RA. Transient myocardial thickening in a Bartonella henselae-positive cat. J Vet Cardiol 2018;20:198—203.

[47] Simpson KE, Devine BC, Gunn-Moore D. Suspected toxoplasma-associated myocarditis in a cat. J Feline Med Surg 2005;7:203—8.

[48] Varanat M, Broadhurst J, Linder KE, Maggi RG, Breitschwerdt EB. Identification of Bartonella henselae in 2 cats with pyogranulomatous myocarditis and diaphragmatic myositis. Vet Pathol 2012;49:608—11.

[49] Matsuu A, Kanda T, Sugiyama A, Murase T, Hikasa Y. Mitral stenosis with bacterial myocarditis in a cat. J Vet Med Sci 2007;69:1171—4.

[50] Kellum HB, Stepien RL. Third-degree atrioventricular block in 21 cats (1997—2004). J Vet Intern Med 2006;20:97—103.

[51] Kaneshige T, Machida N, Itoh H, Yamane Y. The anatomical basis of complete atrioventricular block in cats with hypertrophic cardiomyopathy. J Comp Pathol 2006;135:25—31.

[52] Bharati S, McAnulty JH, Lev M, Rahimtoola SH. Idiopathic hypertrophic subaortic stenosis with split His bundle potentials. Electrophysiologic and pathologic correlations. Circulation 1980;62:1373—80.

[53] Johansson BW. Portable ECG tape recorder in clinical practice. Lakartidningen 1976;73:1423—7.

[54] Nakao S, Hirakawa A, Fukushima R, Kobayashi M, Machida N. The anatomical basis of bradycardia-tachycardia syndrome in elderly dogs with chronic degenerative valvular disease. J Comp Pathol 2012;146:175—82.

[55] Alpert MA, Flaker GC. Arrhythmias associated with sinus node dysfunction. Pathogenesis, recognition, and management. JAMA 1983;250:2160—6.

[56] Jordan JL, Yamaguchi I, Mandel WJ. Studies on the mechanism of sinus node dysfunction in the sick sinus syndrome. Circulation 1978;57:217—23.

[57] Bharati S. Anatomy of the atrioventricular conduction system. Circulation 2001;103:63—4.

[58] Kaplan BM, Langendorf R, Lev M, Pick A. Tachycardia-bradycardia syndrome (so-called "sick sinus syndrome"). Pathology, mechanisms and treatment. Am J Cardiol 1973;31:497—508.

[59] Kulbertus HE, De Leval-Rutten F, Demoulin JC. Sino-atrial disease: a report on 13 cases. J Electrocardiol 1973;6:303—12.

[60] Thery C, Gosselin B, Lekieffre J, Warembourg H. Pathology of sinoatrial node. Correlations with electrocardiographic findings in 111 patients. Am Heart J 1977;93:735—40.

[61] Sugiura M, Ohkawa S. A clinicopathologic study on sick sinus syndrome with histological approach to the sinoatrial node. Jpn Circ J 1980;44:497—504.

[62] Benson DW, Wang DW, Dyment M, Knilans TK, Fish FA, Strieper MJ, Rhodes TH, George Jr AL. Congenital sick sinus syndrome caused by recessive mutations in the cardiac sodium channel gene (SCN5A). J Clin Invest 2003;112:1019—28.

[63] Ward JL, DeFrancesco TC, Tou SP, Atkins CE, Griffith EH, Keene BW. Outcome and survival in canine sick sinus syndrome and sinus node dysfunction: 93 cases (2002—2014). J Vet Cardiol 2016;18:199—212.

[64] Moneva-Jordan A, Corcoran BM, French A, Dukes-McEwan J, Martin MW, Luis Fuentes V, Hitchcock LS,

Bonagura JD. Sick sinus syndrome in nine West Highland white terriers. Vet Rec 2001;148:142—7.

[65] Burrage H. Sick sinus syndrome in a dog: treatment with dual-chambered pacemaker implantation. Can Vet J 2012;53:565—8.

[66] Hamlin RL, Smetzer DL, Breznock EM. Sinoatrial syncope in miniature Schnauzers. J Am Vet Med Assoc 1972;161: 1022—8.

[67] European Society of Cardiology (ESC), European Heart Rhythm Association (EHRA), Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliot PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task forceon cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Europace 2013;15:1070—118.

[68] Tanaka H, Atsuchi Y, Tanaka N, Nishi S, Kanehisa T. Persistent atrial standstill due to atrial inexcitability. An electrophysiological and histological study. Jpn Heart J 1975;16:639—53.

