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Artificial cardiac pacemaker placement in dogs with a cohort of myocarditis suspects and association of ultrasensitive cardiac troponin I with survival☆

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Abstract *Introduction:* Artificial cardiac pacemakers (APs) are a common treatment for symptomatic bradyarrhythmias in dogs, some of which may be triggered by underlying myocarditis. Severely elevated cardiac troponin I (cTnI) concentrations support a diagnosis of myocarditis. The association of ultrasensitive-cTnI (US-cTnI) concentration with survival in a large cohort of dogs receiving APs is not described.
Animals, materials, and methods: The study included 110 dogs receiving APs over a 5-year period. Medical records were retrospectively reviewed to characterize the entire population receiving APs, with further analysis in dogs with preprocedural US-cTnI concentrations (n = 64) classified as normal/group 1 (n = 11), mildly to moderately elevated/group 2 (n = 27), and severely elevated/myocarditis suspects/group 3 (n = 26).
Results: Median survival time was 1079 days for the entire population, 1167 days for group 2, 949 days for group 3, and not met in group 1. There was not a statistically

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significant difference in survival between group 2 and group 3. Overall, US-cTnI had a mild, negative association with survival. Age had a stronger negative association. Infectious etiologies were identified in a minority of group 3 cases. A possible association between severely elevated US-cTnI and a sudden death outcome was noted. *Conclusions:* The negative association of US-cTnI with survival outcomes was mild, with age having a larger effect. Although a sudden death outcome may be seen more commonly in myocarditis suspects, group 3 survival time was similar to that of the entire canine population. Plausible infectious causes of myocarditis were infrequently identified.

Abbreviations

3AVB	third-degree atrioventricular block
APs	artificial cardiac pacemakers
AV	atrioventricular
CHF	congestive heart failure
CI	confidence interval
cTnI	cardiac troponin I
DCM	dilated cardiomyopathy
HR	hazard ratio
IFA	indirect fluorescent antibody
LVIDsN	normalized left ventricular internal diameter at end systole
MMVD	myxomatous mitral valve disease
MST	median survival time
US-cTnI	ultrasensitive cardiac troponin I

Introduction

The use of artificial cardiac pacemakers (APs) to treat symptomatic bradyarrhythmias in veterinary medicine is commonplace. Third-degree atrioventricular block (3AVB) is the most frequently encountered bradyarrhythmia prompting pacemaker implantation in the dog [1—3]. The underlying lesion leading to 3AVB in dogs is most often believed to be non-specific fibrosis or fibrofatty replacement of the atrioventricular (AV) conduction system [4,5].

Although less frequently reported, 3AVB can also arise in dogs with inflammatory lesions affecting the AV conduction system associated with myocarditis. Definitive diagnosis of the causative etiologies of acute myocarditis in dogs is often elusive, as noted in multiple case reports with histopathologic confirmation of lymphocytic myocarditis affecting the cardiac conduction system [6—10]. One confirmed etiology leading to myocarditis and AV block in dogs in the southern United States is Chagas disease, or trypanosomiasis [11]. An association between dogs with positive *Bartonella* titers, symptomatic AV block, and elevated cardiac troponin I (cTnI) levels in a small cohort of dogs has also been reported, although a cause-and-effect relationship between these factors remains unestablished [12].

Gold standard diagnosis for myocarditis in humans involves endomyocardial biopsy [13—15]. While endomyocardial biopsies are seldom performed in veterinary patients, cTnI is a sensitive and specific marker of myocardial injury that supports the diagnosis of myocarditis in both humans [15,16] and dogs [6,12,17,18]. Elevated cTnI levels in humans with biopsy-proven myocarditis have a high specificity and high positive predictive value for the diagnosis of myocarditis, but sensitivity remains low [16]. A lack of sensitivity likely correlates with sample timing, as most myocyte injury and necrosis occur within the first month of the disease, after which cTnI utility may decline [16].

Across a variety of cardiac diseases, cTnI concentrations above 1 ng/mL have been associated with a poorer prognosis and shorter survival time in dogs [19]. In people, increased cTnI concentrations provide strong prognostic information in acute coronary syndromes and other forms of cardiovascular disease, with noted exceptions in pericarditis, myopericarditis, and Takutsubo cardiomyopathy [20—23]. Previous large-scale reviews of APs in veterinary medicine have not investigated the prognostic significance of preprocedural cTnI or commented on a possible subpopulation presenting with myocarditis [1,2]. Only dogs with positive titers for Chagas disease and presumed chagasic myocarditis requiring APs have been specifically studied [11].

