Hereditary transthyretin amyloidosis presenting with carpal tunnel syndrome

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■ Cite as: *CMAJ* 2024 January 29;196:E95-9. doi: 10.1503/cmaj.230671

We admitted a 65-year-old right-handed man to the general internal medicine service with decompensated heart failure and gastrointestinal bleeding. Seven years previously, he had presented to his family physician with intermittent, nocturnal numbness and paresthesias of the first 3 digits of his right hand, which progressively worsened and later involved the left hand. He was diagnosed clinically with bilateral carpal tunnel syndrome and was treated unsuccessfully with wrist splints. Two years later he noted tingling in both feet and was diagnosed with atrial fibrillation. Four years after his initial presentation he reported progressive ascending numbness causing gait instability. Nerve conduction studies and electromyography showed bilateral median neuropathy at the wrist (severe on the right, moderate on the left), and length-dependent symmetric axonal sensorimotor polyneuropathy. Despite right carpal tunnel release, his symptoms persisted.

The patient was referred to a neurologist; on physical examination he had a positive Romberg test, absent proprioceptive sensation in the toes, stocking gradient sensory loss to the midshins, absent lower-extremity reflexes, 5/5 proximal strength and 4/5 distal strength. Investigations for acquired axonal neuropathy (Table 1) were unremarkable. A year later, his neuropathy had worsened to the point where he required a walker to ambulate. He also developed non-bloody watery stools alternating with constipation.

Genetic testing for inherited neuropathy found a pathogenic variant consistent with hereditary transthyretin amyloidosis. The patient was started on inotersen (an antisense oligonucleotide inhibitor of hepatic transthyretin production) to treat the polyneuropathy. He noted improvement in his neuropathy and balance, but neurologic examination was unchanged. He was seen by a geneticist who elicited a history of neurologic and cardiac disease in his father and uncle.

Screening cardiac magnetic resonance imaging (MRI) suggested cardiac amyloidosis with an ejection fraction of 38%, asymmetric septal hypertrophy and diffuse delayed enhancement (Figure 1). The patient was seen by a cardiologist, who did not recommend any treatment specific for cardiac amyloidosis. Six months after the diagnosis of hereditary transthyretin amyloidosis, he developed progressive orthopnea and dyspnea on exertion, and months later we admitted him under our care with anasarca secondary to decompensated heart failure, gastrointestinal bleeding and marked functional decline.

Key points

- Transthyretin amyloidosis typically presents with entrapment neuropathy, polyneuropathy or heart failure; some patients may experience autonomic dysfunction or symptoms of central nervous system pathology.
- While signs of transthyretin amyloidosis (e.g., bilateral carpal tunnel syndrome, autonomic and length-dependent neuropathies, heart failure, atrial fibrillation) are common among those without the condition, a high level of suspicion is warranted when patients present with more than 1 classic feature, especially when refractory to treatment, as well as with a family history.
- The diagnosis of transthyretin amyloidosis is made by Congo red stain of tissue biopsies or genetic testing.
- Inotersen and tafamidis are new treatments that may slow the progression of cardiac and neurologic disease and improve quality of life.

The patient's hemoglobin level was 49 g/L on admission. We found severe portal hypertensive gastropathy and severe esophagitis in the distal esophagus on upper endoscopy. We treated him with intravenous pantoprazole twice daily and with transfusions, with no further bleeding during his admission.

Electrocardiography showed low voltage on the limb leads (Figure 2), and transthoracic echocardiography showed increased septal thickening (Figure 3). A pyrophosphate scan showed mild diffuse myocardial tracer uptake suggestive of cardiac amyloidosis. During admission, the cardiology service thought that because of the patient's New York Heart Association (NYHA) class IV symptoms he was unlikely to benefit from tafamidis. We treated him with diuretics and discharged him on standard heart failure therapy. Repeat MRI showed a poorer ejection fraction of 24%. We started him on topical sildenafil for vasomotor neuropathic symptoms, which has provided relief. He continues to live independently despite his NYHA class III symptoms.