[69] Fonfara S, Loureiro JF, Swift S, James RA, Pereira YM, Lopez-Alvarez J, Summerfield N, Dukes-McEwan J. English springer spaniels with significant bradyarrhythmias — presentation, troponin I and follow-up after pacemaker implantation. J Small Anim Pract 2010;51:155—61.

[70] Allensworth DC, Rice GJ, Lowe GW. Persistent atrial standstill in a family with myocardial disease. Am J Med 1969;47:775—84.

[71] Schmitt KE, Lefbom BK. Long-term management of atrial myopathy in two dogs with single chamber permanent transvenous pacemakers. J Vet Cardiol 2016;18: 187—93.

[72] Bomassi E, Rousselot J, Libermann S, Raymond Letron I, Etchepareborde S, Misbach C. Atrial cardiomyopathy in an adult laborador retriever dog. Schweiz Arch Tierheilkd 2017;159:594—9.

[73] Nakamura RK, Russell NJ, Shelton GD. Adult-onset nemaline myopathy in a dog presenting with persistent atrial standstill and primary hypothyroidism. J Small Anim Pract 2012;53:357—60.

[74] Cervenec RM, Stauthammer CD, Fine DM, Kellihan HB, Scansen BA. Survival time with pacemaker implantation for dogs diagnosed with persistent atrial standstill. J Vet Cardiol 2017;19:240—6.

[75] Thomanson JD, Kraus MS, Fallw TL, Calvert CA. Survival of 4 dogs with persistent atrial standstill treated by pacemaker implantation. Can Vet J 2016;57:297—8.

[76] Bloomfield DA, Sinclair-Smith BC. Persistent atrial standstill. Am J Med 1965;39:335—40.

[77] Woolliscroft J, Tuna N. Permanent atrial standstill: the clinical spectrum. Am J Cardiol 1982;49:2037—41.

[78] Bensaid J, Vallat JM, Amsallem D, Bernard Y, Rauscher M, Borsotti JP. Total permanent auricular paralysis. Review of the literature apropos of 109 cases. Ann Cardiol Angeiol 1995;44:139—45.

[79] Talwar KK, Dev V, Chopra P, Dave TH, Radhakrishnan S. Persistent atrial standstill — clinical, electrophysiological, and morphological study. Pacing Clin Electrophysiol 1991;14:1274—80.

[80] Jeraj K, Ogburn PN, Edwards WD, Edwards JE. Atrial standstill, myocarditis and destruction of cardiac conduction system: clinicopathologic correlation in a dog. Am Heart J 1980;99:185—92.

[81] Robinson WF, Thompson RR, Clark WT. Sinoatrial arrest associated with primary atrial myocarditis in a dog. J Small Anim Pract 1981;22:99—107.

[82] Wesselowski S, Abbot J, Borgarelli M, Tursi M. Presumptive partial atrial standstill secondary to atrial cardiomyopathy in a Greyhound. J Vet Cardiol 2017;19: 276—82.

[83] Rosen KM, Loeb HS, Sinno MZ, Rahimtoola SH, Gunnar RM. Cardiac conduction in patients with symptomatic sinus node disease. Circulation 1971;43:836—44.

[84] Demiralp E, Kirilmaz A, Cebeci BS, Ulusoy RE. Partial atrial standstill: a case report. J Electrocardiol 2005;38: 252—5.

[85] Ross AM, Proper MC, Aronson AL. Sinoventricular conduction in atrial standstill. J Electrocardiol 1976;9: 161—4.

[86] Pariaut R, Oxford EM, Santilli RA. ECG of the month. J Am Vet Med Assoc 2018;252:1350—3.

[87] Gavaghan BJ, Kittleson MD, McAloose D. Persistent atrial standstill in a cat. Aust Vet J 1999;77:574—9.

[88] Nakazato Y, Nakata Y, Hisaoka T, Sumiyoshi M, Ogura S, Yamaguchi H. Clinical and electrophysiological characteristics of atrial standstill. Pacing Clin Electrophysiol 1995;18:1244—54.

[89] MacDonald K. Dvm360com. Get with the beat! Analyzing and treating cardiac arrhythmias. In: Proceedings CVC; August, 1, 2011. Kansas City.

[90] Puppala VK, Dickinson O, Benditt DG. Syncope: classification and risk stratification. J Cardiol 2014;63:171—7.

[91] Van Dijk JG, Sheldon R. Is there any point to vasovagal syncope? Clin Auton Res 2008;18:167—9.

