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Bradyarrhythmias and Pacemaker Therapy in Dogs with Chagas Disease

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Background: Chagas disease (Trypanosomiasis) is a cause of myocarditis in the southern United States causing cardiac conduction abnormalities, arrhythmias, and heart failure.

Objectives: To report clinical findings and outcome in Chagas positive (CP) dogs requiring pacemaker implantation for bradyarrhythmias.

Animals: One hundred and forty-four client-owned dogs requiring pacemaker implantation.

Methods: Retrospective case series. Information regarding history, physical exam, laboratory and diagnostic imaging findings, treatment, and survival were obtained from medical records, with additional follow-up information obtained by contacting referring veterinarians and owners.

Results: Of the 144 dogs requiring pacemaker implantation from January 2001 to May 2010, 83 (57.6%) had a Chagas titer performed and 9 (10%) were CP. Concurrent ventricular arrhythmias (odds ratio 1.61, $P = .005$) or atrioventricular (AV) block (odds ratio 4.18, $P < .001$) increased the likelihood that a Chagas titer was submitted. Median age for CP dogs was 6.2 years (range, 0.3–10); 7 were male. Bradyarrhythmias included high-grade 2nd or 3rd degree AV block (n = 8) and sinus bradycardia with 1st degree AV block (n = 1); 5 had concurrent ventricular arrhythmias. A positive Chagas titer had a negative impact on survival (hazard ratio 4.04; 95% CI 1.36–12.1, $P = .012$) with a reported median survival time of 365 days (interquartile range, 84–973 days).

Conclusions and Clinical Importance: Bradyarrhythmias can result in clinical signs requiring pacemaker implantation in CP dogs, and although the diagnosis negatively impacts survival, pacemaker therapy is a viable treatment option.

Key words: Arrhythmias; Atrioventricular block; Canine; Myocarditis.

Chagas disease, caused by the protozoan organism *Trypanosoma cruzi*, is a cause of myocarditis in dogs in the southern United States and Latin American countries.[1–3] Transmission requires a bite from or ingestion of an infected insect vector, although it can be transmitted via blood transfusions and by transplacental or transmammary infection.[1] Trypomastigotes enter cardiac myocytes and develop into amastigotes in about 14 days. The amastigotes multiply, causing myocyte destruction, parasite release into circulation, and an inflammatory response that results in lethargy, enlargement of liver, spleen, or lymph nodes, as well as disturbances within the conduction system of the heart.[1] Myocarditis in the chronic stage of the disease can result in conduction abnormalities, arrhythmias, ventricular myocardial dysfunction, heart failure, and sudden death.[4,5] Similar findings are documented in humans with Chagasic myocarditis where any portion of the conduction system can be affected and in which bradyarrhythmias require pacemaker implantation.[6,7] In humans with Chagas disease, pacemakers are typically required at a younger age than those paced for bradyarrhythmias without Chagas disease and myocardial function worsens over time.[8] Poor prognostic indicators in humans with Chagas disease include ventricular tachycardia, left ventricular systolic dysfunction, and the development of 3rd degree atrioventricular (AV) block.[8,9] Seventy-two percent of human patients receiving pacemaker implantation were Chagas positive (CP) and had significantly lower

Abbreviations:

ACVIM	American College of Veterinary Internal Medicine
AV	atrioventricular
CN	Chagas negative
CP	Chagas positive
cTnI	cardiac troponin I
IQR	interquartile range
LA/Ao	left atrium to aorta ratio
LVIDd-N	left ventricular internal dimensions in diastole normalized to body weight
LVIDs-N	left ventricular internal dimensions in systole normalized to body weight
NT	not tested
VHS	vertebral heart size

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quality of life scores compared with those without Chagas disease.[10] The most common rhythm abnormality requiring pacemaker implantation in humans with Chagas disease is sinus node dysfunction followed by 2nd and 3rd degree AV block and atrial fibrillation with AV block.[11]

Pacemaker implantation is a well-described treatment option for high-grade 2nd degree AV block, 3rd degree AV block, and sick sinus syndrome in dogs.[12,13] Vector-borne infectious diseases including *Bartonella* spp. and *Trypanosoma cruzi* have been rarely reported in dogs with bradyarrhythmias.[5,13,14] The objective of this study was to report the clinical findings and outcome in CP dogs requiring pacemaker implantation for bradyarrhythmias.

