

# Cardiac Manifestations of *Trypanosoma cruzi* Infection in a Domestic Dog



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## INTRODUCTION

Chagas disease, caused by the protozoan parasite *Trypanosoma cruzi*, is a well-recognized cause of infectious myocarditis in humans worldwide. It is endemic in Latin America and increasingly recognized throughout the southern half of the United States, where more than 11 triatomine insect vectors are documented.<sup>1</sup> Expanding vector and wildlife distribution patterns, human migration, and global travel increase the potential for disease transmission.<sup>1</sup> Geographic location and travel history that includes an area with infected vectors or reservoir hosts increase the clinical suspicion for Chagas myocarditis. Transmission occurs most often through interaction with the triatomine insect vector, with other less common methods including vertical (from mother to offspring), food contamination, blood transfusion, and organ transplantation.<sup>1</sup>

Dogs and other mammals have been identified as domestic and peridomestic hosts and serve as reservoirs in nature.<sup>1</sup> Seroprevalence in dogs ranges from 7% in shelters up to 50% in some kennels and is influenced by animal purpose and location as well as type of diagnostic test used to determine disease status.<sup>2-4</sup> Similar to humans, infected dogs may not have clinical signs; a subset of dogs will develop arrhythmias, a dilated cardiomyopathy (DCM) phenotype, congestive heart failure, and sudden death as a consequence of myocarditis.<sup>4,5</sup> This case demonstrates the utility of echocardiography when evaluating arrhythmias to reach a diagnosis of *T cruzi* infection in dogs.

## CASE PRESENTATION

A 16-month-old, 15-kg, female, spayed, mixed-breed dog was presented to the referral institution for evaluation of an auscultation abnormality (abnormal heart sound or arrhythmia) detected by the primary care clinician during an evaluation of a nonpainful swelling over the left eye. No clinical signs of heart disease or elevated body temperature had ever been reported. During a routine wellness examination 5 months before presentation to the referral institution, the dog tested negative for the following vector-borne organisms: *Dirofilaria immitis*, *Borrelia burgdorferi*, *Ehrlichia canis*, *Ehrlichia ewingii*, *Anaplasma phagocytophilum*, and *Anaplasma platys* (SNAP 4Dx Plus;

IDEXX Laboratories, Westbrook, ME). The dog was originally found as a puppy along with its littermates on the side of a road in south Texas. The remaining littermates were reported to have died at various ages and for unknown reasons. Given the recent concern for a diet associated DCM phenotype in dogs eating a variety of exotic ingredient, or grain-free diets, a thorough diet history was obtained. The dog remained on a diet that met World Small Animal Veterinary Association nutritional guidelines since having been acquired by the current owners and was maintained on this diet throughout the duration of follow-up. The dog was receiving monthly oral heartworm prevention and was currently vaccinated against distemper, adenovirus, parainfluenza, parvovirus, influenza, leptospirosis, and rabies.