Table 1: Differential diagnosis of acquired axonal polyneuropathy, possible corresponding blood tests, and results for our patient

Category	Diagnosis	Investigations*	Results for the patient
Metabolic disorders	Diabetes	Hemoglobin A_{1c}†	5.6%
Nutritional	Vitamin deficiency	Vitamin B_6 Vitamin E Vitamin B_{12}† Folate	48 nmol/L (normal 20–96 nmol/L) 17 µmol/L (normal 12–46 µmol/L) 592 pmol/L (normal > 220 pmol/L) Not performed
Autoimmune disorders	Sjögren syndrome	Anti-Ro Anti-La	< 0.2 < 0.2
	Systemic lupus erythematosus	Antinuclear antibody	Negative
	ANCA-associated vasculitis	Antineutrophilic cytoplasmic antibodies	Negative
	Thyroid disease	Thyroid-stimulating hormone	1.79 mIU/L (normal 0.35–5 mIU/L)
Infectious	HIV	HIV serology†	Not performed
Malignancy	Paraneoplastic syndrome	Anti-AQU4 Anti-MOG Anti-GAD65 Anti-MAG Paraneoplastic disease profile Neurologic disease profile	Negative Negative Negative Negative Negative Negative
	Chemotherapy induced	Medication review	No prior chemotherapy
Infiltrative disorders	Transthyretin amyloidosis	Transthyretin (*TTR*) gene sequencing	c.238A > G (p.Thr80Ala) Known pathogenic variant
	AL amyloidosis	Serum protein electrophoresis† Free light chain ratio†	No M protein detected 1.09 (normal 0.26–1.65)
	Sarcoidosis	Angiotensin-converting enzyme level	Not performed
Toxic exposures	Heavy metals	Mercury Thallium Copper Lead	1.11 µcg/L (normal 0–3.7 µcg/L) (0.06 nmol/L [normal 0–0.2 nmol/L]) 0.06 nmol/L (normal 0–0.19 nmol/L) 12.1 µmol/L (normal 11–22 µmol/L) 16.8 µg/L (normal 0–20 µg/L)
	Alcohols	Ethanol level	Not performed
	Solvents, insecticides	Not applicable	Not performed

Note: AL = amyloid light chain, ANCA = antineutrophil cytoplasmic antibodies, AQU4 = aquaporin-4, GAD = glutamic acid decarboxylase, MAG = myelin-associated glycoprotein, MOG = myelin oligodendrocyte glycoprotein.
*Recommended to be done in a staged fashion considering the most likely causes on the differential diagnosis.
†Suggested initial testing for acquired axonal polyneuropathy based on the most prevalent causes.[1]