Materials and Methods

Criteria for Case Selection

The Texas A&M University Veterinary Medical Teaching Hospital (TAMU-VMTH) electronic medical records database was searched to identify all dogs with pacemaker implantation between January 2001 and May 2010. Indirect immunofluorescent assay for *Trypanosoma cruzi* (Texas Veterinary Medical Diagnostic Laboratory, College Station, TX) test results were recorded for those dogs on which the test had been performed. Dogs with an antibody titer of 1 : 80 or 1 : 160 were classified as CP in the study analysis.

Medical Records Review

Information recorded for each dog included signalment, history, electrocardiographic rhythm diagnosis, results of serum biochemistry, serology and cardiac troponin I (cTnI) when available, results of diagnostic imaging (thoracic radiography, echocardiography), pacing information, and follow-up. Thoracic radiographs were reviewed to evaluate heart size including vertebral heart size (VHS)[15] and for evidence of congestive heart failure. Measurements obtained from echocardiographic studies included left ventricular internal dimension in diastole and in systole normalized to body weight (LVIDd-N and LVIDs-N),[16] fractional shortening and left atrium to aorta ratio (LA/Ao) from m-mode.[17,18] Serum cTnI concentration was determined using the Immulite analyzer with a lower detection limit of 0.2 ng/mL as previously described.[19] Follow-up data to document survival time and cause of death were obtained from the medical record or telephone interviews with owners and referring veterinarians.

Statistical Analysis

Descriptive statistics including medians and ranges were calculated for ordinal and continuous variables such as age and survival after pacemaker implantation. Categorical variables, including signalment, presenting clinical signs, and diagnostic findings, were summarized by counts and percentages. Continuous variables were compared across groups (CP, Chagas negative [CN], not tested [NT]) using Kruskal–Wallis tests overall with significant differences followed by pairwise Mann–Whitney *U* tests with Bonferroni adjustment for multiple comparisons. Categorical variables were compared across groups using Pearson chi-squared tests with significant differences followed by pairwise chi-squared or Fisher exact tests with Bonferroni adjustment of *P* values.

Survival time of study dogs was evaluated using bivariable Cox proportional hazards regression to identify factors associated with survival. Evaluated variables included Chagas testing status, signalment, presenting clinical signs, and electrocardiographic findings. Dogs that were alive or lost to follow-up were considered censored at the date corresponding to the last available observation time. Wald $P < .20$ was employed for the descriptive presentation of factors associated with survival. A multivariable model was created starting with all variables significant at the $P < .20$ level in the bivariable models and using a backwards elimination technique based on Wald statistics. Bivariable logistic regression was employed to identify factors associated with the clinical decision to test dogs for Chagas disease. Evaluated variables included signalment, presenting clinical signs, and electrocardiographic findings. All analyses were performed using commercially available software,[a,b] and interpreted at the 5% level of significance unless otherwise stated.

Results

Patient Data

Of the 144 dogs requiring pacemaker implantation from January 2001 to May 2010, 83 (57.6%) had a Chagas titer performed. The presence of concurrent ventricular arrhythmias or AV block increased the likelihood that a Chagas titer was submitted (Table 1). In addition, the number of Chagas tests submitted was higher in dogs paced after 2007 than in earlier years. Of those tested, 9 (10%) dogs were CP. Median age at the time of pacemaker placement for CP dogs was 6.2 years (interquartile range [IQR], 2–10 years) and for CN dogs was 9 years (IQR, 4–11 years), both of which were significantly younger than those NT (median, 10 years; IQR, 8.5–12 years) ($P < .01$). No difference was found between groups in regards to breed, sex, presenting clinical sign, type of AV block, or biochemistries.

With regard to descriptive information for the CP dogs, 7 were male (5 neutered, 2 intact) and 2 were

Table 1. Bivariable logistic regression for the prediction of Chagas testing in 144 dogs requiring pacemaker implantation at a veterinary referral institution during 2001–2010.

Variable	Parameter Estimate ($\hat{\beta}$)	*P* Value (Wald)	Odds Ratio (95% CI)
Age at implantation (years)	—	.001	—
≥ 11	Referent	—	—
6–10	2.92	<.001	18.5 (3.97, 85.9)
≤ 5	0.34	.370	1.41 (0.67, 2.96)
Exercise intolerance	−0.55	.123	0.58 (0.29, 1.16)
Implantation 2007 or later	0.82	.018	2.27 (1.15, 4.46)
2nd or 3rd degree AV block	1.43	<.001	4.18 (1.95, 8.98)
Sick sinus syndrome	−1.76	<.001	0.17 (0.08, 0.40)
Ventricular arrhythmia	1.61	.005	5.02 (1.65, 15.3)
CHF before implantation	1.79	.021	5.99 (1.31, 27.4)

CI, confidence interval; CHF, congestive heart failure.

spayed females. Breeds included 2 Cavalier King Charles Spaniels and one each of Australian Heeler, Pug, Brittany Spaniel, Standard Poodle, Poodle, Miniature Schnauzer, and mixed. Dogs originated from the following Texas counties: Bell, Brazos, Camp, Denton, Harris, Nacogdoches, Tarrant, Travis, and Wichita.