On physical examination at the referral institution, the dog was bright and alert, with a normal respiratory rate and effort. No murmur was auscultated. Heart rate was 60 beats/min (reference range, 70–160 beats/min) with strong femoral pulse quality and occasional deficits appreciated. There were no other abnormalities documented on physical examination. As part of a cardiac evaluation, two-dimensional transthoracic echocardiography was performed using a 5.0-MHz probe and a Vivid E95 cardiac ultrasound system (GE Healthcare, Milwaukee, WI). The left ventricle was mildly dilated (Figure 1, Videos 1–3), with internal dimensions measuring 3.92 cm in diastole (1.74 normalized to body weight; prediction interval, 1.20–1.64) and 2.53 cm in systole (0.88 normalized to body weight; prediction interval, 0.55–0.96).<sup>6</sup> Additionally, there was abnormal ventricular septal wall motion, attributed in part to an arrhythmia. Ejection fraction was at the low end of the reference range at 46.3% (reference interval, 46.0%–82.5%).<sup>6</sup> The left atrium was of normal diameter (2.85 cm; 1.23 normalized to body weight; prediction interval, 1.14–1.65) when measured in a right parasternal long-axis view.<sup>6</sup> Transmitral inflow and lateral annular tissue Doppler peak velocities were normal (E 0.64 m/sec, A 0.33 m/sec, E' 0.1 m/sec, A' 0.05 m/sec). The right ventricular intraluminal diameter measured 2.31 cm from a left parasternal long-axis four-chamber view and was considered subjectively mild to moderately dilated because the luminal diameter was >50% of but not larger than the diameter of the left ventricle.<sup>7</sup> Areas of wall thinning were observed at the apex of both ventricles (Figure 2, Video 2). Tricuspid annular plane systolic excursion was at the low end of the reference range at 7.1 mm (reference range for body weight, 7.0–14.4 mm; Figure 3).<sup>8</sup> Transtricuspid inflow measurement was not available. Tricuspid annular velocities obtained with pulsed-wave tissue Doppler imaging suggested impaired relaxation (E' 0.5 m/sec, A' 0.7 m/sec) and reduced systolic function (S' 0.6 m/sec; reference interval, 0.8–2.1 m/sec).<sup>8</sup> Right atrial diameter was normal when measured from a right parasternal long-axis view parallel to the tricuspid annulus (2.31 cm; reference interval, 1.61–2.85 cm).<sup>9</sup> Mild low-velocity (1.8 m/sec) tricuspid valve regurgitation and trace pulmonic valve regurgitation were documented. The electrocardiogram obtained during the echocardiographic study showed a sinus rhythm with an average heart rate of approximately 80 beats/min conducted with

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## VIDEO HIGHLIGHTS

**Video 1:** Transthoracic echocardiographic cine loop in a right parasternal short-axis view at initial evaluation that shows mild to moderate dilation of the right ventricle and abnormal ventricular septal wall motion associated with the arrhythmia. A sinus rhythm conducted with a RBBB and a single ventricular premature beat are present on the electrocardiogram.

**Video 2:** Transthoracic echocardiographic cine loop in a right parasternal long-axis four-chamber view at initial evaluation that shows mild to moderate dilation of the right ventricle and thinning of the apical region of both ventricles. A sinus rhythm conducted with a RBBB is present on the electrocardiogram.

**Video 3:** Transthoracic echocardiographic cine loop in a left apical four-chamber view at initial evaluation that shows mild to moderate dilation of the right ventricle. A sinus rhythm conducted with a RBBB is present on the electrocardiogram.

**Video 4:** Transthoracic echocardiographic cine loop in a right parasternal short-axis view at the 15-month recheck evaluation that shows progressive dilation of the right ventricle. A sinus rhythm conducted with a RBBB is present on the electrocardiogram.

**Video 5:** Transthoracic echocardiographic cine loop in a right parasternal long-axis four-chamber view at the 15-month recheck evaluation that shows progressive dilation and thinning of the apical region of the right ventricle. A sinus rhythm conducted with a RBBB is present on the electrocardiogram.

**Video 6:** Transthoracic echocardiographic cine loop in a left apical four-chamber view at the 15-month recheck evaluation that shows progressive dilation of the right ventricle. Multiple areas of mottled myocardium are present within the papillary muscle in the right ventricle and in the interventricular septum. A sinus rhythm conducted with a RBBB is present on the electrocardiogram.

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right bundle branch block (RBBB) and frequent premature ventricular complexes that were further characterized with 24-hour ambulatory electrocardiography. The ambulatory electrocardiographic findings included sinus rhythm conducted with RBBB and with intermittent periods of first-degree atrioventricular block. Ventricular ectopy was frequent and complex, including 38,421 ectopic beats (21.9% of beats recorded over 24 hours) occurring as multiform single and paired premature ventricular complexes, with periods of ventricular bigeminy and paroxysms of idioventricular rhythm.