[92] Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A, Fedorowski A, Furlan R, Kenny RA, Martın A, Probst V, Reed MJ, Rice CP, Sutton R, Ungar A, van Dijk JG. The task force for the diagnosis and management of syncope of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) Endorsed by: European Academy of Neurology (EAN), European Federation of Autonomic Societies (EFAS), European Federation of Internal Medicine (EFIM), European Union Geriatric Medicine Society (EUGMS), European Society of Emergency Medicine (EuSEM). Eur Heart J 2018;39:1883—948.

[93] Fukushima R, Areie T, Itou N, Kawaguchi T, Yamada S, Yoshimura A, Goya S, Shimada K, Uchide T, Kishimoto M, Machida N. Canine case of swallowing syncope that improved after pacemaker implantation. Can Vet J 2018; 80:460—4.

[94] Davies JA, Snead ECR, Pharr JW. Tussive syncope in a pug with lung-lobe torsion. Can Vet J 2011;52:656—60.

[95] Grubb BP, Wolfe DA, Nelson LA, Hennessy JR. Malignant vasovagally mediated hypotension and bradycardia: a possible cause of sudden death in young patient with asthma. Pediatrics 1992;90:983—6.

[96] Sousa PA, Candeias R, Marques N, Jesus I. Reflex vasovagal syncope is there a benefit in pacemaker therapy? Rev Port Cardiol 2014;33:297—303.

[97] Connolly SJ, Sheldon R, Roberts RS, Gent M. The North American Vasovagal Pacemaker Study (VPS). A randomized trial of permanent cardiac pacing for the prevention of vasovagal syncope. J Am Coll Cardiol 1999;33:16—20.

[98] Fox PR, Harpster NK. Diagnosis and management of feline arrhythmias. In: Fox PR, Sisson D, Moise NS, editors. Textbook of Canine and Feline Cardiology. Philadelphia: WB Saunders; 1988. p. 375—99.

[99] Naito M, Dreifus LS, David D, Michelson EL, Mardelli TJ, Kmetzo JJ. Reevaluation of the role of atrial systole to

cardiac hemodynamics: evidence for pulmonary venous regurgitation during abnormal atrioventricular sequencing. Am Heart J 1983;105:295—302.

[100] Miller MS, Tilley LP, Smith F, Fox PR. Electrocardiography. In: Fox PR, Sisson D, Moise NS, editors. Textbook of Canine and Feline Cardiology. 2nd ed. Philadelphia: W. B. Saunders; 1999. p. 375.

[101] Dutton E, Dukes-McEwan J, Cripps PJ. Serum cardiac troponin I in canine syncope and seizures. J Vet Cardiol 2017;19:1—13.

[102] Alboni P. The different clinical presentations of vasovagal syncope. Heart 2015;101:674—8.

[103] Accurso V, Winnicki M, Shamsuzzaman AS, Wenzel A, Johnson AK, Somers VK. Predisposition to vasovagal syncope in subjects with blood/injury phobia. Circulation 2001;104:903—7.

[104] Brignole M, Menozzi C, Gianfranchi L, Oddone D, Lolli G, Bertulla A. Neurally mediated syncope detected by carotid sinus massage and head-up tilt test in sick sinus syndrome. Am J Cardiol 1991;68:1032—6.

[105] Stryjewski PJ, Kuczaj A, Badacz L, Opara M, Nowalany-Kozielska E, Nowak J, Nessler J. Signification of NT-proBNP in the differential diagnosis of syncope in adults. Przegl Lek 2014;71:249—53.

[106] Santilli RA, Perego M. Heart rhythm characterization during unexplained episodes of transient loss of consciousness in 55 dogs. J Vet Intern Med 2010;1:157.

[107] Porteiro Porteiro Vazquez DM, Perego M, Santos Luis, Gerou-Ferriani M, Martin MWS, Santilli RA. Paroxysmal atrial fibrillation in seven dogs with presumed neurally-mediated syncope. J Vet Cardiol 2016;18:1—9.

[108] Brignole M. Different electrocardiographic manifestations of the cardioinhibitory vasovagal reflex. Europace 2009; 11:144—6.

[109] Locati ET, Vecchi AM, Vargiu S, Cattafi G, Lunati M. Role of extended external loop recorders for the diagnosis of unexplained syncope, pre-syncope, and sustained palpitations. Europace 2014;16:914—22.