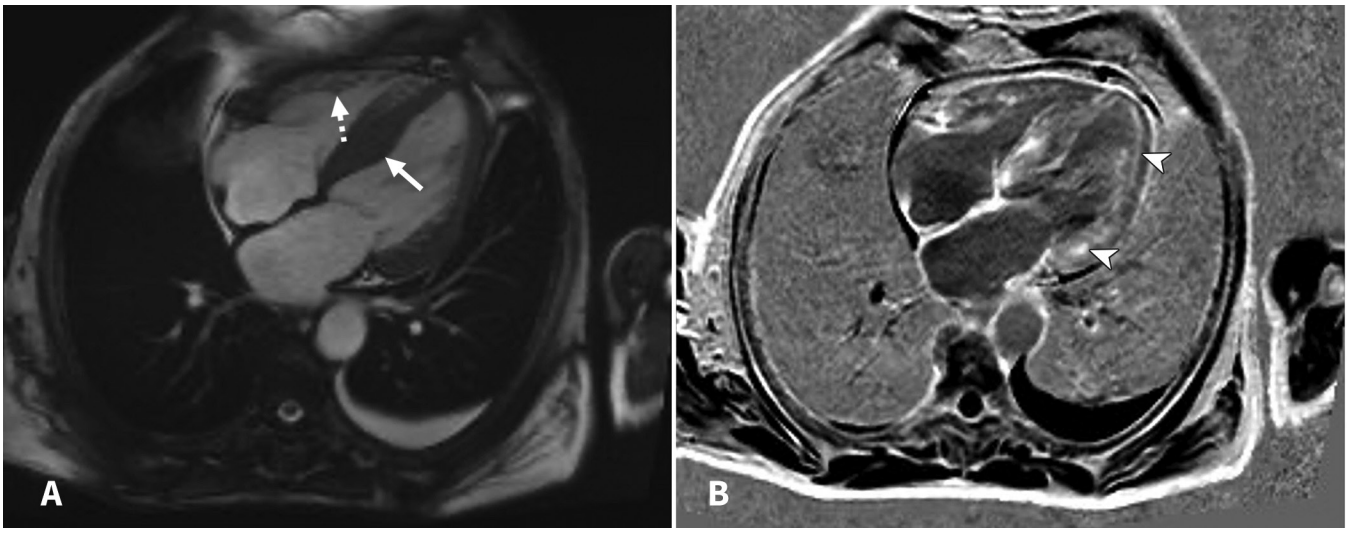

Figure 1: Cardiac magnetic resonance imaging (MRI) in a 65-year-old man with decompensated heart failure and neuropathy. The left ventricular outflow tract (4-chamber) steady state free precession cardiac MRI (A) shows left ventricular dilatation with asymmetric hypertrophy (solid arrow) and right ventricular hypertrophy (dashed arrow). The left ventricular outflow tract (4-chamber) delayed-enhancement cardiac MRI (B) shows diffuse delayed enhancement (arrowheads).

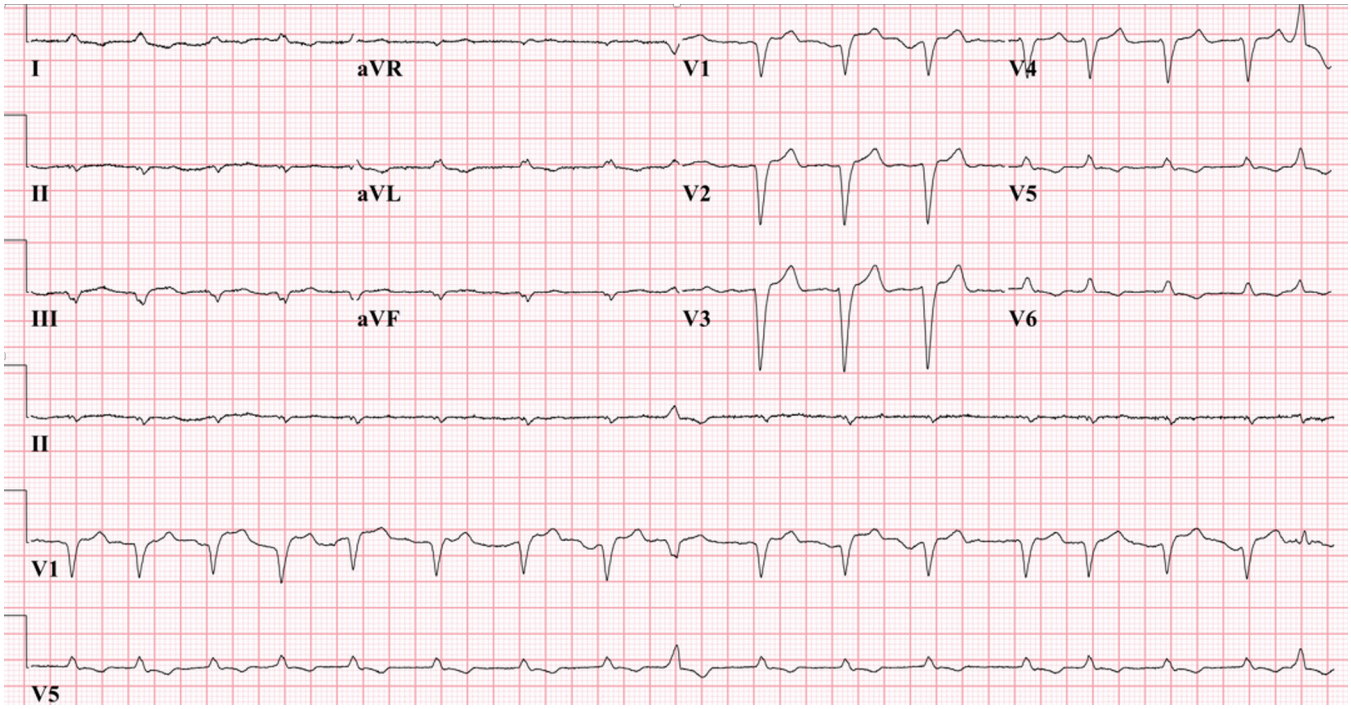

Figure 2: Electrocardiogram showing atrial fibrillation and low voltages in the limb leads, a common feature in amyloidosis.[2]

