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CASE REPORT

Antiparasitic treatment with itraconazole and amiodarone in 2 dogs with severe, symptomatic Chagas cardiomyopathy

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Abstract

Chagas cardiomyopathy, caused by the protozoal parasite *Trypanosoma cruzi*, is characterized by arrhythmias, myocardial damage, heart failure, and sudden death. We describe 2 dogs with severe, symptomatic Chagas cardiomyopathy characterized by myocardial dysfunction and electrocardiographic abnormalities that were managed with a combination of cardiac medications and antiparasitic treatment with itraconazole and amiodarone. Both dogs died suddenly within 6 months of diagnosis. These cases highlight the need for early detection of Chagas disease in dogs and continued research to develop effective antiparasitic treatment protocols.

KEYWORDS
canine, myocarditis, treatment, *Trypanosoma cruzi*, ventricular tachycardia

1 | INTRODUCTION

Chagas disease, caused by the protozoal organism *Trypanosoma cruzi*, is an important cause of myocarditis and cardiomyopathy in dogs and people in the Western Hemisphere.[1] *Trypanosoma cruzi* is transmitted by insects in the Reduviidae family, subfamily triatominae, commonly referred to as "kissing" bugs. In people infected with *T cruzi*, the disease occurs in 2 phases: an acute phase occurring within a few weeks after initial infection, and a chronic phase which is subcategorized into indeterminate, cardiac, digestive, or mixed forms.[1,2] Chronic Chagas cardiomyopathy (CCM) occurs in an estimated 20% to 30% of infected people, and clinical manifestations of CCM include diffuse conduction abnormalities, tachyarrhythmias, bradyarrhythmias, thromboembolism, ventricular aneurysms, heart failure, and sudden cardiac death.[3] Sudden cardiac death accounts for 55% to 65% of deaths in people with CCM, and also occurs in dogs with CCM.[1,4-7] Dogs infected with *T cruzi* can remain asymptomatic for life and the proportion of infected dogs that progress to chronic disease is unknown but might be similar to that of people.[8]

Treatment for *T cruzi* infection in dogs and people is challenging. In people, treatment protocols do not consistently provide a cure nor prevent cardiac damage or sudden death despite conversion to negative PCR test results for *T cruzi* infection.[9] Medications evaluated as antitrypanosomal treatment, including nifurtimox and benznidazole, have high adverse-effect profiles at standard doses.[10] The Benznidazole Evaluation for Interrupting Trypanosomiasis trial in people failed to demonstrate benznidazole's effect on preventing the progression of CCM, leading to the evaluation of efficacy and safety of additional dosing protocols for the treatment of Chagas disease.[9] The Centers for Disease Control and Prevention recommends treatment with benznidazole for people with acute infections, immune compromise, babies with congenital (vertical) transmission, and acknowledges potential benefit in chronic infections.[11]

Abbreviations: CCM, Chagas cardiomyopathy; IFA, immunofluorescent antibody; TAMU VMTH, Texas A&M University Veterinary Medical Teaching Hospital.