In addition to screening for Chagas disease, we frequently assess cTnI concentrations in dogs presenting for APs placement, in an attempt to identify dogs that may have myocarditis as an underlying cause for their bradyarrhythmias. The

objective of this study was to analyze the baseline characteristics, complications, and survival of a large cohort of dogs receiving APs in a region perceived to have a relatively high caseload of myocarditis suspects (based on historical experience at the authors' institution), with an exploratory analysis of the subset in which cTnI was assessed to determine whether the preprocedural cTnI level was associated with survival.

Animals, materials and methods

A search of the Texas A&M University Veterinary Medical Teaching Hospital's veterinary medical information system identified 110 dogs that received APs between June 2012 and June 2017. Records were retrospectively reviewed, with the following information recorded as available: body weight, age, sex, ECG diagnosis, presence of concurrent supraventricular or ventricular arrhythmias on 6-lead ECG or contemporaneous ECG monitoring during echocardiography (ventricular arrhythmias were grouped as none, singlet, or complex in cases with ventricular tachycardia, multiform ventricular beats, or ventricular couplets), presence or absence of congestive heart failure (CHF) at presentation, underlying cardiac disease, cTnI concentration, renal values, Chagas indirect fluorescent antibody (IFA) test,[a] other infectious disease testing, method of pacemaker placement (transvenous or epicardial), indication for epicardial pacing, and complications. Survival was assessed at 30 days and 6 months after pacemaker implantation. Additionally, the last date of admission was recorded in each case, and referring veterinarians and/or clients were contacted to determine if the patient was still living and the circumstances of their death if they were not. A last known alive date was determined based on this information. Deaths were stratified as cardiac or non-cardiac based on the available medical records and/or client interview. All sudden deaths were considered to be cardiac deaths.

Early in the studied timespan, the authors' institution transitioned from a standard cTnI assay[b] validated in dogs [24,25] with a lower detection limit of 0.2 ng/mL to an ultrasensitive cTnI assay[c] (US-cTnI) with a lower detection limit of 0.006 ng/mL, also validated in dogs [26]. Owing to a lack of adequate correlation data between the two assays, only samples run on the US-cTnI assay were used for statistical survival analysis. Dogs were categorized into three groups based on their US-cTnI level. The US-cTnI ranges defining these groups were based on previously published data for the assay that was used [26], with group 1 considered normal (US-cTnI $\leq$ 0.128 ng/mL), group 2 encompassing a previously reported US-cTnI range documented in dogs with congenital heart disease and varying severities of preclinical and clinical myxomatous mitral valve disease (MMVD) (0.129—1.405 ng/mL), and group 3 exceeding this range and considered to be myocarditis suspects (>1.405 ng/mL). In all patients, samples were submitted for cTnI analysis and Chagas IFA before APs placement, with results not available until several days postoperatively.

Descriptive statistics are presented throughout the text and tables as median (range). The association of US-cTnI with survival was examined using Kaplan—Meier survival plots and Cox regression. Univariate models using dog age, weight, and US-cTnI were fitted first, with US-cTnI considered as a continuous variable. The process was then repeated with US-cTnI as a categorical variable (divided into groups as described previously). Multivariable models were assessed for improved fit using the likelihood ratio test, and the proportionality assumption was analyzed using Schoenfeld residuals. The logrank test was used to compare survival between different US-cTnI groups.

Results

One hundred and ten dogs received APs during the study period. Descriptive statistics for the age, sex, and weight of the population are presented in Table 1. Most dogs were purebred (n = 100), with a total of 43 different breeds represented and only 10 dogs of mixed breed origin. The most commonly represented breeds included Labrador retriever (n = 8), miniature schnauzer (n = 8), schnauzer (n = 7), cocker spaniel (n = 5), Chihuahua (n = 5), and three each of Boston terrier, Australian shepherd, Pekingese, German shorthaired pointer, and Yorkshire terrier.

The most common indication for pacing was 3AVB in 60 dogs (54.5%), followed by sick sinus syndrome in 25 dogs (22.7%) and high-grade second-degree AV block in 19 dogs (17.2%). Baseline characteristics associated with the various indications for pacing are presented in Table 1.

[a] Canine *Trypanosoma cruzi* indirect fluorescent antibody test, Texas A&M Veterinary Medical Diagnostic Laboratory, College Station, TX, USA.
[b] Immulite 2000; Diagnostic Products Corp. CA, USA.
[c] ADVIA Centaur TnI-Ultra; Siemens Medical Solutions Diagnostics, New York, NY, USA.

Table 1 Baseline characteristics, indication for pacing, and method of pacing in dogs receiving artificial cardiac pacemakers presented as median (range).