[110] Bulmer BJ. VDD pacing in dogs: when, why and how to perform single-lead atrial synchronous, ventricular inhibited (VDD) pacing. J Vet Cardiol 2006;8:25—39.

[111] Rasmussen CE, Falk T, Domanjko Petrič A, Schaldemose M, Zois NE, Moesgaard SG, Ablad B, Nilsen HY, Ljungvall I, Höglund K, Häggström J, Pedersen HD, Bland JM, Olsen LH. Holter monitoring of small breed dogs with advanced myxomatous mitral valve disease with and without a history of syncope. J Vet Intern Med 2014;28:363—70.

[112] Goodwin JK. Holter monitoring and cardiac event recording. Vet Clin North Am Small Anim Pract 1998;28: 1391—407.

[113] Miller RH, Lehmkuhl LB, Bonagura JD, Beall MJ. Retrospective analysis of the clinical utility of ambulatory electrocardiography (Holter) recordings in syncopal dogs: 44 cases (1991—1995). J Vet Intern Med 1999;13: 111—22.

[114] Bright JM, Cali JV. Clinical usefulness of cardiac event recording in dogs and cats examined because of syncope, episodic collapse, or intermittent weakness: 60 cases (1997—1999). J Am Vet Med Assoc 2000;216: 1110—4.

[115] Santilli RA, Ferasin L, Voghera SG, Perego M. Evaluation of the diagnostic value of an implantable loop recorder in dogs with unexplained syncope. J Am Vet Med Assoc 2010; 236:78—82.

[116] Sanders R, Olivier NB. Novel cutaneous use of implantable loop recorders in two dogs with unexplained episodes of collapse. J Am Anim Hosp Assoc 2012;48:269—72.

[117] MacKie BA, Stepien RL, Kellihan HB. Retrospective analysis of an implantable loop recorder for evaluation of syncope, collapse, or intermittent weakness in 23 dogs (2004—2008). J Vet Cardiol 2010;12:25—33.

[118] James R, Summerfield N, Loureiro J, Swift S, Dukes-McEwan J. Implantable loop recorders: a viable diagnostic tool in veterinary medicine. J Small Anim Pract 2008;49:564—70.

[119] Willis R, McLeod K, Cusack J, Wotton P. Use of an implantable loop recorder to investigate syncope in a cat. J Small Anim Pract 2003;44:181—3.

[120] Crosara S, Borgarelli M, Perego M, Haggstrom J, La Rosa G, Tarducci A, Santilli RA. Holter monitoring in 36 dogs with myxomatous mitral valve disease. Aust Vet J 2010;88:386—92.

[121] Saunders AB, Gordon SG, Rector MH, DeMaster A, Jackson N, Clubb FJ, Fosgate GT, Miller MW. Bradyarrhythmias and pacemaker therapy in dogs with Chagas disease. J Vet Intern Med 2013;27:890—4.

[122] Staessen J, Ector H, De Geest H. The underlying heart rhythm in patients with an artificial cardiac pacemaker. Pacing Clin Electrophysiol 1982;5:801—7.

[123] Bonagura JD, Helphrey ML, Muir WW. Complications associated with permanent pacemaker implantation in the dog. J Am Vet Med Assoc 1983;182:149—55.

[124] Ward JL, DeFrancesco TC, Tou SP, Atkins CE, Griffith EH, Keene BW. Complication rates associated with transvenous pacemaker implantation in dogs with high-grade atrioventricular block performed during versus after normal business hours. J Vet Intern Med 2015;29:157—63.

[125] Andersen HR, Pless P. Trans-oesophageal dual-chamber pacing. Int J Cardiol 1984;5:745—8.

[126] Lamas GA, Orav EJ, Stambler BS, Ellenbogen KA, Sgarbossa EB, Huang SK, Marinchak RA, Estes 3rd NA, Mitchell GF, Lieberman EH, Mangione CM, Goldman L. Quality of life and clinical outcomes in elderly patients treated with ventricular pacing as compared with dual-chamber pacing. Pacemaker Selection in the Elderly Investigators. N Engl J Med 1998;338:1097—104.

[127] Toff WD, Camm AJ, Skehan JD, United Kingdom Pacing and Cardiovascular Events Trial Investigators. Single-chamber versus dual-chamber pacing for high-grade atrioventricular block. N Engl J Med 2005;353:145—55.

[128] Castelnuovo E, Stein K, Pitt M, Garside R, Payne E. The effectiveness and cost-effectiveness of dual-chamber pacemakers compared with single-chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome: systematic review and economic evaluation. Health Technol Assess 2005;9:1—246.