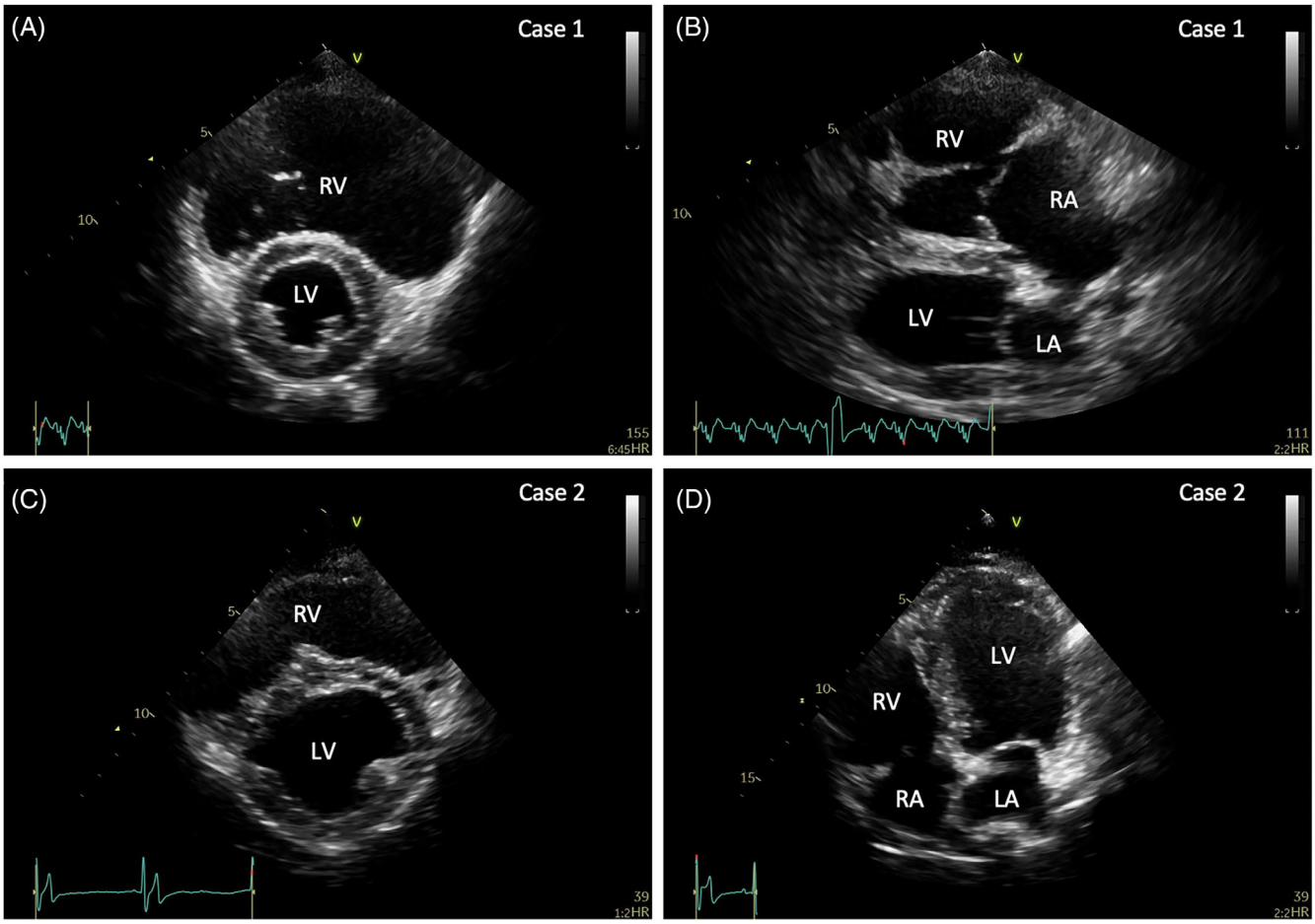

FIGURE 1 Transthoracic echocardiographic images documenting dilatation of the right ventricle (RV) in both dogs with chronic Chagas cardiomyopathy. Case 1 includes images obtained in right parasternal short axis (A) and long axis (B) views to show very severe right atrial and ventricular enlargement compared to the left heart. Case 2 includes images obtained from right parasternal short axis (C) and left apical long axis (D) views to show moderate to severe right ventricular enlargement. LA, left atrium; LV, left ventricle; RA, right atrium

Treatment in people with chronic infections does not consistently provide clinical benefit in established CCM.[1] Treatment protocols for *T cruzi* infection in dogs are not well established. Two studies evaluating the effects of benznidazole at a standard dose of 7 mg/kg PO twice daily for 60 days in dogs with experimentally induced chronic Chagas disease reported temporary reduction in *T cruzi* parasitemia based on PCR and blood culture assays.[12,13] In both studies, treatment with benznidazole was ineffective in preventing the development and progression of CCM.[12,13] Challenges with obtaining cure, preventing CCM, and adverse effects of antiparasitic medications have led to further research exploring alternative dosing strategies and other medical treatment options.[14,15] A combination of amiodarone and itraconazole has been described in the treatment of infected people and dogs with Chagas disease.[6,14] In 1 study, dogs that received this combination had improvement in clinical signs and lived an average of 7.5 months longer compared to a small control population.[6]

This report describes the clinical findings, diagnostic test results, and outcome in 2 dogs that received cardiac medications in addition to antiparasitic treatment with a combination of amiodarone and itraconazole for symptomatic CCM.