Baseline characteristics in dogs receiving artificial cardiac pacemakers					
	n	Weight (kg)	Age (years)	Sex	
				M/N	F/S
All	110	9.7 (2.4–63)	9.4 (0.3–16)	49/40	61/54
Indication for pacing					
• 3AVB	60	17.9 (2.4–63)	9.3 (0.3–16)	29/23	31/27
• HG2AVB	19	9.2 (3.6–35.6)	10 (3.7–15.8)	5/4	14/12
• SSS	25	8.2 (4.3–36.6)	9.8 (3.6–16)	11/11	14/14
• AS	4	13.4 (5.8–30.3)	6.6 (3.1–7.3)	2/2	2/1
• Presumptive vasovagal syncope	1	49	1.3	1/0	–
• Bradycardia + atrial fibrillation	1	37.2	7.2	1/0	–
Method of pacing					
• Transvenous	74	15.9 (2.5–49.4)	9.3 (1.3–16)	32/26	42/37
• Epicardial	36	8.2 (2.4–63)	9.6 (0.3–14.8)	17/14	19/17

3AVB, third-degree atrioventricular block; AS, atrial standstill; F, number of total females (spayed and intact); HG2AVB, high-grade second-degree atrioventricular block; M, number of total males (neutered and intact); N, number of neutered males, SSS, sick sinus syndrome; S, number of spayed females.

At presentation, 11 dogs had active or historically managed CHF requiring furosemide therapy. There were 58 dogs with historical syncopal episodes and one dog with presyncopal episodes. This was the most commonly reported clinical sign. Clients reported exercise intolerance and/or lethargy in 30 dogs and labored breathing related to CHF in five dogs. In 21 dogs, the indication for pacing was discovered incidentally, with no cardiac-related clinical signs reported.

Pre-existing cardiac disease was identified in 72/110 (65.4%) dogs. The spectrum of pre-existing cardiac disease in dogs is presented in Table 2. No cases were categorized as having a dilated cardiomyopathy (DCM) phenotype, although five dogs did have a normalized left ventricular internal diameter at end-systole (LVIDsN) above 1.26 (range: 1.31–1.54) [27], suggesting that systolic dysfunction was present. Fractional shortening remained normal in all five cases, and ejection fraction was also normal in the 4/5 cases in which this measurement was available.

Ventricular arrhythmias were noted in 20/110 (18.1%) dogs and included 12 dogs with complex ventricular arrhythmias, seven with single ventricular premature contractions, and one with an accelerated idioventricular rhythm. Supraventricular arrhythmias were noted in 8/110 (7.3%) dogs and included paroxysms of supraventricular tachycardia in six dogs (five of which had diagnoses of sick sinus syndrome) and atrial fibrillation in two dogs.

Chagas IFA was submitted on 80 dogs. Of dogs that were tested, 71 were negative, seven were positive, and two were seropositive but beneath the level that was considered confirmatory for Chagas disease (1:20) at the authors' institution. Two dogs with a positive IFA did not have

Table 2 Pre-existing cardiac disease in dogs receiving artificial cardiac pacemakers.

Pre-existing cardiac disease	N (%)
None	38 (34.5%)
Single disease	
• Myxomatous mitral valve disease - ACVIM stage B1/B2 (39) - ACVIM stage C/D (4)	43 (39.1%)
• Mild subaortic stenosis	4 (3.6%)
• Bradycardia-related changes*	10 (9.1%)
• Interventricular septal dyskinesia	1 (0.9%)
• Pulmonary hypertension (moderate)	2 (1.8%)
Multiple diseases	
• Myxomatous mitral valve disease + pulmonary hypertension - Borderline/mild pulmonary hypertension (5) - Moderate pulmonary hypertension (4) - Severe pulmonary hypertension (1)	10 (9.1%)
• Severe aortic stenosis + myxomatous mitral valve disease	1 (0.9%)
• Severe pulmonic stenosis + tricuspid valve dysplasia	1 (0.9%)

ACVIM, American College of Veterinary Internal Medicine.
*Global cardiac dilation, often in combination with mild elevations in the aortic outflow velocity.

concurrent cTnI levels. There were 37/110 (33.6%) dogs that had additional infectious disease testing that included various tick serology or screening tests for leptospirosis and histoplasmosis. One dog was seropositive for *Ehrlichia canis* alone, four were seropositive for *Rickettsia rickettsii*, and two were seropositive for both agents, one of which had a positive Chagas IFA as well.