Dogs presented for syncope (n = 4), exercise intolerance (n = 3), and bradycardia (n = 2). Heart rate at presentation ranged from 28 to 80 beats/min (median, 50 beats/min). Bradyarrhythmias included high-grade 2nd or 3rd degree AV block (n = 8) and sinus bradycardia with 1st degree AV block (n = 1). An atropine response test was performed in 4 dogs and did not improve AV nodal conduction or increase the ventricular escape rate. Dogs with concurrent ventricular arrhythmias do not typically have an atropine response test performed in the authors' institution. Concurrent ventricular arrhythmias were documented in 5 dogs and included uniform or multiform ventricular premature beats or paroxysmal ventricular tachycardia.

Baseline echocardiographic data were available for all 9 dogs. The median LVIDd-N was 1.78 (range, 1.33–2.71) and was greater than the 95% confidence interval of 1.27–1.85 in 3/9 (33%).[16] The median LVIDs-N was 0.99 (range, 0.65–1.34) and was greater than the 95% confidence interval of 0.71–1.26 in 2/9 (22%).[16] Median fractional shortening was 44.9% (range, 23.5–59.4%). Median LA/Ao m-mode was 1.54 (range, 0.87–2.28) and was >1.3 in 7/9 (77%). Two dogs had subjective right ventricular enlargement based on comparison to left ventricular size. Three dogs (Cavalier King Charles Spaniel, Miniature Schnauzer, Poodle) had degenerative mitral valve disease (DMVD) classified as American College of Veterinary Internal Medicine (ACVIM) stage B2 (n = 2) or stage C (n = 1).[20] Two of the three had pulmonary hypertension with estimated pulmonary artery systolic pressures of 36.9 and 83.6 mmHg based on tricuspid regurgitation velocities and estimated right atrial pressure. Radiographic VHS was a median of 12.1 (range, 10.5–14.25, >10.7 indicates cardiomegaly) and was greater than 11.5 in 6/8 (75%).[15] Radiographic evidence of pulmonary edema was observed in 1 dog with DMVD.

An echocardiogram was performed in 5 dogs a median of 1.5 months (range, 1–12) after pacemaker implantation. The median LVIDd-N and LVIDs-N were 1.53 (range, 1.33–2.37) and 1.04 (range, 0.76–1.42), respectively. Values between echocardiogram studies were unchanged in 1 dog, continued to increase above the 95% confidence intervals in 1 dog and reduced in size in both diastole and systole in the remaining 4 dogs. Median fractional shortening was 37.5% (range, 20.8–53.9%). Median LA/Ao m-mode was 1.57 (range, 1.04–2.35) and was >1.3 in 3/5 (60%). One dog had progressive right ventricular enlargement on serial echocardiographic examinations performed for 2.5 years after pacemaker implantation.

At initial presentation, alanine transferase activity was above the reference range of 10–130 μm/L in 3/9 (33%) dogs (individual values were 131, 610, 861 μm/L), none of which had right-sided heart enlargement. Serological analysis using an indirect immunofluorescent assay to detect antibodies against *Ehrlichia canis, Babesia canis, Rickettsia rickettsii, Bartonella vinsonii* subsp. *berkhoffi,* and *Bartonella henselae* and an ELISA for *Borrelia burgdorferi, Ehrlichia canis,* and *Anaplasma* spp. were submitted in 7/9 (77%) dogs. Antibodies were not detected in any of the dogs tested. Cardiac troponin I (cTnI) was detected in all 5 dogs tested. Values were 0.38, 0.45, 0.7, 1.15 and 17.83 ng/mL.

Eight dogs had a pacemaker implanted with a bipolar endocardial (7) or epicardial (1) system with various pacing modes (VVI, VVIR, DDD) and a range of heart rates. One dog was euthanized before permanent pacemaker implantation as further described in the following outcome section. Two pacemaker-related issues occurred after implantation. One dog had a low battery warning that required replacement of the pulse generator after approximately 1 year, and 1 dog had partial dislodgement of the lead 4 weeks after pacing attributed to lead retraction from twisting of the lead, characterized as twiddler's syndrome.