Differential diagnoses for the arrhythmias and echocardiographic changes included myocarditis, nutritional deficiency, and arrhythmogenic right ventricular cardiomyopathy. Because this dog was from an area endemic for Chagas disease, had previously tested negative for other infectious disease, and was not demonstrating any signs of illness, the dog was tested with an immunofluorescent antibody titer for *T cruzi* and was positive at >1:1,280. The presence of electrocardiographic and echocardiographic abnormalities with a positive immunofluorescent antibody titer is currently the standard for

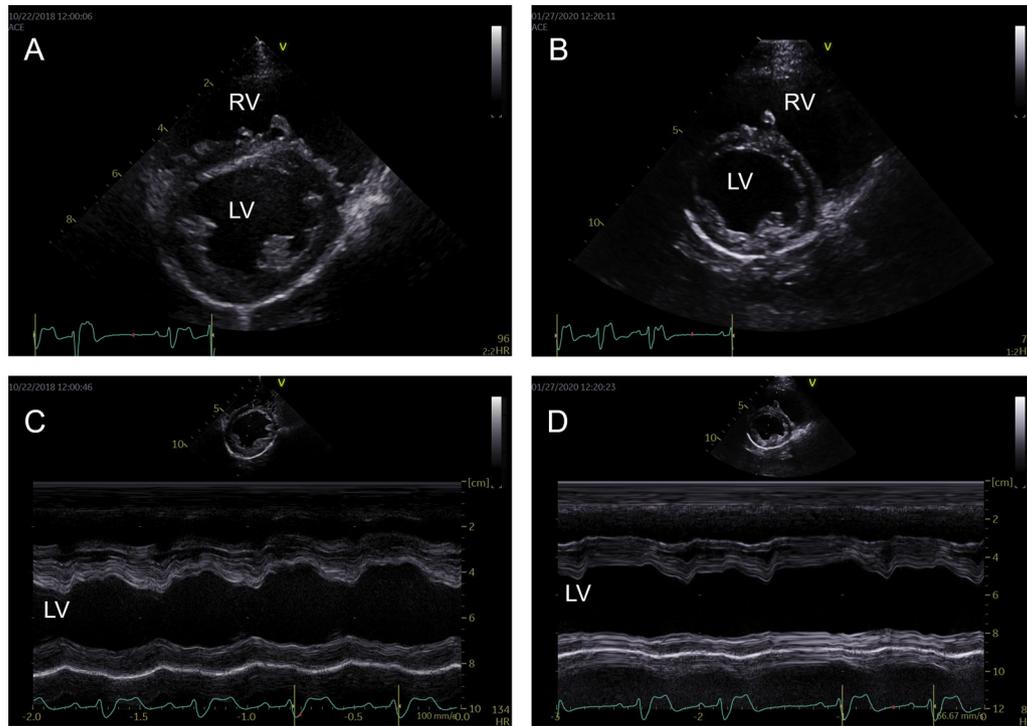
diagnosis of Chagas myocarditis in the dog. Confirmation with a second positive test result, the recommended standard for diagnosis in humans, is not routinely possible in dogs. Rapid tests to detect antibodies are not currently approved for clinical use in dogs, and polymerase chain reaction testing on blood is frequently negative in chronic disease when organisms are less likely to be in the circulation. The dog's arrhythmia was managed with sotalol (1.9 mg/kg every 12 hours) and monitored serially over the next 15 months with echocardiography and ambulatory electrocardiography. Although the dog continued to remain free of clinical signs, progressive changes were documented on diagnostic tests. Echocardiographic changes consisted of progressive chamber enlargement and systolic dysfunction (Figures 1-3, Videos 4-6). Left ventricular internal diameter in diastole was unchanged at 3.90 cm, while systolic diameter increased to 2.81 cm (0.98 normalized to body weight; prediction interval, 0.55–0.96). Left ventricular ejection fraction decreased to 40.6%. The left atrium increased in size but remained within reference range (3.01 cm; 1.30 normalized to body weight; prediction interval, 1.14–1.65) when measured in a right parasternal long-axis view. The right ventricular intraluminal diameter increased to 3.17 cm from a left parasternal long-axis four-chamber view and was considered to be severely dilated because it was subjectively equal to or larger in luminal diameter than the diameter of the left ventricle.<sup>7</sup> Tricuspid annular tissue Doppler profiles were unchanged, and a further reduction in tricuspid annular plane systolic excursion (5.9 mm) was documented. Tricuspid valve regurgitation remained mild and low velocity. The diameter of the right atrium increased to 2.55 cm. There were multiple areas of mottled myocardium identified within the papillary muscle in the right ventricle and in the interventricular septum (Video 6).