Cardiac troponin I level was tested in 73 dogs. There were 64 dogs tested with the US-cTnI assay. The median US-cTnI concentration was 1.05 ng/mL (range: 0.009–18.093 ng/mL). There were 11 dogs (17%) in group 1, 27 dogs (42%) in group 2, and 26 dogs (41%) in group 3. The median age of dogs in these groups was 5 years, 8 years, and 9 years, respectively. The median US-cTnI of these groups was 0.071 ng/mL, 0.377 ng/mL, and 2.759 ng/mL, respectively. Three dogs from group 3 were positive for Chagas disease, with 22 dogs testing negative and one dog not tested. Pre-existing cardiac disease in group 3 included preclinical MMVD in 12 dogs (two with concurrent mild pulmonary hypertension and one with concurrent moderate pulmonary hypertension), one dog with mild subaortic stenosis, and three dogs with echocardiographic changes attributed to bradycardia (global cardiac dilation, often in combination with mild elevations in transaortic velocity). There were also three dogs in group 3 with an increased LVIDsN (two with preclinical MMVD and one with global cardiac dilation attributed to bradycardia).

There were nine dogs tested with the standard sensitivity cTnI assay that were not used for statistical analysis; however, the cTnI level, summary data, and survival time for these dogs are presented as supplemental data (Supplementary Table 1). The median cTnI in these dogs was 3.44 ng/mL (range: 0.19–23.5 ng/mL). One of the nine dogs was Chagas positive, with a cTnI of 0.19 ng/mL, indicating it was below the limit of detection of the test. Of the remaining eight dogs, seven were seronegative for Chagas disease, and one was not tested.

Renal values were available for 108/110 dogs, with 2/110 dogs having reportedly normal biochemistry profiles the day of presentation at a referring facility that were not available for review. Mild to moderate elevations in blood urea nitrogen were noted in 24 dogs, only five of which had concurrent elevations in creatinine (mild in three cases and moderate in two cases). Of dogs with an US-cTnI included in statistical analysis, one had a mild elevation in both renal values, while 11 had mild elevations in blood urea nitrogen alone and two did not have values available for review.

The method of pacing was transvenous in 74 dogs (67.3%) and epicardial in 36 dogs (32.7%). Two of the 74 transvenous pacemakers were dual chamber systems, and the remaining 72 were single chamber. Weight, age, and sex distribution across the two different pacing methods are presented in Table 1. The indications for epicardial pacemaker placement are presented in Table 3. In most instances, a single issue was documented as the indication; however, in three cases, there were two issues. Overall, the most common indications for epicardial pacing were the presence of prothrombotic comorbidities (61.1%) and the need for a contemporaneous surgical procedure (22.2%) that either required avoidance of the neck (n = 1) or concurrent intra-abdominal or intrathoracic access (n = 7).

Fifteen complications were noted in 13 dogs, with one dog having three complications. These complications are summarized in Table 4. The three most common complications were perforation of the right ventricle (n = 3), infection associated with implanted pacemaker equipment (n = 3), and lead dislodgement (n = 3). In 2/3 dogs with dislodgements, no intervention was required. All three right ventricular perforations occurred in dogs implanted with active fixation transvenous leads. Affected dogs were of various sizes (7.6-kg Lhasa apso, 14.7-kg Australian shepherd, and 36.6-

Table 3 Indication for selecting an epicardial pacemaker rather than a transvenous pacemaker in the dogs of this study.

Indication for epicardial pacemaker in dogs	n (%)
Prothrombotic comorbidity • Protein-losing disease (15) • Hyperadrenocorticism (3) • Immune-mediated disease (2) • Intracardiac spontaneous echocontrast during transthoracic echocardiography (1) • Hepatic disease (1)	22 (61.1%)
Concurrent surgical procedure required • Parathyroidectomy (1) • Liver biopsy (4) • Splenectomy (1) • Lung biopsy (1) • Cystotomy (1)	8 (22.2%)
Small patient size	3 (8.3%)
Immature body size at time of pacemaker placement	2 (5.5%)
Pyoderma	1 (2.8%)
Highly active lifestyle	1 (2.8%)
Concurrent jaw fracture and neck wounds	1 (2.8%)
Undocumented	1 (2.8%)

Table 4 Reported complications in dogs receiving artificial cardiac pacemakers in this study.

Complications	n	Clinical consequence			
		No/minimal therapy required	Second procedure required	Led to owner-elected euthanasia or death	Owner-elected monitoring
Right ventricular perforation	3	—	2	1	—
Infection	3	—	2	1	—
Lead dislodgement					
• Atrial lead only (ventricular lead functioning normally)	1	1	—	—	—
• Transvenous ventricular lead (functioning normally)	1	1	—	—	—
• Epicardial lead (one broken suture)	1	—	1	—	—
Transvenous lead microfracture	1	—	—	—	1
Faulty generator locking pin mechanism	1	—	1	—	—
Poor lead—header interface connection	1	—	1	—	—
Lung laceration during epicardial pacemaker placement	1	—	1	—	—
Seroma	1	1	—	—	—
Postoperative development of SIRS/ARDS	1	—	—	1	—
Total	15	3	8	3	1

ARDS, acute respiratory distress syndrome; SIRS, systemic inflammatory response syndrome.

kg boxer), were not positive for Chagas disease, and were not in CHF at presentation. In 2/3 cases, a substantially elevated cTnI was measured pre-procedurally (3.44 ng/mL in the Lhasa apso and 10.2 ng/mL in the Australian shepherd), potentially suggesting a connection between myocarditis and poor myocardial integrity. The boxer had an US-cTnI of 0.13 ng/mL. In two cases, a second procedure was performed when the perforation was detected (2 and 4 weeks postoperatively) to place an epicardial pacemaker and remove the transvenous system. In the third case, the perforation was detected one day postoperatively, and the owners declined a second procedure and requested euthanasia.