One dog presented for initial evaluation with a diagnosis of ACVIM Stage C DMVD and was receiving enalapril 0.62 mg/kg [1.36 mg/lb], PO, q24h, furosemide 1.25 mg/kg [2.75 mg/lb], PO, q24h and pimobendan 0.16 mg/kg [0.35 mg/lb], PO, q12h for historical congestive heart failure, and had radiographic evidence of mild pulmonary edema. At discharge, changes were made to the heart failure medications (enalapril 0.31 mg/kg [0.68 mg/lb], PO, q12h, furosemide 1.25 mg/kg [2.7 mg/lb], PO, q12h, pimobendan 0.31 mg/kg [0.68 mg/lb], PO, q12h), and sotalol 1.8 mg/kg [3.9 mg/lb], PO, q12h was initiated for treatment of ventricular arrhythmias.

Outcome

A positive Chagas titer negatively impacted survival (hazard ratio, 4.04; 95% CI 1.36–12.10; $P = .012$). Median survival was shorter at 365 days (IQR, 84–973 days) for CP dogs compared with dogs categorized as CN (median 533 days, IQR 303–1020 days) and NT (median 577 days, IQR 311–1095 days) (Fig 1). After pacemaker implantation, 2 dogs were alive at 1.5 and 7 years and 1 dog was lost to follow-up at 36 months. The remaining 6 dogs were no longer alive with a median survival time of 12.6 months (range, 0–34 months). One dog died suddenly and 5 dogs were euthanized for cardiac (4) and noncardiac (1) causes. In 1 dog that presented at 4 months of age, the presence of multiform ventricular arrhythmias, cardiac troponin I of 17.8 ng/mL, positive Chagas titer, and difficulty maintaining capture with a temporary pacemaker led the owner to elect euthanasia before permanent pacemaker implantation.

A partial necropsy was performed in a CP Cavalier King Charles Spaniel with DMVD euthanized for pro-

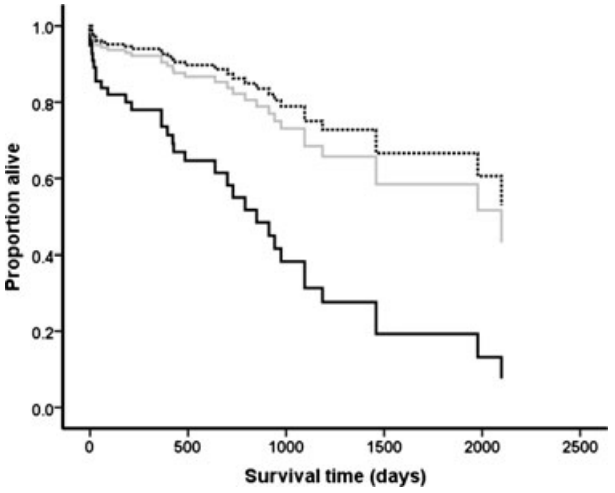

Fig 1. Adjusted Cox proportional hazards analysis survival curves for 9 Chagas positive dogs (black line), 74 Chagas negative dogs (gray line), and 61 untested dogs (dashed line) requiring pacemaker implantation at a veterinary referral institution during 2001–2010.

gressive signs of left-sided heart failure. The heart was fixed in 10% formalin and the sinoatrial and AV nodes were sectioned, embedded in paraffin wax, cut at 5 μm thickness, and stained with H&E and trichrome for histopathological evaluation. The histopathology results revealed a very mild amount of chronic lymphoplasmacytic inflammation and fibrosis surrounding the sinoatrial node, and a moderate amount of similar inflammation and fibrosis surrounding the AV node and left and right bundle branches. The AV node displayed mild vacuolar degeneration. Although no evidence of amastigotes was found within the examined sections, the chronic inflammation and fibrosis in this case is most likely attributed to chronic Chagasic myocarditis. The dog had 2 courses of benznidazole[c] within a 2-year period before developing 3rd degree AV block and had a cTnI of 1.15 ng/mL.

Discussion

Specific details regarding clinical information and outcome that may be useful when making therapeutic decisions and providing owners with prognostic information are limited for dogs with Chagas disease and bradyarrhythmias. The current study demonstrates that although Chagas disease negatively impacts survival, clinically important bradyarrhythmias can be managed with pacemaker placement in most dogs. In general, dogs with bradyarrhythmias that require a pacemaker tend to be older.[12,13] In 2 large retrospective studies on dogs, the most common bradyarrhythmias that required pacemaker implantation were 3rd degree AV block and sick sinus syndrome at a mean age of 10 years in 1 study and a median age of 8 years for dogs with 3rd degree AV block in the 2nd study.[12,13] Similar to the reports on humans with Chagas disease,[11] pacemakers were often required at a younger age (median 6.2 years) for dogs with Chagas disease and bradyarrhythmias in our study.

