

Letter to the Editor

Ventricular Assist Device Support in End-Stage Heart Failure From Cardiac Amyloidosis

Dear Editor,

A 46-year-old female presented with recurrent heart failure admissions over 3 months. Clinical examination revealed bilateral pleural effusions, raised jugular venous pressure and bilateral swelling of the lower limbs. During her initial admission, a transthoracic echocardiogram showed moderate concentric left ventricular (LV) hypertrophy with moderate global hypokinesia. Left ventricular ejection fraction (LVEF) was moderately impaired. The left ventricular end-diastolic diameter (LVEDD) was 3.5 cm, with restrictive LV filling pattern. There was concomitant moderate to severe tricuspid regurgitation. Her electrocardiogram showed sinus tachycardia and small voltas in the praecordial leads. Serum high-sensitive troponin T was 279 pg/ml (normal: <14 pg/ml) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) 24,800 pg/ml (normal: <150 pg/ml). Computed tomography (CT) coronary angiogram demonstrated normal coronary arteries. Cardiac magnetic resonance imaging (MRI) confirmed depressed LVEF of 39% and a concomitant reduced right ventricular (RV) ejection fraction of 30%. T1-weighted scout image showed that the myocardium could not be nulled. Together with global diffuse subendocardial late gadolinium enhancement seen on late images, the MRI findings were strongly suggestive of cardiac amyloidosis. While an endomyocardial biopsy was not performed, amyloid deposits were detected on a rectal biopsy sample. Serum electrophoresis did not show the presence of a monoclonal band, but immunofixation detected a monoclonal lambda band with serum free light chain assay showing lambda free light chain concentration of 400 mg/L (normal: 5.7–26.3 mg/L) while the kappa free light chain was within normal limits. A subsequent bone marrow biopsy was also not diagnostic of multiple myeloma. She was diagnosed with Mayo stage IV light chain (AL) amyloidosis and commenced on a chemotherapy regime involving bortezomib, dexamethasone and cyclophosphamide.

Although the serum lambda free light chain levels returned to normal following 2 cycles of chemotherapy, she continued to have recurrent heart failure symptoms despite medical treatment. Her low blood pressure (BP) (systolic BP: 70s) precluded the use of any renin-angiotensin-aldosterone-system inhibitors or beta blockers. A low dose of loop

diuretics frusemide resulted in the development of acute kidney injury.

She was wheelchair-bound within 3 months of her initial heart failure presentation and was hospitalised 3 times for decompensated heart failure. She was 1.51 metres tall and weighed 41 kg. Her body surface area (BSA) was 1.32 m². Preoperative right heart study showed cardiac index of 1.27 L/min/m², RV stroke work index of 60.5 mmHg.ml/m² and pulmonary vascular resistance of 3.3 Wood units. After extensive discussion, she decided to undergo a high-risk left ventricular assist device (LVAD) implantation. Via median sternotomy, we modified the LVAD inflow cannula implantation by fashioning a conduit out of a 20 mm Gore-Tex[®] (WL Gore & Associates, Arizona, United States of America [USA]) interposition graft, implanting one end to the interatrial septum and the other end to the anterior right atrial wall. The HeartWare[™] HVAD[™] (HeartWare International, Massachusetts, USA) inflow cannula was connected to the Gore-Tex[®] graft on the right atrial wall (Fig. 1). The outflow graft was trimmed and subsequently connected to the ascending aorta. The tricuspid valve was bicuspidised by closing off the posterior leaflet by stitching between the adjacent commissures. At the end of the procedure, the HVAD was anchored to the right-sided rib cage before the chest was closed. Figures 2 and 3 show the position of the LVAD anterior to the right atrium as seen on CT scans.

Postoperatively, the patient was nursed in the intensive care unit (ICU) and extubated on the second postoperative



Fig. 1. The Heartware[™] HVAD[™] inflow cannula was connected to the Gore-Tex[®] graft that was sewn in the interatrial septum.

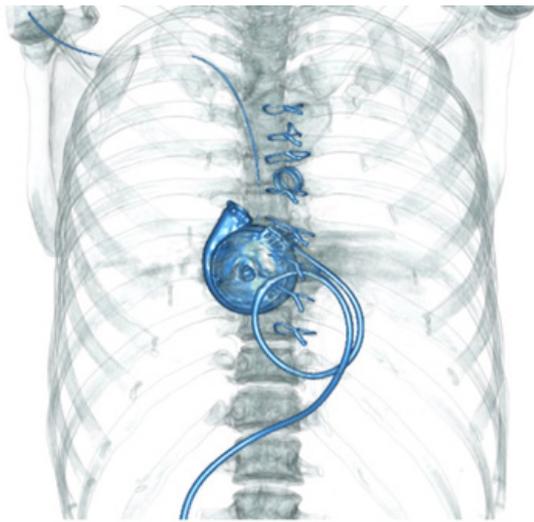


Fig. 2. Computed tomography scan image of the position of the left ventricular assist device shows it was positioned anterior to the right atrium.