2 | CLINICAL CASE REPORTS

2.1 | Case 1

A 9-year-old female, spayed Australian Shepherd weighing 18.8 kg was referred to the Texas A&M University Small Animal Veterinary Medical Teaching Hospital (TAMU VMTH) for a cardiology evaluation. The dog lived in South Texas (Cuero, DeWitt county) and had been lethargic for a week before presentation to the primary veterinarian. Thoracic radiographs obtained 3 days before referral were reported to show cardiomegaly and pleural effusion. The dog was administered furosemide 2.67 mg/kg/day and digoxin 0.01 mg/kg/day. At the time of presentation to the TAMU VMTH, a grade II/VI left parasternal systolic heart murmur and irregular heart rhythm with pulse deficits were noted. Thoracic radiographic findings included generalized cardiomegaly (vertebral heart size 12.6) with a mild diffuse unstructured interstitial pattern and no pleural effusion. A complete blood count was within normal limits and chemistry panel was normal except for mild hypomagnesemia (1.5 mg/dL; reference range, 1.7-2.1 mg/dL). An echocardiogram revealed thickening of the mitral valve leaflets with mild mitral regurgitation, normal left atrial and

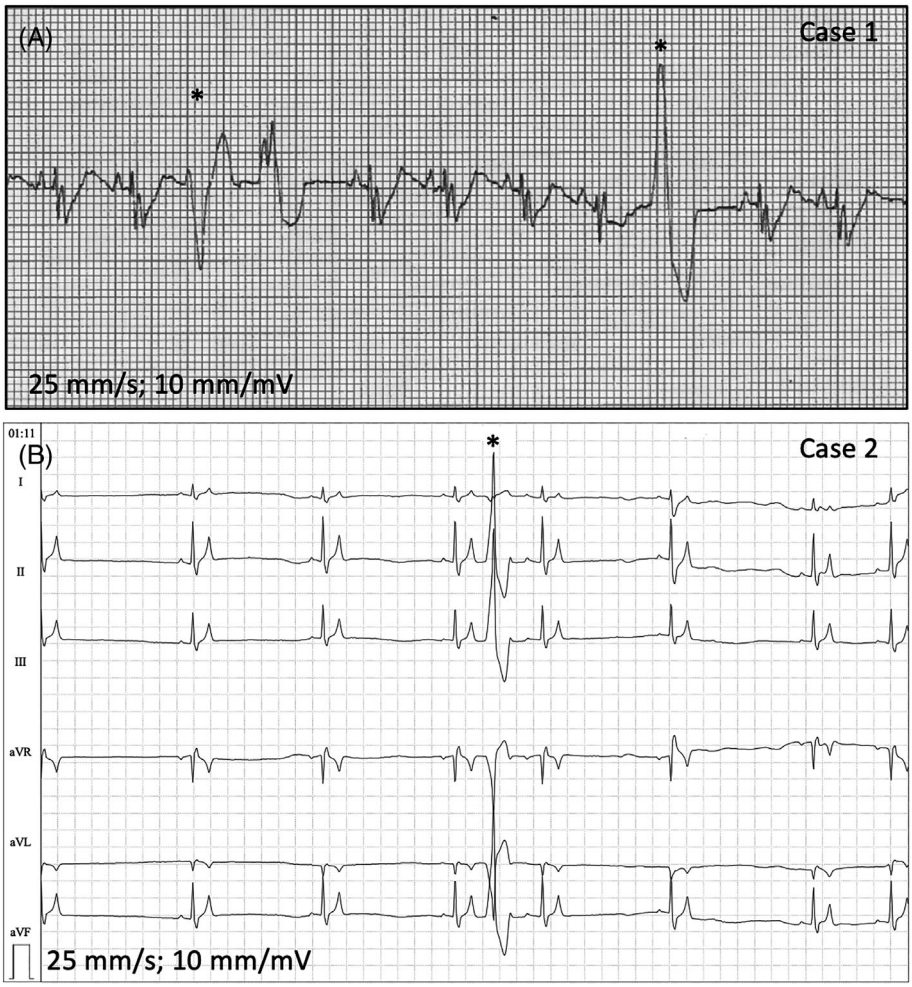

FIGURE 2 Lead II ECG in case 1 (A) documenting a sinus rhythm with complexes that are splintered and multiform ventricular premature complexes (*), and a 6-lead ECG in case 2 (B) documenting a sinus bradycardia (heart rate range, 36-65 beats/min) with wide complexes and a single ventricular premature complex (*) that was upright in lead II suggesting a right ventricular origin. Case 2 was receiving sotalol at the time of the ECG recording

ventricular size, normal left ventricular systolic function, and trace pericardial effusion. The right atrium and ventricle were severely dilated, both larger than the left atrium and ventricle, with a tricuspid annular plane systolic excursion of 10.1 mm (4.3 mm/kg$^{0.28}$; reference >3.2 mm/kg$^{0.28}$),[16,17] moderate tricuspid regurgitation of normal velocity (2.4 m/s), and a dilated coronary sinus suggestive of elevated right atrial pressure (Figure 1; Video S1). An abdominal ultrasound identified mild