At the 30-day postoperative time point, there was one dog lost to follow-up (1%), six dogs that had died (5%), and 103 dogs alive (94%). Data on the six dogs with early deaths (<30 days) are summarized in Table 5. There was one anesthetic-related death, in which the patient developed respiratory arrest and decompensated after induction with alfaxalone despite appropriate capture with a temporary pacemaker, one postoperative death related to apparent development of systemic inflammatory response syndrome and acute respiratory distress syndrome after epicardial pacemaker placement, and the remaining four cases were considered cardiac deaths. At the 6-month postoperative time point, there were six dogs lost to follow-up (5%), 14 dogs that had died (13%), and 90 dogs alive (82%). Of dogs that had died, seven died or were euthanized because of non-cardiac causes, while seven had cardiac-related deaths. In total, there were seven cases of sudden death within the entire population. Two of these were early deaths that are described in Table 5. In the other five cases, dogs died suddenly at 82 days, 149 days, 385 days, 530 days, and 787 days after pacemaker placement. Chagas status in these dogs was negative, negative, positive, positive, and unknown, respectively. The US-cTnI levels were 1.728 ng/mL, 2.918 ng/mL, unknown, 0.862 ng/mL, and unknown, respectively.

Median survival time (MST) for the entire population was 1079 days. There were 54 dogs with known death dates. Thirty-two had non-cardiac causes of death, 16 had cardiac causes of death, and six dogs had unknown circumstances surrounding their death or euthanasia. For this reason, survival analysis was conducted using all-cause mortality. Univariate analysis revealed that both age and US-cTnI were significantly (and negatively) associated with survival, while weight was not. Age and US-cTnI were retained in the final multivariable model, which showed significantly improved fit to the data (likelihood ratio test $\chi^2 = 24.48$;

Table 5 Summary and survival data of dogs experiencing early (<30 days) cardiac deaths after placement of an artificial cardiac pacemaker.

Dogs experiencing early cardiac deaths	Indication for pacing	Age (years)	Survival time (days)	Died (D) or euthanized (E)	Circumstances of death or euthanasia	Cardiac troponin I (ng/mL)	Chagas status	Concurrent ventricular arrhythmias	Concurrent disease(s)
Dog 1	3AVB	10.9	0	D	Anesthetic-related death	0.2*	Negative	None	Moderate pulmonary hypertension
Dog 2	AS	7.3	2	D	Sudden death at home	1.758*	NA	Complex	Global cardiac enlargement
Dog 3	3AVB	7.5	3	D	Sudden death at home	18.093*	Negative	None	MMVD-B2
Dog 4	SSS	8.1	1	D	In-hospital death associated with SIRS/ARDS	NA	NA	None	Hyperadrenocorticism, Hypothyroidism, MMVD-B1
Dog 5	3AVB	8.3	1	E	Euthanized because of right ventricular perforation	10.2	Negative	None	MMVD-B1
Dog 6	3AVB	7.5	24	E	Euthanized because of pacemaker implant infection	NA	NA	None	None

3AVB, third-degree atrioventricular block; ARDS, acute respiratory distress syndrome; AS, atrial standstill; MMVD, myxomatous mitral valve disease; SSS, sick sinus syndrome; SIRS, systemic inflammatory response syndrome.
*Cardiac troponin I concentrations derived from the ultrasensitive assay.

$p < 0.0001$). In this model, the hazard ratios (HRs) associated with age and US-cTnI were 1.298 (95% confidence interval [CI]: 1.162—1.449; $p < 0.001$) and 1.121 (95% CI: 1.014—1.240; $p = 0.026$), respectively, which were minimally different from those in the univariate analyses, providing evidence against a confounding effect of age on the association between US-cTnI and survival. Median survival time for US-cTnI group 1 was not reached, MST for group 2 was 1167 days, and MST for group 3 was 949 days. These data are represented graphically in Figure 1. Survival among the different groups was not significantly different (multivariable Cox regression HR = 1.216 [95% CI: 0.693—2.135; $p = 0.496$] logrank test $\chi^2 = 4.78$; $p = 0.092$). Assumption of proportional hazard was appropriately met in all models. From a broad perspective, there was a wide range of survival times across the range of US-cTnI levels. This is depicted graphically in Figure 2.