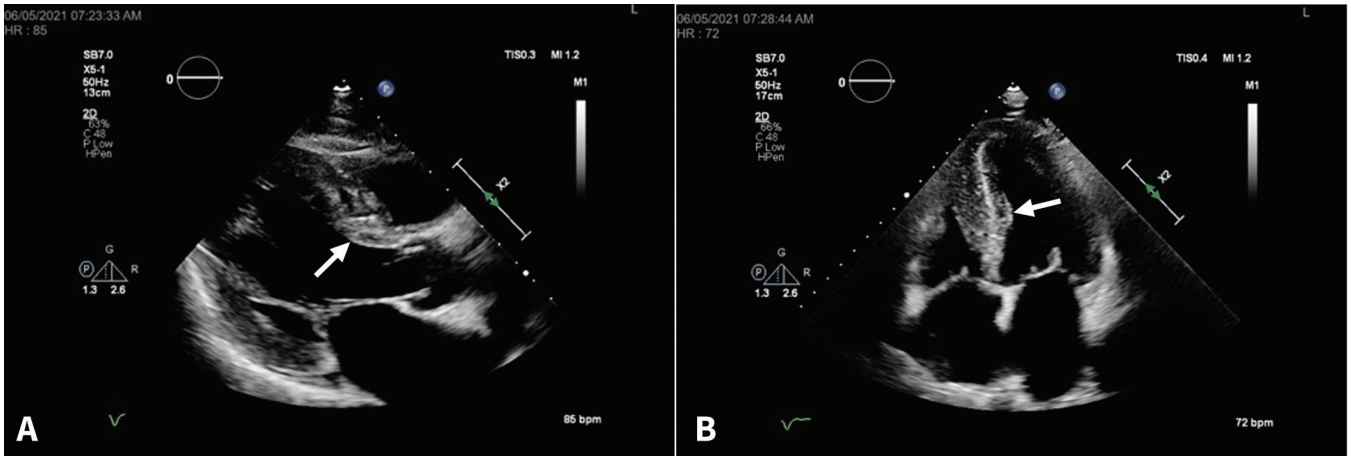

Figure 3: Transthoracic echocardiogram (parasternal long axis [A], apical 4 chamber [B]) showing increased septal thickening (arrows).

Discussion

Carpal tunnel syndrome is the most common presenting feature of transthyretin amyloidosis.[2] However, carpal tunnel syndrome is also the most common mononeuropathy in the general population,[3] and only a small proportion of patients with carpal tunnel syndrome have amyloidosis (Table 2). Thus, determining which patients with carpal tunnel syndrome should be investigated for amyloidosis is a challenge.

Carpal tunnel syndrome can be diagnosed clinically in patients with classic symptoms and signs. However, clinicians should consider amyloidosis in patients with carpal tunnel syndrome in both wrists or who have had multiple or ineffective carpal tunnel releases.[2] Ultrasonography of the median nerve can help identify transthyretin amyloidosis–associated carpal tunnel syndrome. In carpal tunnel syndrome with transthyretin amyloidosis, there may be no increase in median nerve cross-sectional area at the wrist, which is typically found in patients with carpal tunnel syndrome not associated with amyloidosis. A mismatch between electrodiagnostic severity on nerve conduction studies and ultrasonography cross-sectional area suggests amyloidosis.[3]

When transthyretin amyloidosis is suspected in patients with carpal tunnel syndrome, tenosynovial biopsy during carpal tunnel release can be helpful. In a retrospective analysis involving 126 788 patients undergoing trigger finger or carpal tunnel release, amyloidosis was diagnosed with a cumulative 10-year incidence of 0.26% (95% confidence interval 0.18%–0.34%) in patients undergoing trigger finger release, 0.6% in patients undergoing carpal tunnel release, and 0.8% in patients undergoing trigger finger release and carpal tunnel release compared

Table 2: Causes of carpal tunnel syndrome[4]