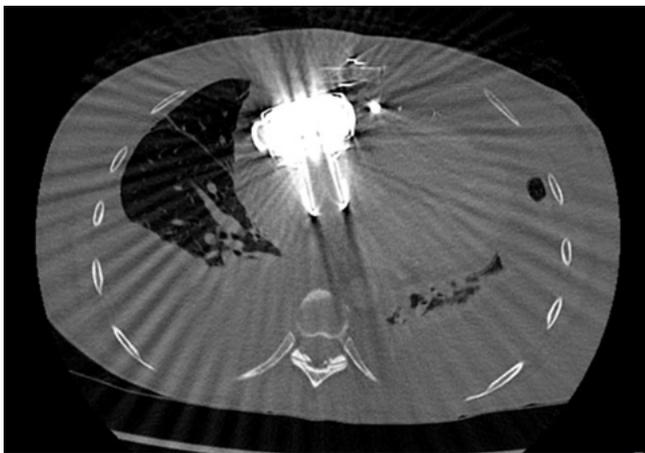


Fig. 3. Computed tomography scan image shows the left ventricular assist device anterior to the right atrium. It is connected to the left atrium through the right atrium via a Gore-Tex[®] conduit.

day (POD). Perioperative RV failure was managed with judicious inotropes. She was transferred to the general ward after 7 days in the ICU and high dependency unit. She was discharged back to her home on POD 21.

The patient's HeartWare[™] HVAD[™] pump speed was initially set at 2500 rpm at a pump flow of 3.0 L/min immediately at the end of surgery. It was subsequently increased during the hospital stay to 2640 rpm at a pump flow of 4.0 L/min at discharge. She was anticoagulated with aspirin (100 mg) every morning and warfarin titrated to an international normalised ratio of 2.0–3.0. Her other medications included sildenafil (25 mg) that was taken 3 times a day, and spironolactone (25 mg) and furosemide (80 mg) that were taken every morning. At 90 days after

hospital discharge, she has not had any LVAD complications nor hospital readmission and is community-ambulant and undergoing outpatient cardiac rehabilitation.

Discussion

The outcome of patients with AL amyloidosis is highly dependent on the spectrum and severity of organ involvement, especially cardiac involvement.¹ Amyloid deposition in the heart results in rapidly progressive heart failure because of restrictive cardiomyopathy (RCM).² The ventricular walls are concentrically thickened with normal or reduced cavity size. The ventricular ejection fraction can be normal or only slightly decreased, but impaired ventricular filling limits cardiac output.³ The severity of organ involvement—especially the heart—usually determines early outcome with cardiac biomarkers such as cardiac troponin T and NT-ProBNP that strongly predict 1-year mortality.⁴ Long-term outcomes are more likely to be determined by factors related to the underlying clonal disorder.⁵

The Mayo staging system based on cardiac biomarkers and clonal markers is a widely accepted staging method for AL amyloidosis.⁵ The median overall survival from diagnosis for those with stages I, II, III and IV disease was 94.1, 40.3, 14.0 and 5.8 months, respectively. Our patient was stage IV at the time of diagnosis and could not tolerate most heart failure medications due to low BP. The typical course of treatment would be palliative care. However, in view of the patient's wishes to pursue treatment to extend her survival and improve her quality of life despite high perioperative risks, the option of using LVAD to treat her refractory heart failure secondary to RCM was discussed and subsequently undertaken.

Although LVAD is primarily implanted in patients with advanced heart failure with reduced ejection fraction, it is also a feasible, life-saving therapy for end-stage heart failure related to RCM.⁶ In a retrospective study involving 28 patients with end-stage RCM receiving LVAD implantation, the 1-year survival rate for patients with LVADs without transplantation was 64%.⁷ This rate was not significantly different between amyloidosis and non-amyloidosis patients. Prior to LVAD implantation, our patient had persistent lower limb swelling, New York Heart Association (NYHA) IV functional class, was home-bound and could ambulate only a few steps. After LVAD implantation, she improved to NYHA II functional capacity and has not had a hospital admission 90 days after discharge.