Chagas testing in dogs has increased over time according to data from a large diagnostic laboratory in Texas.[2] This was confirmed in our institution as well. In our pacemaker population, the presence of AV block or concurrent ventricular arrhythmias increased the likelihood of having a Chagas titer performed. The authors do not tend to routinely test dogs diagnosed with sick sinus syndrome. Dogs with sinus node dysfunction were more likely to be tested if they were presented at a young age or had concurrent ventricular arrhythmias.

Sporting and working breeds represent the majority of positive cases in Texas.[2] Medium and large breeds are most commonly affected in another retrospective study.[5] In our study, as in a previous study, CP dogs were from both urban and rural areas.[2] Small breeds represented half of the dogs in our study, three of which had DMVD. While Chagas disease can affect both the right and left sides of the heart, it is most often characterized as predominately affecting the right side of the heart[1,4] which was not identified in the dogs in this report. In this report, predominately left heart enlargement was documented before pacemaker implantation which was complicated by the presence of DMVD in 3 dogs. Reductions in left ventricular dimensions in diastole and systole after pacemaker placement suggest concurrent bradycardia affected heart size as well. Chagasic myocarditis may be characterized by an intense inflammatory infiltration of the myocardium resulting in myocardial dilatation, arrhythmias, and elevations in cTnI.[21] Inflammation, fibrosis, myonecrosis, and myodegeneration associated with *Trypanosoma cruzi* infection can affect all parts of the cardiac conduction system including the sinus node, AV node, and bundle branches predisposing infected dogs to conduction disturbances and ventricular arrhythmias.[7] Dogs can enter a chronic stage of the disease often characterized by progressive myocardial fibrosis.[1] Mild to moderate lymphoplasmacytic inflammation and fibrosis were documented surrounding the sinoatrial node, AV node, and bundle branches in 1 dog in our report that had DMVD. Cardiac troponin I, a marker of myocardial damage, was elevated in this dog with histopathologic evidence of inflammation and fibrosis and in other dogs in our study. Elevated cTnI concentrations have also been reported in a cohort of dogs requiring pacemaker implantation, including a subset of dogs that were positive for *Bartonella* spp.[14] Further evaluation of the utility of cTnI in detecting myocardial injury and providing prognostic information would be useful in this population.

Ventricular arrhythmias and sudden death occur in dogs that required pacemaker placement and also in dogs with Chagas disease.[2,12,13] Sudden death occurs in 7–13% of paced dogs[12,13] and was reported in 1 dog in this study. The cause of sudden death in these dogs is unknown but could be related to ventricular arrhythmias. Chagas disease is often associated with malignant ventricular arrhythmias and increased risk of sudden death that can be managed with antiarrhythmic medications and implantable cardioverter

defibrillators.[7,8] Combined implantation of a defibrillator and pacemaker was used to manage ventricular arrhythmias and AV block in a human with Chagas disease.[22] One dog in our report received benznidazole therapy. Antiparasitic medications such as benznidazole and nifurtimax are more effective in the acute stage of human Chagas disease.[8] The efficacy of these medications is unknown in human patients with pre-existing heart disease. In a model of chronic Chagas disease in dogs, a reduction in parasitemia was documented within 1 month of treatment with benznidazole followed by a rebound in the long term that was accompanied by progressive cardiomegaly and ventricular systolic dysfunction.[23]

Limitations to the present retrospective case series include the small number of CP dogs and incomplete and variable follow-up information available. In addition, not all paced dogs were tested for Chagas disease, and CP dogs were predominately diagnosed with an indirect immunofluorescent assay and not histopathology, thus some dogs with Chagas disease could have gone undetected.

In summary, bradyarrhythmias can result in clinical signs requiring pacemaker implantation in CP dogs. While progressive cardiac disease and sudden death are possible outcomes in this population, management of bradyarrhythmias with pacemaker therapy is a viable treatment option.

Footnotes

[a] IBM SPSS Statistics Version 20, International Business Machines Corp., Armonk, NY
[b] Epi Info, version 6.04, CDC, Atlanta, GA
[c] Acquired from the Centers for Disease Control and Prevention, Atlanta, GA

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Conflict of Interest: Authors disclose no conflict of interest.

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