Mechanical causes	Endocrine disorders	Inflammatory disorders	Infiltrative disorders	Miscellaneous
• Overuse injuries • Vibratory injuries (e.g., use of power tools) • Local fractures or dislocations • Osteoarthritis • Cysts and tumours	• Diabetes mellitus • Hypothyroidism • Acromegaly	• Systemic lupus erythematosus • Rheumatoid arthritis • Scleroderma • Dermatomyositis	• Amyloidosis • Sarcoidosis • Multiple myeloma • Leukemia	• Renal failure • Long-term hemodialysis treatment • Alcohol use disorder • Pregnancy • Obesity • Hereditary neuropathy with predisposition to pressure palsies • Idiopathic

with 0.053% of matched controls.[5] Sood and colleagues developed a risk nomogram to predict the risk of amyloidosis at 10 years and guide tenosynovial biopsy during carpal tunnel release; risk factors included increasing age, male sex, race, multiple myeloma, rheumatoid arthritis, atrial fibrillation, spinal stenosis and a history of bilateral carpal tunnel release.[5]

Amyloidosis is a disorder of protein misfolding and accumulation within tissues.[6] The 2 most common types of systemic amyloidosis are transthyretin amyloidosis and immunoglobin light chain amyloidosis. Transthyretin amyloidosis can be divided into hereditary transthyretin amyloidosis, which presents at around 30–50 years of age, and acquired (wild-type) transthyretin amyloidosis, which is seen most often in older adults.[7]

Hereditary transthyretin amyloidosis is uncommon; the prevalence and phenotype depends on the specific genetic variant identified.[6,7] There are 3 predominant phenotypes: neuropathy, cardiomyopathy and leptomeningeal involvement.[6,7] Neuropathy is the first manifestation of the disease in 80% of patients. This includes mononeuropathy such as carpal tunnel syndrome (which typically predates cardiac symptoms by 6–10 yr), length-dependent sensorimotor polyneuropathy, and small-fibre and autonomic neuropathies.[6,7] Autonomic neuropathy may cause orthostatic hypotension, altered bowel habits, urinary retention, early satiety and erectile dysfunction.[7] Cardiac involvement is present in approximately 40% of patients with transthyretin amyloidosis, resulting in congestive heart failure with preserved ejection fraction. Patients can also experience arrhythmias, especially atrial fibrillation and atrioventricular blocks, and chest pain.[6] Echocardiography typically shows increased left ventricular and interatrial septal wall thickness, elevated left ventricular filling pressures, and normal-to-reduced diastolic function; in the advanced disease, systolic function may also be impaired.[8] Cardiac MRI often shows a thickened myocardium and diffusely delayed gadolinium enhancement.[7] Rare manifestations due to leptomeningeal involvement include seizures, strokes and dementia.[6]

The p.Thr80Ala variant identified in our patient primarily causes cardiac disease with autonomic neuropathy (75%) and only about 25% of patients have substantial sensorimotor neuropathy at presentation.[9] Prognosis of the cardiac disease associated with the p.Thr80Ala variant is worse than for other pathogenic variants.[9]

The gold standard for diagnosing hereditary transthyretin amyloidosis is a biopsy, preferably from abdominal subcutaneous fatty tissue; 2 sites are recommended because of the patchy distribution of amyloid deposits.[2,6,8] Congo red staining shows amyloid fibrils with apple-green birefringence on polarized light microscopy.[2,6] Patients with neuropathy and suspected hereditary transthyretin amyloidosis should undergo sequencing of the *TTR* gene. If a pathogenic or likely pathogenic variant is identified, patients should receive genetic counselling, and cascade screening of at-risk family members should be offered.[8] Confirmatory biopsy is recommended, as there can be incomplete penetrance of individuals having the risk allele.[8]

For patients with cardiac symptoms, echocardiographic or cardiac MRI findings supportive of amyloidosis, and exclusion of light chain disease (i.e., normal free light chain ratio and protein electrophoresis), a pyrophosphate scan without biopsy showing cardiac uptake of the pyrophosphate tracer can confirm the diagnosis.[8,10] If light chain disease is present, a biopsy is necessary for diagnosis.[8]