Medical therapy with pimobendan (0.29 mg/kg by mouth every 12 hours) and enalapril (0.44 mg/kg by mouth every 12 hours) was instituted. Inadequate ventricular arrhythmia control documented on serial electrocardiography prompted the addition of mexiletine (3.85 mg/kg by mouth every 8 hours) to the antiarrhythmic therapy. In addition to RBBB and frequent multiform premature ventricular complexes, the P-R interval became consistently instead of intermittently prolonged; this may have been related to continued pathology or sotalol administration (Figure 4). At the time of publication (approximately 18 months after diagnosis), the dog does not have clinical signs reported by the owners.

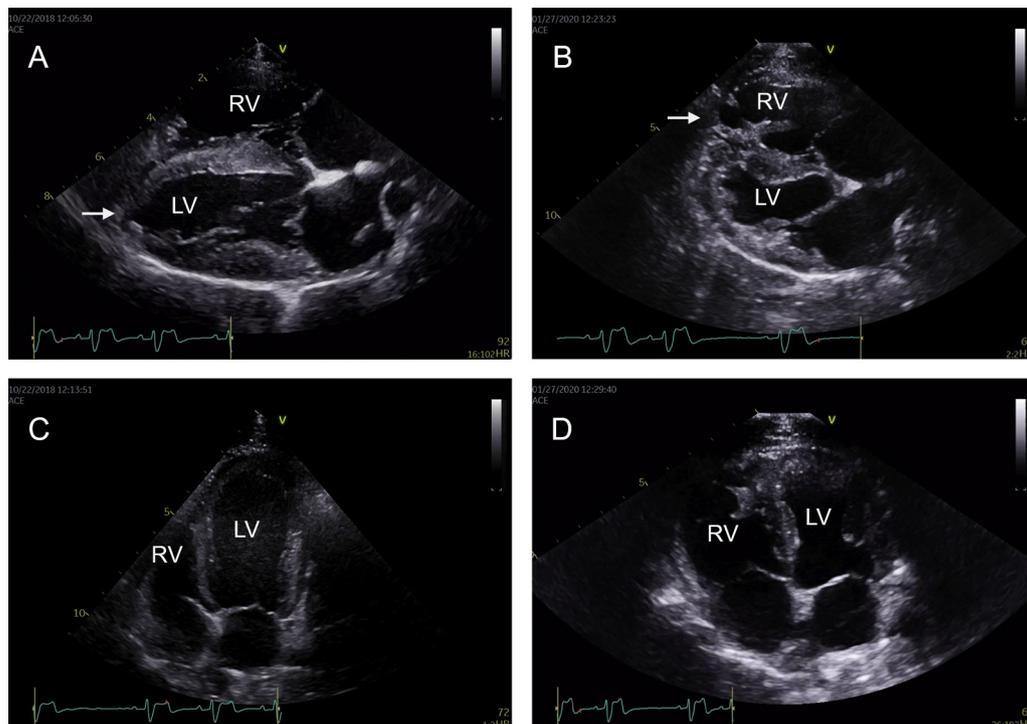
## DISCUSSION

Chronic infection with *T cruzi* results in clinical abnormalities in approximately 20% to 30% of infected humans and dogs over the course of months to years in the form of a chronic, progressive myocarditis affecting any of the four cardiac chambers and the conduction system.<sup>10,11</sup> Manifestations of chronic Chagas myocarditis in humans often initially include conduction abnormalities (RBBB or left anterior fascicular block) and ventricular wall motion abnormalities.<sup>1,10</sup> Conduction abnormalities can also affect wall motion, and this may have been a contributing factor in the echocardiographic appearance of the ventricular septum of the dog reported here. Over time, electrical dysfunction can progress to more complex and multiform ventricular arrhythmias, sinus node dysfunction, and complete heart block. End-stage chronic Chagas disease is characterized by the development of a DCM phenotype and refractory congestive heart failure.<sup>1</sup>