[129] Nielsen JC, Thomsen PE, Højberg S, Møller M, Vesterlund T, Dalsgaard D, Mortensen LS, Nielsen T, Asklund M, Friis EV, Christensen PD, Simonsen EH, Eriksen UH, Jensen GV, Svendsen JH, Toff WD, Healey JS, Andersen HR, DANPACE Investigators. A comparison of single-lead atrial pacing with dual-chamber pacing in sick sinus syndrome. Eur Heart J 2011;32:686—96.

[130] Estrada AH, Pariaut R, Hemsley S, Gatson BH, Moïse NS. Atrial-based pacing for sinus node dysfunction in dogs: initial results. J Vet Intern Med 2012;26:558—64.

[131] Vallin H, Edhag O. Associated conduction disturbances in patients with symptomatic sinus node disease. Acta Med Scand 1981;210:263—70.

[132] Tripp IG, Armstrong GP, Stewart JT, Hood MA, Smith WM. Atrial pacing should be used more frequently in sinus node disease. Pacing Clin Electrophysiol 2005;28:291—4.

[133] Nielsen JC, Kristensen L, Andersen HR, Mortensen PT, Pedersen OL, Pedersen AK. A randomized comparison of atrial and dual-chamber pacing in 177 consecutive patients with sick sinus syndrome: echocardiographic and clinical outcome. J Am Coll Cardiol 2003;42:614—23.

[134] Sweeney MO. Minimizing right ventricular pacing: a new paradigm for cardiac pacing in sinus node dysfunction. Am Heart J 2007;153:34—43.

[135] Wilkoff BL, Cook JR, Epstein AE, Greene HL, Hallstrom AP, Hsia H, Kutalek SP, Sharma A, Dual Chamber and VVI Implantable Defibrillator Trial Investigators. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial. JAMA 2002;288: 3115—23.

[136] Ferasin L, Faena M, Henderson SM, Langford K, Darke PG. Use of a multi-stage exercise test to assess the responsiveness of rate-adaptive pacemakers in dogs. J Small Anim Pract 2005;46:115—20.

[137] Gwinn N, Leman R, Kratz J, White JK, Zile MR, Gillette P. Chronotropic incompetence: a common and progressive finding in pacemaker patients. Am Heart J 1992;123: 1216—9.

[138] Bulmer BJ, Sisson DD, Oyama MA, Solter PF, Grimm KA, Lamont L. Physiologic VDD versus nonphysiologic VVI pacing in canine 3rd-degree atrioventricular block. J Vet Intern Med 2006;20:257—71.

[139] Shapland JE, MacCarter D, Tockman B, Knudson M. Physiologic benefits of rate responsiveness. Pacing Clin Electrophysiol 1983;6:329—32.

[140] Karlof I. Haemodynamic effect of atrial triggered versus fixed rate pacing at rest and during exercise in complete heart block. Acta Med Scand 1975;197:195—206.

[141] Masuyama T, Kodama K, Uematsu M, Nanto S, Taniura K, Kitabatake A, Inoue M. Beneficial effects of atrioventricular sequential pacing on cardiac output and left ventricular filling assessed with pulsed Doppler echocardiography. Jpn Circ J 1986;50:799—807.

[142] Greenberg B, Chatterjee K, Parmley WW, Werner JA, Holly AN. The influence of left ventricular filling pressure on atrial contribution to cardiac output. Am Heart J 1979; 98:742—51.

[143] Genovese DW, Estrada AH, Maisenbacher HW, Heatwole BA, Powell MA. Procedure times, complication rates, and survival times associated with single-chamber versus dual-chamber pacemaker implantation in dogs with clinical signs of bradyarrhythmia: 54 cases (2004—2009). J Am Vet Med Assoc 2013;242:230—6.

[144] Lamas GA, Knight JD, Sweeney MO, Mianulli M, Jorapur V, Khalighi K, Cook JR, Silverman R, Rosenthal L, Clapp-Channing N, Lee KL, Mark DB. Impact of rate-modulated pacing on quality of life and exercise capacity — evidence from the advanced elements of pacing randomized controlled trial (ADEPT). Heart Rhythm 2007;4:1125—32.

[145] Toff WD, Skehan JD, De Bono DP, Camm AJ. The United Kingdom pacing and cardiovascular events (UKPACE) trial. United Kingdom pacing and cardiovascular events. Heart 1997;78:221—3.