hepatosplenomegaly and hepatic venous congestion. On 6-lead ECG, there was an underlying sinus rhythm at a rate of 136 beats/min with frequent multifocal ventricular ectopic beats occurring as singlets, couplets, and triplets, with episodes of nonsustained repetitive multifocal ventricular tachycardia at a rate of 200 to 300 beats/min.[18] The sinus beats had abnormal complex morphology with wide (0.08 seconds) and splintered QRS complexes (rsr's), small R waves (0.3 mV), and depression of the ST segment indicative of aberrant and delayed ventricular conduction (Figure 2).[18] Serum cardiac troponin I concentration was abnormal (0.278 ng/mL; reference, <0.128 ng/mL).[19] The dog was hospitalized and administered lidocaine IV at a constant rate infusion of 50 mcg/kg/min. Once the arrhythmia improved with no further ventricular tachycardia observed, the dog was transitioned to oral antiarrhythmics and was discharged from the hospital with sotalol 4.25 mg/kg/day, mexiletine 15.9 mg/kg/day, benazepril 0.53 mg/kg/day, furosemide 2.1 mg/kg/day, pimobendan 0.53 mg/kg/day, spironolactone 2.6 mg/kg/day, and potassium gluconate 0.85 mEq/kg/day. Two days after discharge, a positive *T cruzi* immunofluorescent antibody (IFA; Texas A&M Veterinary Medical Diagnostic Laboratory, College Station, Texas) was reported with an end titer of 1 : 1280, resulting in a diagnosis of Chagas disease. The dog was administered amiodarone 10.6 mg/kg/day and itraconazole 7.9 mg/kg/day for antiparasitic and antiarrhythmic treatment, sotalol was discontinued, and a Holter monitor recording was recommended but not pursued by the owner.[6] Twenty days after being discharged, the dog developed hyporexia, lethargy, diarrhea, and weight loss. The owner discontinued amiodarone, mexiletine, and itraconazole. In consultation with the local veterinarian, amiodarone and mexiletine were restarted. The dog was continued on all medications, except itraconazole, and over the next 2 months the dog's energy level and appetite improved. Biochemistry panels during this time were normal. Approximately 5 months after initial diagnosis, the dog died suddenly at home. A necropsy was not performed.