Patients should be referred to the appropriate specialty depending on manifestations (e.g., cardiology, neurology).[10] Baseline renal function tests, electrocardiography, brain-type natriuretic peptide, troponin and 6-minute walk test are recommended.[10] Electrocardiography every 6 months is recommended to identify conduction system disease.[10] Nerve conduction studies and an echocardiogram should be monitored annually for disease progression.[10] If the initial pyrophosphate scan was negative, it can be repeated 3 years later if myocardial wall thickness increases on echocardiogram or cardiac MRI.[10] If there is suspicion for renal involvement due to transthyretin amyloidosis, renal function and urine albumin and protein should be tested.[10]

The 2 medications that we considered for this patient were inotersen and tafamidis. We prescribed inotersen because of the patient's considerable polyneuropathy. Inotersen inhibits the hepatic production of transthyretin protein and has been shown to slow progression and improve quality of life in patients with polyneuropathy.[6] One small study showed that inotersen may be safe in patients with transthyretin amyloid cardiomyopathy;

however it has not been approved for this indication.[11] Tafamidis, which stabilizes the transthyretin tetramer, preventing protein misfolding, has been approved for transthyretin amyloidosis and has been shown to improve survival and reduce cardiovascular hospital admissions in patients with NYHA class I and II disease.[12] No benefit was found in patients with class III symptoms.[12]

Conclusion

The number of patients with transthyretin amyloidosis is increasing because the disease is more commonly being considered and confirmatory tests ordered. Clinicians should consider this diagnosis in patients with symptoms compatible with the disease because new, effective treatments are now available to slow disease progression and preserve quality of life.

References

1. Mirian A, Aljohani Z, Grushka D, et al. Diagnosis and management of patients with polyneuropathy. *CMAJ* 2023;195:E227-33.
2. Donnelly JP, Hanna M, Sperry BW, et al. Carpal tunnel syndrome: a potential early, red-flag sign of amyloidosis. *J Hand Surg Am* 2019;44:868-76.
3. Salvalaggio A, Coraci D, Cacciavillani M. Nerve ultrasound in hereditary transthyretin amyloidosis: red flags and possible progression biomarkers. *J Neurol* 2021;268:189-98.
4. Aroori S, Spence RAJ. Carpal tunnel syndrome. *Ulster Med J* 2008;77:6-17.
5. Sood RF, Lipira AB. Risk of amyloidosis and heart failure among patients undergoing surgery for trigger digit or carpal tunnel syndrome: a nationwide cohort study with implications for screening. *J Hand Surg Am* 2022;47:517-25.e4.
6. Muchtar E, Dispenzieri A, Magen H, et al. Systemic amyloidosis from A (AA) to T (ATTR): a review. *J Intern Med* 2021;289:268-92.
7. Sekijima Y. Transthyretin (ATTR) amyloidosis: clinical spectrum, molecular pathogenesis and disease-modifying treatments. *J Neurol Neurosurg Psychiatry* 2015;86:1036-43.
8. Adams D, Ando Y, Beirão JM, et al. Expert consensus recommendations to improve diagnosis of ATTR amyloidosis with polyneuropathy. *J Neurol* 2021;268:2109-22.
9. Sattianayagam PT, Hahn AF, Whelan CJ, et al. Cardiac phenotype and clinical outcome of familial amyloid polyneuropathy associated with transthyretin alanine 60 variant. *Eur Heart J* 2012;33:1120-7.
10. Adams D, Algalarrondo V, Polydefkis M, et al. Expert opinion on monitoring symptomatic hereditary transthyretin-mediated amyloidosis and assessment of disease progression. *Orphanet J Rare Dis* 2021;16:411.
11. Dasgupta NR, Rissing SM, Smith J, et al. Inotersen therapy of transthyretin amyloid cardiomyopathy. *Amyloid* 2020;27:52-8.
12. Maurer MS, Schwartz JH, Gundapaneni B, et al.; ATTR-ACT Study Investigators. Tafamadis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med* 2018;379:1007-16.

Competing interests: Patrick Frosk reports a grant from the Canadian Foundation for Innovation and Research Manitoba for creation of computational tools for genetics research, unrelated to the current manuscript, and reports continuing medical education coverage from Doctors Manitoba. No other competing interests were declared.

This article has been peer reviewed.

The authors have obtained patient consent.

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Contributors: All of the authors contributed to the conception and design of the work, drafted the manuscript, revised it critically for important intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Acknowledgements: The authors thank Christopher Nolan and Brett Memauri for their assistance in obtaining echocardiography and MRI images, respectively, for this report.

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