A major concern with implanting LVADs in patients with end-stage RCM is the association of smaller LV with worse LVAD outcomes.^{8,9} These studies reported that an LVEDD of <64 mm was associated with an increased

30-day morbidity and mortality and RV failure. Most patients recruited in these studies were indicative of dilated cardiomyopathy in aetiology. Possible reasons for poorer outcome in patients with smaller LV sizes include: 1) the risk for “suck-down” events due to the ventricular septum or LV walls resulting in ventricular arrhythmias or reduced LVAD preload, 2) shifting of the ventricular septum to the left leading to altered right ventricle geometry, hence worsening RV function, and 3) small LV cavity presenting technical challenges to optimal inflow cannula implantation, hence suboptimal device placement and inadequate LVAD support.⁷ In our patient, we anticipated that postoperative LVAD inflow cannula obstruction was likely as the LVEDD was only 3.5 cm. She also had a small body size (BSA: 1.32 m²). We used a modified approach for the implantation of the LVAD inflow cannula, previously described by Maeda et al¹⁰ in a paediatric patient with hypertrophic cardiomyopathy. This transatrial left atrial cannulation technique removed the risk of the inflow cannula sucking down on the LV walls. It also limited surgery to the low-pressure chambers of the left and right atrium, avoided surgery to the high-pressure left ventricle, thereby potentially reducing the risk of postoperative bleeding. Our patient did not experience postoperative bleeding nor re-opening despite having concomitant thrombocytopenia with a nadir of 44×10^9 U/L preoperatively.

In the same series of LVAD in RCM patients described by the Mayo Clinic group, the mean hospitalisation time was 24 ± 18 days, while the most common postoperative complication was RV failure.⁷ Postoperative recovery of our patient was also not different from the typical course of LVAD patients of dilated cardiomyopathy aetiology. She was discharged 21 days after surgery. Postoperative RV failure in our patient was initially treated with intravenous dopamine, followed by levosimendan infusion. She was also subsequently put on sildenafil (25 mg) 3 times a day for RV afterload reduction.

While short-term outcome was achieved in our patient, long-term prognosis remains guarded—limited largely by potential complications while on LVAD support. Prior to the LVAD, she was ineligible for multi-organ transplant in view of her frailty and renal impairment. With the LVAD implanted, her clinical condition has much improved, making it possible to bridge her to a potential sequential heart and autologous bone marrow transplantation¹¹ or novel anti-amyloid therapy that may reverse the infiltrative cardiomyopathy. Several treatment regimens that aid in the clearance of amyloid deposits in end organs are actively being investigated. One such treatment regime is with the drug (R)-1-[6-[(R)-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl] pyrrolidine-2-carboxylic acid followed by an

antiserum amyloid protein antibody that has been shown to safely trigger clearance of amyloid deposits from the liver and other tissues in a phase I clinical trial.¹²

Conclusion

LVAD is a feasible therapy for end-stage restrictive cardiomyopathy secondary to cardiac amyloidosis. A modified surgical technique of implanting the LVAD inflow cannula into the left atrium via a conduit/baffle may reduce the risks of postoperative LVAD complications and can be considered in patients with small left ventricles.

REFERENCES

1. Kyle RA, Greipp PR, O'Fallon WM. Primary systemic amyloidosis: multivariate analysis for prognostic factors in 168 cases. *Blood* 1986;68:220–4.
2. Jeyamalar R, Pathmanathan R, Yap SF, Kannan P. Primary cardiac amyloidosis. *Ann Acad Med Singapore* 1991;20:795–7.
3. Falk RH. Diagnosis and management of the cardiac amyloidoses. *Circulation* 2005;112:2047–60.
4. Dispenzieri A, Gertz MA, Kyle RA, Lacy MQ, Burritt MF, Therneau TM, et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. *J Clin Oncol* 2004;22:3751–7.
5. Kumar S, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Colby C, et al. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. *J Clin Oncol* 2012;30:989–95.
6. Topilsky Y, Pereira NL, Shah DK, Boilson B, Schirger JA, Kushwaha SS, et al. Left ventricular assist device therapy in patients with restrictive and hypertrophic cardiomyopathy. *Circ Heart Fail* 2011;4:266–75.
7. Grupper A, Park SJ, Pereira NL, Schettle SD, Gerber Y, Topilsky Y, et al. Role of ventricular assist therapy for patients with heart failure and restrictive physiology: improving outcomes for a lethal disease. *J Heart Lung Transplant* 2015;34:1042–9.
8. Topilsky Y, Oh JK, Shah DK, Boilson BA, Schirger JA, Kushwaha SS, et al. Echocardiographic predictors of adverse outcomes after continuous left ventricular assist device implantation. *JACC Cardiovasc Imaging* 2011;4:211–22.
9. Imamura T, Kinugawa K, Kato N, Muraoka H, Fujino T, Inaba T, et al. Late-onset right ventricular failure in patients with preoperative small left ventricle after implantation of continuous flow left ventricular assist device. *Circ J* 2014;78:625–33.
10. Maeda K, Nasirov T, Rosenthal DN, Dykes JC. An alternative approach by HeartWare ventricular assist device in hypertrophic cardiomyopathy. *Ann Thorac Surg* 2018;106:e231–2.
11. Sivathanan C. Heart transplantation in Singapore. *Ann Acad Med Singapore* 2009;38:309–14.
12. Richards DB, Cookson LM, Berges AC, Barton SV, Lane T, Ritter JM, et al. Therapeutic clearance of amyloid by antibodies to serum amyloid P component. *N Engl J Med* 2015;373:1106–14.

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