2.2 | Case 2

A 5-year-old female, spayed Labrador Retriever weighing 38.5 kg from Central Texas (Austin, Travis county) was referred to the TAMU

VMTH for further evaluation of Chagas disease. Approximately 2 weeks before referral, the dog was presented to the primary veterinarian for a transient loss of consciousness. The owners reported 2 other similar episodes 1 year before. An ECG performed at the referring veterinarian revealed ventricular arrhythmias. The dog was administered sotalol 2.1 mg/kg/day and referred to a local specialist where an IFA test for *T cruzi* was positive with a titer of 1 : 320. The dog was administered benazepril 0.52 mg/kg/day, pimobendan 0.52 mg/kg/day, fish oil supplement, and the sotalol was increased to 4.2 mg/kg/day. The dog was subsequently referred to the TAMU VMTH for further evaluation of Chagas disease. Before referral, the dog had been apparently healthy at home with a good energy level and appetite and no further episodes of loss of consciousness. Physical examination findings included an irregular heart rhythm with no auscultable murmur and normal pulse quality. An echocardiogram revealed moderate to severe dilatation of the right atrium and ventricle with a tricuspid annular plane systolic excursion of 11.2 mm (3.9 mm/kg$^{0.28}$; reference, >3.2 mm/kg$^{0.28}$) and trace pericardial effusion.[16,17] The left atrium and ventricle were normal size with normal left ventricular systolic function (Figure 1; Video S2). On 6-lead ECG, there was a sinus bradyarrhythmia (36-65 beats/min) attributed to the use of sotalol, with frequent monomorphic singlet and couplet ventricular premature complexes with a morphology suggestive of right ventricular origin (Figure 2).[18] The sinus beats had wide QRS complexes (0.10 seconds) consistent with a left bundle branch block, and all other measurements were normal.[18] Serum cardiac troponin I was abnormal at (0.298 ng/mL; reference, <0.128 ng/mL).[19] Polymerase chain reactions performed on buffy coat and whole blood were negative for *T cruzi* DNA using a quantitative, real-time PCR that targets *T cruzi* satellite DNA and a conventional assay with 121/122 primers that targets *T cruzi* kinetoplast DNA.[20] The owners were instructed to continue the benazepril, pimobendan, fish oil, and reduce the sotalol over 3 days and then discontinue. The dog was administered amiodarone 10.4 mg/kg/day and itraconazole 7.8 mg/kg/day.[6] Approximately 1 month after evaluation, 2 weeks after initiation of amiodarone and itraconazole, and 1 week before scheduled re-evaluation, the dog collapsed while playing outside and died suddenly.

3 | DISCUSSION

These cases describe the use of cardiac medications in combination with antiparasitic treatment with itraconazole and amiodarone for *T cruzi* to manage CCM. Based on the clinical presentation and diagnostic findings, both dogs were presumed to be chronically infected with *T cruzi*. In chronic infections, myocardial histopathology is characterized predominately by fibrosis.[21] Although endomyocardial biopsy can provide information about myocarditis, it was not considered in these 2 dogs because of an increased risk of right ventricular perforation in the presence of right ventricular dilatation.[22] In people, antiparasitic treatment is recommended in the acute phase of the disease, for immunosuppressed patients, patients with transplacental infection, women of childbearing age, pediatric patients in the chronic phase, and patients with reactivation of *T cruzi* infection.[1,11] However, thus far, antitrypanosomal treatment in people with CCM has limited the ability to change clinical outcome despite evidence of reduced parasite load, and medications like benznidazole have not been routinely accessible.[1,9] This has prompted studies evaluating dosing protocols and reports of alternative drugs used for antiparasitic treatment. In a canine model of acute Chagas disease, benznidazole and itraconazole were not able to reduce parasite burden with resistant strains of *T cruzi*.[15] A recent study reported clinical improvement and 7.5 months longer mean survival time with combination treatment of amiodarone and itraconazole in *T cruzi*-infected dogs compared to a control population.[6] Acute death was reported in 4 dogs in both treatment and control groups.[6] Sudden cardiac death in dogs occurs in both acute and chronic stages of Chagas disease with and without clinical signs.[5-7]