Discussion

Previous publications reviewing APs in veterinary medicine have not provided insights into a possible subpopulation affected by myocarditis [1,2]. As endomyocardial biopsies are rarely performed, definitive diagnosis of myocarditis in veterinary medicine has largely relied on histopathologic confirmation at necropsy. Well-defined parameters for antemortem diagnosis in veterinary medicine remain unestablished, and many cases likely go undiagnosed. The results of this study shed some light on population-wide data at an institution with

Figure 1 Kaplan—Meier plots to illustrate the survival of dogs receiving artificial cardiac pacemakers in three ordered categories based on ultrasensitive cardiac troponin I levels (see text for full details). Group 1 had normal ultrasensitive cardiac troponin I levels, and groups 2 and 3 had elevated ultrasensitive cardiac troponin I levels, with group 3 elevations severe enough to be considered 'myocarditis suspects'. There was no statistically significant difference in survival between groups.

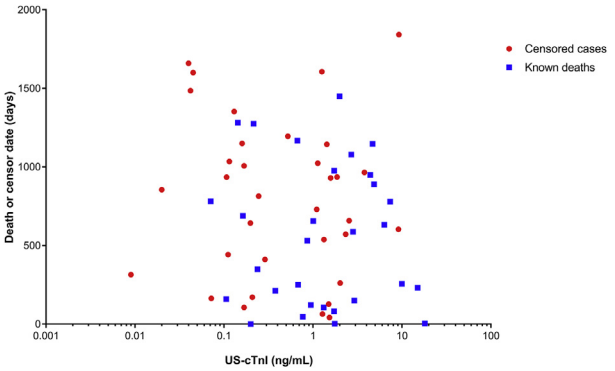

Figure 2 Relationship between ultrasensitive cardiac troponin I (US-cTnI) concentration when admitted for artificial pacemaker implantation and survival in dogs. 'Survival' here is used to define the time of death or the last follow-up for surviving animals. Note that the x-axis is on a logarithmic scale.

a cohort of myocarditis suspects treated with APs, in addition to looking specifically at the association of US-cTnI with survival.

The overall population studied here does not appear to differ remarkably from previous large-scale veterinary reviews of APs [1,2] with regard to baseline characteristics or complications, although a few distinctions may be of note. While the mean age of this population (8.9+/-3.6 years) is not substantially different from the mean age reported in the previous studies (8.5+/-3.7 years [1] and 10+/-3.5 years [2]), when age was broken into subcategories by Wess et al. [2], there were subtle distinctions between that population and this one. The percentage of dogs <5 years is similar (14.5% in this study vs 13% [2]), whereas the percentage of dogs between 5 and 10 years (44.5% in this study versus 23% [2]) and the number of dogs >10 years (41% in this study versus 64% [2]) differ. The population presented here has a higher percentage of middle-aged dogs. While there is a tendency to associate a diagnosis of myocarditis with young patients, and in human reports children and neonates do develop myocarditis that often exhibits a more fulminant form [28], the mean age associated with a diagnosis of myocarditis in people is 42 years [29]. It is possible that middle-aged dogs should be viewed with the same degree of suspicion for myocarditis as any dog presenting younger than the age of 5 years, although data specifically addressing this question would be required to confirm this possibility.

The current population did have a higher frequency of ventricular arrhythmias (18.2%) than the previous reports, which ranged between 8% and 9% [1,2]. Whether this relates to a higher prevalence of myocarditis is unknown, although it is interesting to note that no ventricular arrhythmias were noted in group 1 dogs, while seven dogs in group 2 had ventricular arrhythmias (five complex) and ten dogs in group 3 had ventricular arrhythmias (seven complex). Additionally, no dogs were categorized as having a DCM phenotype at the time of pacemaker placement in the current population, whereas this diagnosis was made in 2/105 dogs in one previous study [2] and 7/154 in another [1]. A DCM phenotype can be appreciated in some patients with chronic myocarditis due to persistent autoimmune processes or persistent infection that leads to myocardial remodeling and damage [13]. These cases are largely indistinguishable from idiopathic DCM and, in the absence of multiple clinical data points documenting progressive systolic dysfunction in combination with a previous elevation of cTnI, likely fail to be recognized altogether in most veterinary cases. While data on follow-up echocardiograms were not analyzed for the entire study population, of the five cases in which an increased LVIDsN was identified before APs placement, 3/5 dogs developed progressive systolic dysfunction after pacemaker placement, while 2/5 dogs did not have follow-up echocardiograms due to sudden death (2 days) and euthanasia (42 days) postoperatively. Three of these dogs had US-cTnI values that categorized them as group 3, while two did not have cTnI tested. These findings suggest that elevations in LVIDsN, even minor, may be a red flag for future deterioration of systolic function.