[146] Ellenbogen KA, Gilligan DM, Wood MA, Morillo C, Barold SS. The pacemaker syndrome — a matter of definition. Am J Cardiol 1997;79:1226—9.

[147] Heldman D, Mulvihill D, Nguyen H, Messenger JC, Rylaarsdam A, Evans K, Castellanet MJ. True incidence of pacemaker syndrome. Pacing Clin Electrophysiol 1990;13: 1742—50.

[148] Kruse I, Arnman K, Conradson TB, Rydén L. A comparison of the acute and long-term hemodynamic effects of ventricular inhibited and atrial synchronous ventricular inhibited pacing. Circulation 1982;65:846—55.

[149] Rediker DE, Eagle KA, Homma S, Gillam LD, Harthorne JW. Clinical and hemodynamic comparison of VVI versus DDD pacing in patients with DDD pacemakers. Am J Cardiol 1988;61:323—9.

[150] Sulke N, Chambers J, Dritsas A, Sowton E. A randomized double-blind crossover comparison of four rate-responsive pacing modes. J Am Coll Cardiol 1991;17: 696—706.

[151] Menozzi C, Brignole M, Moracchini PV, Lolli G, Bacchi M, Tesorieri MC, Tosoni GD, Bollini R. Intra-patient comparison between chronic VVIR and DDD pacing in patients affected by high degree AV block without heart failure. Pacing Clin Electrophysiol 1990; 13:1816—22.

[152] Lau CP, Butrous GS, Ward DE, Camm AJ. Comparison of exercise performance of six rate-adaptive right ventricular cardiac pacemakers. Am J Cardiol 1989;63: 833—8.

[153] Nishimura RA, Gersh BJ, Vlietstra RE, Osborn MJ, Ilstrup DM, Holmes Jr DR. Hemodynamic and symptomatic consequences of ventricular pacing. Pacing Clin Electrophysiol 1982;5:903—10.

[154] Perrins EJ, Morley CA, Chan SL, Sutton R. Randomised controlled trial of physiological and ventricular pacing. Br Heart J 1983;50:112—7.

[155] Linde-Edelstam C, Nordlander R, Undén AL, Orth-Gomér K, Rydén L. Quality-of-life in patients treated with atrioventricular synchronous pacing compared to rate modulated ventricular pacing: a long-term, double-blind, crossover study. Pacing Clin Electrophysiol 1992;15: 1467—76.

[156] Lukl J, Doupal V, Heinc P. Quality-of-life during DDD and dual sensor VVIR pacing. Pacing Clin Electrophysiol 1994; 17:1844—8.

[157] Estrada AH, Maisenbacher 3rd HW, Prosek R, Schold J, Powell M, VanGilder JM. Evaluation of pacing site in dogs with naturally occurring complete heart block. J Vet Cardiol 2009;11:79—88.

[158] Maisenbacher HW, Estrada AH, Prosek R, Shih AC, Vangilder JM. Evaluation of the effects of transvenous pacing site on left ventricular function and synchrony in healthy anesthetized dogs. Am J Vet Res 2009;70: 455—63.

[159] Cojoc A, Reeves JG, Schmarkey L, Strieper MJ, Joyner RW, Wagner MB, Campbell RM, Vinten-Johansen J, Frias PA. Effects of single-site versus biventricular epicardial pacing on myocardial performance in an immature animal model of atrioventricular block. J Cardiovasc Electrophysiol 2006;17:884—9.

[160] Blendea D, Singh JP. Lead positioning strategies to enhance response to cardiac resynchronization therapy. Heart Fail Rev 2011;16:291—303.

[161] Weder C, Monnet E, Ames M, Bright J. Permanent dual chamber epicardial pacemaker implantation in two dogs with complete atrioventricular block. J Vet Cardiol 2015; 17:154—60.

[162] Fox PR, Moise NS, Woodfield JA, Darke PG. Techniques and complications of pacemaker implantation in four cats. J Am Vet Med Assoc 1991;199:1742—53.

[163] Coté E, Laste NJ. Transvenous cardiac pacing. Clin Tech Small Anim Pract 2000;15:165—76.

[164] DeFrancesco TC, Hansen BD, Atkins CE, Sidley JA, Keene BW. Noninvasive transthoracic temporary cardiac pacing in dogs. J Vet Intern Med 2003;17:663—7.

[165] Noomanova N, Perego M, Perina A, Santilli RA. Use of transcutaneous external pacing during transvenous implantation in dogs. Vet Rec 2010;167:241—4.

Available online at www.sciencedirect.com

ScienceDirect