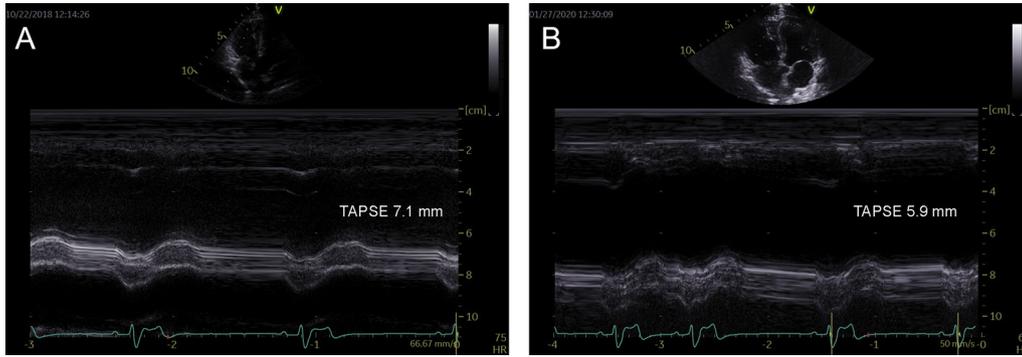
The presence of an arrhythmia on physical examination in addition to ventricular arrhythmias identified on electrocardiography were recently described as the most common reasons for testing



**Figure 1** Transthoracic echocardiographic images obtained in a dog seropositive for *T. cruzi* from a right parasternal short-axis view of the left ventricle (LV) in two dimensions and M-mode at initial presentation (**A, C**) and at recheck evaluation 15 months later (**B, D**). The left ventricular internal dimensions at initial presentation were within normal limits, and ejection fraction was at the low end of the reference range. The right ventricle (RV) was mild to moderately dilated. At recheck evaluation, the left ventricular diastolic dimension was unchanged, and the systolic dimension had increased. The RV was severely dilated. The associated electrocardiogram shows a sinus rhythm conducted with a RBBB in all panels and a single ventricular premature beat in (**A**).



**Figure 2** Transthoracic echocardiographic images from the same dog in **Figure 1** comparing right parasternal (**A, B**) and left apical (**C, D**) four-chamber views obtained at initial presentation (**A, C**) and at recheck evaluation 15 months later (**B, D**). Thinning at the apex of both ventricles can be appreciated (arrows in **A** and **B**). Progressive right ventricular dilation is best appreciated in the left apical long-axis view. The associated electrocardiogram shows a sinus rhythm conducted with a RBBB in all panels. LV, Left ventricle; RV, right ventricle.



**Figure 3** Transthoracic echocardiography of tricuspid annular plane systolic excursion (TAPSE) determined by M-mode at the lateral tricuspid annulus from a left apical four-chamber view to demonstrate a reduction from the initial evaluation to the 15-month recheck.

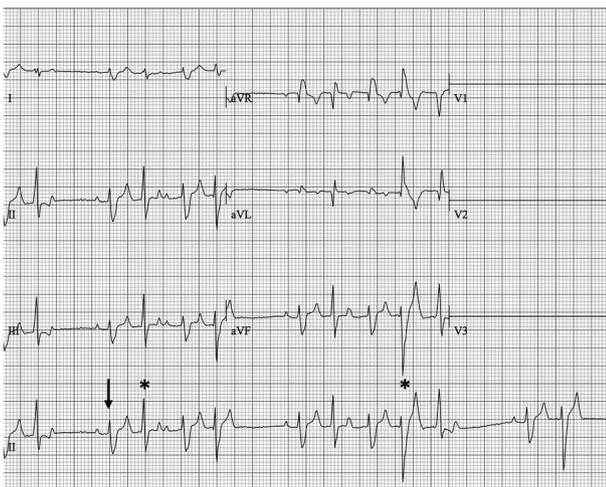
for *T. cruzi* infection in dogs that live within or have a history of travel to a region where Chagas disease is endemic.<sup>12</sup> Other reasons to test include the presence of an infected littermate or housemate, heart failure, and echocardiographic ventricular enlargement with systolic dysfunction.<sup>12</sup> Chagas disease in domestic dogs shares some similarities with the human disease process but is not as well described; research efforts continue to expand the literature. For example, gastrointestinal infection, reported in humans, has not been documented in dogs, and the role of the immune system in disease response is an area with more information available in humans with Chagas disease than in dogs.<sup>1</sup> Chronic Chagas cardiomyopathy, characterized by development of a DCM phenotype, was initially documented in dogs >30 years ago.<sup>4</sup> Repeated echocardiographic studies in the dog reported here documented progressive systolic dysfunction and ventricular dilation with apical wall thinning in both ventricles. Aneurysmal ventricular dilation is a feature of human Chagas cardiomyopathy that is associated with an increased embolic risk in humans.<sup>1,13</sup> Aneurysmal dilation has been much