Cardiac troponin I is a sensitive and specific marker of myocardial injury. While severe elevations are most commonly associated with acute myocardial infarction [30], there are a multitude of other causes for troponin elevation, both cardiac and non-cardiac, that have been summarized in previous human [31–34] and veterinary reviews [35,36]. Elevated cTnI levels support a diagnosis of myocarditis in the absence of coronary artery disease in humans [15,16] and have been associated with myocarditis in veterinary medicine as well [6,12,17,18].

In the setting of bradyarrhythmias, elevated prepacemaker implantation cTnI has been reported in several small cohorts of dogs [12,19,37–39]. Myocarditis was strongly suspected in some instances based on reversion from 3AVB back to normal sinus rhythm within 6 months (n = 2) [39] or the development of progressive systolic dysfunction in combination with severe cTnI elevation and evidence of *Bartonella* exposure (n = 4) [12]. Some have postulated that myocardial

hypoxia and subsequent cardiomyocyte injury due to prolonged bradycardia may contribute to prepacemaker cTnI elevation, independent of myocarditis or concurrent cardiac disease [37]. While this may be plausible in some cases, there are examples of dogs in this study and in others [12,19,37—39] where normal cTnI levels are documented in the face of bradyarrhythmias. This argues against an inescapable myocardial injury due to bradycardia alone.

In this study, elevated cTnI levels were detected in a large proportion of tested dogs, with only 17% having a normal US-cTnI and comprising group 1. Forty-two percent of the population was in group 2, having US-cTnI levels within the range previously reported to encompass dogs with a variety of congenital heart diseases as well as dogs with MMVD in preclinical and clinical stages [26]. The remaining 41% of dogs exceeded this range and were categorized as group 3, having values more than 10 times the upper limit reported as normal for the US-cTnI assay used [26].

Dogs with US-cTnI elevations severe enough to be categorized as group 3 ($n = 26$) were considered to be myocarditis suspects. In three of these cases (11.5%), concurrent testing for Chagas disease was positive and provided a likely causative etiology for on-going inflammatory cardiac disease. There were also eight dogs in this group that had a variety of additional infectious disease testing, only one of which revealed a mildly positive titer for *R. rickettsii* (1:16). Of dogs tested with the standard sensitivity cTnI assay, three dogs were seropositive for *E. canis* and/or *R. rickettsii* in combination with a substantially elevated cTnI.

Reported causes of myocarditis in dogs encompass a variety of etiologies, including *Typanosoma cruzi* [11,18,40], *Borrelia burgdorferi* [41], *Bartonella* spp. [17,42], *Leishmania infantum chagasi* [43], canine parvovirus 2 [44], West Nile virus [45], *Neospora caninum* [46], and *Citrobacter koseri* [47], among others. Recent work suggests that infection with *E. canis* does not result in significant hcanges in US-cTnI level, echocardiographic, or electrocardiographic parameters [48]. This argues against a cause-and-effect relationship between a possible coinfection with *E. canis* and an elevated US-cTnI level in dogs that were seropositive in this study. Infections with *R. rickettsii* are rarely associated with myocarditis in humans [49,50] and have not definitively been linked to myocarditis in dogs. Infected dogs do develop widespread vasculitis in multiple tissues (including the heart) during the acute phase of the disease when both anemia and severe thrombocytopenia are present [51]. While widespread inflammation may well cause elevations in cTnI, it is unlikely that a dog in the acute stages of Rocky Mountain spotted fever would have gone unnoticed at the time of their prepacemaker evaluation and laboratory workup, suggesting that this disease may be an unlikely cause of active myocarditis in this study, despite the identification of several seropositive dogs. Overall, infectious causes of myocarditis in this patient population were infrequently identified. It is important to note, however, that different geographic areas may be endemic for different infectious diseases; thus, the data presented here may not be entirely reflective of patient populations in other regions. In particular, Chagas disease (diagnosed in 9% of the dogs tested in this study, four of which were a part of the 64 dogs included in statistical analysis of US-cTnI levels and survival) is rarely diagnosed outside the southern United States but can be diagnosed in dogs with a travel history to or rescued from the southern United States.