The dogs in this report lived in regions where infected insect vectors are common, had evidence of myocardial disease, predominately right heart enlargement, and ventricular arrhythmias, and both died suddenly within 6 months of diagnosis. Sudden death accounts for roughly 55% to 65% of all deaths in people with CCM, and can occur in up to 20% of asymptomatic patients.[4,23] In the majority of people with Chagas disease, sudden death occurs with severe cardiac disease, although in both people and dogs, sudden death is also reported with minimal or no evidence of gross heart disease.[5,23] In people with CCM, sudden death is attributed to cardiovascular causes including malignant ventricular arrhythmias, congestive heart failure, and thromboembolic events.[4,23,24] Risk scores have been developed to predict sudden death and other adverse outcomes in people with CCM. The Rassi score incorporates 6 factors associated with increased risk of death in people including New York Heart Association class III or IV, presence of cardiomegaly on thoracic radiography, echocardiographic segmental or global wall motion abnormalities, nonsustained ventricular tachycardia on ambulatory ECG, low QRS voltage, and male sex.[25] In dogs with CCM, right ventricular enlargement as well as ventricular arrhythmias with a high, modified Lown score have been associated with worse outcomes.[26,27] Development of risk assessment scores might be useful in predicting survival including risk for sudden death in dogs with CCM.

Both dogs in the current report had evidence of CCM and ECG abnormalities and were managed with cardiac medications and antiparasitic treatment with amiodarone and itraconazole. Amiodarone was prescribed because of its multipurpose indications as an antiarrhythmic medication for ventricular arrhythmias and potential antitrypanosomal activity.[6] However, the severity of the heart disease and irreversible damage to cardiac myocytes combined with relatively short duration of treatment in these 2 dogs might have precluded the clinical benefit of antiparasitic treatment. The antiparasitic dosing protocol for these drugs and whether they clear or suppress infection has not been prospectively evaluated. Both amiodarone and itraconazole have the potential for proarrhythmia, which can result in worsening of arrhythmias or the development of new arrhythmias.[28,29] Both medications can prolong the QT interval leading to an increased potential for fatal ventricular arrhythmias and sudden death.[28,29] In the current report, the initial QT interval in both dogs was normal and was not able to be reevaluated after starting treatment with amiodarone and itraconazole before sudden death. A meta-analysis of amiodarone use

in people with Chagas disease showed an effective reduction in ventricular arrhythmias but described a variety of adverse effects (eg, corneal microdeposits, gastrointestinal, dermatological, sinus bradycardia, and drug discontinuation) with no evidence of a reduction in sudden death.[30] Amiodarone can require a high initial loading dose because of a large volume of distribution and prolonged time to reach steady state and is associated with an increased risk of adverse effects during the loading dose and also with long-term use.[31] Adverse effects of amiodarone in dogs have been reported with loading and long-term maintenance use and include gastrointestinal tract upset, hepatopathy, ophthalmologic abnormalities, and alteration of thyroid hormone concentrations.[31] Adverse effects of itraconazole in dogs are mainly gastrointestinal in origin (eg, reduced appetite, vomiting, and diarrhea) but include hepatopathy and ulcerative dermatitis.[32] Shortly after starting the treatment with amiodarone and itraconazole, the dog in the first case developed lethargy, diarrhea, and hyporexia, which were likely attributed to itraconazole as the dog improved after the discontinuation of this medication. The dog in the second case did not develop any reported adverse effects from the medications. Although both dogs had improvement in clinical signs, adequate control of their arrhythmias was not able to be confirmed. In dogs with poorly controlled ventricular arrhythmias, radiofrequency catheter ablation has been described; however, the utility of this intervention in dogs with complex ventricular arrhythmias, conduction disturbances, and severe structural heart changes secondary to Chagas myocarditis is unknown.[33,34]

Blood from 1 of the 2 dogs was tested using PCR before death, with negative results, despite the positive anti-*T cruzi* antibody results and clinical disease supporting a CCM diagnosis. *Trypanosoma cruzi* parasitemia is intermittent and most common after acute infection. For this reason, negative results of *T cruzi* PCR alone should not form the basis of declaring a dog free of the infection, and conversion to PCR-negative status alone should not be interpreted as parasitological cure in *T cruzi* treatment studies. Cross-reactivity with *Leishmania* has been reported on *T cruzi* serology tests; however, dogs with clinical signs compatible with *T cruzi* in regions where *Leishmania* is not endemic would suggest a true positive result for *T cruzi*.[35]

In summary, we described antiparasitic treatment of *T cruzi* in 2 dogs with CCM and sudden death. Early detection of *T cruzi* infection and effective treatment protocols might play a role in improving patient outcome.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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