less frequently described in dogs but has been identified on gross postmortem evaluation of the heart in acute disease and as thinning of the left ventricular apex recently described with cardiac gated magnetic resonance imaging (authors' unpublished data).<sup>14</sup> The dog in this report had visible thinning at the apex of both ventricles detected on transthoracic echocardiography in addition to a mottled appearance (hyperechoic areas) in areas of the ventricular septum and right ventricular papillary muscle. Hyperechoic regions identified throughout the myocardium likely represent areas of inflammation and fibrosis, which are described histopathologically in Chagas disease.<sup>5</sup> Although organisms and inflammation can be detected in many organs, the heart is the primary target organ, perhaps because of a parasite tropism for muscle cells, with tissue damage characterized by inflammation, cellular lysis, and fibrosis. Similar to what has been described in humans, the histopathologic description of Chagas myocarditis differs in acute and chronic infections in dogs. Acute infection is characterized by inflammation and more frequently identified intracellular nests of *T. cruzi* amastigotes, while the chronic stage of the disease is characterized by fibrosis and less frequently identified organisms. The chronic stage of the disease is often preceded by a prolonged asymptomatic period. However, damage to the heart continues during this time and rapid disease progression has been described.<sup>1</sup>

In seropositive dogs, the most frequently detected electrocardiographic abnormalities are ventricular arrhythmias.<sup>4,12</sup> Ventricular arrhythmias and conduction abnormalities are reported in multiple stages of the disease process and reflect damage to the conduction system, areas of active myocardial inflammation, and regions of fibrotic myocardium. In addition to ventricular arrhythmias, the dog in this report displayed the RBBB conduction pattern that is noted in many human patients but is not as commonly reported in dogs with Chagas disease.<sup>4,15</sup> RBBB was not reported in experimentally infected dogs in which ventricular arrhythmias and atrioventricular block were documented but has been reported in retrospective studies in naturally infected seropositive dogs, at a lower frequency than seen in infected humans.<sup>4,15</sup> The severity of the disease and how it manifests in naturally infected dogs can be affected by repeated exposure and *T. cruzi* strain type.<sup>3</sup>

## CONCLUSION

Infection with *T. cruzi* is an important cause of mammalian myocarditis that is clinically manifest as arrhythmias, conduction abnormalities, ventricular dilation, and systolic dysfunction. The presence of an



**Figure 4** A resting six-lead electrocardiogram obtained without sedation approximately 5 months following initial presentation. Lead II demonstrates an underlying sinus rhythm (arrow) conducted with a RBBB and first-degree atrioventricular block. Premature ventricular complexes (asterisk) are of varying morphology. Paper speed 25 mm/sec, amplitude 10 mm/mV.

arrhythmia in this patient prompted cardiac evaluation, leading to a diagnosis of Chagas disease with conduction (RBBB) and anatomic (apical wall thinning) abnormalities more frequently described in infected humans.

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### SUPPLEMENTARY DATA

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Supplementary data related to this article can be found at <https://doi.org/10.1016/j.case.2020.06.002>.

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