While none of the dogs in group 3 had a definitive diagnosis of myocarditis due to the absence of confirmatory endomyocardial biopsy or necropsy data, the magnitude of cTnI elevation in these dogs suggests that there was substantial ongoing myocardial injury, with myocarditis considered a plausible differential in the context of the entire clinical picture. The possible impact of concurrent systemic inflammation, myocardial infarction, renal disease, or increasing age on US-cTnI levels in these patients cannot be discounted [52] and is a limitation of both the US-cTnI test and the retrospective nature of this study. Nevertheless, the categorization of these dogs as myocarditis suspects remains reasonable and provides a starting point for future research. Without similar cTnI data from other institutions/regions to compare with, it is unclear whether there is truly a higher incidence of 'myocarditis suspects' in this population than elsewhere. The addition of cTnI testing to standard prepacemaker workup and evaluation, regardless of region, would help to answer this question.

Unfortunately, given the retrospective nature of the study, not all dogs had cTnI levels measured, and some had cTnI measured on a different assay that could not be included in the statistical survival analysis. This represents a limitation of the study. Furthermore, infectious disease testing was not standardized across all dogs; thus, definitive conclusions about the presence or absence of infectious agents in this population remain poorly defined. Viral agents, which are the leading cause of myocarditis in humans [15], were not tested for at all. Prior research has failed to identify canine

adenovirus type 2, herpesvirus, or parvovirus in association with active myocarditis or a DCM phenotype in dogs, finding a viral link in only a single case with DCM in which canine adenovirus type 1 was isolated from the myocardium [53]. A prospective study assessing an array of infectious disease testing in myocarditis suspects, ideally in combination with endomyocardial biopsy and virus isolation or viral polymerase chain reaction, is desperately needed to better characterize the prevalence of myocarditis in dogs and to better define the most common underlying etiologic agents.

Another limitation of this study relates to reliance on a single cTnI level to alert a clinician to the possibility of myocarditis. The sensitivity of cTnI for this purpose is low, largely due to the importance of sample timing. The majority of the cardiac injury associated with myocarditis appears to occur within the first month, after which cTnI utility drops off substantially [16]. Dogs in US-cTnI group 3 could be plausibly considered myocarditis suspects based on a single US-cTnI sample. Unfortunately, it is impossible to tell whether other dogs that did not meet the criteria for group 3 had prior elevations in cTnI that had already peaked and significantly lowered/normalized before presentation. Thus, even in cases in which cTnI levels were normal or were mildly elevated, the possibility of previous/resolving myocarditis cannot be excluded.

Importantly, whether the current population truly had a higher burden of patients with myocarditis at the time of pacemaker placement or not, the overall MST in dogs was 1079 days, or 3 years, which is similar to previously reported 3-year survival rates of 45% [1] and 55% [2]. Additionally, although elevated US-cTnI was (negatively) associated with survival, the effect was relatively mild (HR of 1.121), with no significant survival difference between dogs in group 2 and group 3 and minimal difference between the MST of these two groups compared with the MST for the entire population. The lack of significant differences between groups with different US-cTnI concentrations could be a result of type II error as the subgroups are relatively small. The impact of age on survival was stronger than the impact of US-cTnI, with an HR of 1.298. The negative impact of age on survival in dogs receiving APs has previously been appreciated [1]. Use of all-cause mortality for survival analysis was considered appropriate given the small numbers of confirmed cardiac deaths and the inherent difficulty in demarcating cardiac deaths from non-cardiac deaths, particularly in cases where owners elect euthanasia and may be biased, consciously or unconsciously, by their dog's underlying cardiac disease when faced with serious non-cardiac illness. Although all-cause mortality likely provides the most clinically relevant survival information in this population, it does not allow for conclusions to be drawn about outcomes tied solely to the underlying cardiac disease that prompted pacemaker placement.

Finally, while the percent of dogs experiencing sudden death (relative to the number of known deaths in the population) was not different in this population (13%) compared with previous reports (7—13%) [1,2], the concurrent cTnI testing in this population provides insight into the possibility of ongoing myocarditis in cases with this outcome. Five of the seven cases of sudden death had US-cTnI levels that categorized them as group 3 (myocarditis suspects). The sixth dog was categorized as group 2, and the seventh did not have a cTnI concentration measured. Despite the sudden nature of these deaths, in three instances, the time of death was 1—2 years postoperatively.

Conclusion

In conclusion, the data presented here recognize a subset of patients presenting for APs placement in which there was severe elevation in US-cTnI, and an underlying myocarditis was possible. Infectious etiologies that could plausibly trigger myocarditis were only identified in a minority of these cases. Despite a mild, negative effect of the US-cTnI level on overall survival outcomes, there was not a statistical difference in MST between dogs with mildly to moderately elevated US-cTnI (1167 days) and dogs with severely elevated US-cTnI (949 days). Furthermore, these values were similar to the MST for the entire population (1079 days). Age had a more significant impact on survival than US-cTnI. A possible association between severe elevation in US-cTnI and a sudden death outcome was noted.

Conflict of interest statement

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

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jvc.2018.09.003.

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