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Implantation of a left ventricular assist device to provide long-term support for end-stage Duchenne muscular dystrophy-associated cardiomyopathy

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Abstract

A young man with Duchenne muscular dystrophy presented to the UT Southwestern Neuromuscular Cardiomyopathy Clinic with advanced heart failure. Despite maximal medical therapy, his cardiac function continued to decline requiring initiation of inotrope therapy. Given the patient's clinical deterioration, a left ventricular assist device (LVAD) was implanted as destination therapy after undergoing a multidisciplinary assessment. The patient tolerated the surgical implantation of the LVAD without any significant complications, and he has had a relatively unremarkable course 38 months post-LVAD implantation. A critical factor contributing to the long-term success of this patient was the decision to select an LVAD that would not disrupt the diaphragm and thus preserve the respiratory muscle strength. This case demonstrates that permanent mechanical LVADs should be considered for appropriately selected Duchenne muscular dystrophy patients with medically refractory end-stage cardiomyopathy.

Keywords DMD-associated cardiomyopathy; Heart failure; LVAD support and multidisciplinary approach

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Introduction

Muscular dystrophies are neuromuscular disorders that cause progressive peripheral skeletal myopathies and often are associated with the development of a cardiomyopathy. Duchenne muscular dystrophy (DMD) is a recessive X-linked neuromuscular disorder resulting from a mutation in the dystrophin gene. The loss of dystrophin function leads to a cycle of muscle degeneration and regeneration in DMD patients, ultimately producing progressive skeletal muscle wasting. In addition, DMD patients develop progressive cardiomyopathy, as loss of dystrophin within cardiomyocytes results in cell death leading to cardiac fibrosis and a decrease in cardiac function. In 2017, the primary mode of death among DMD patients is secondary to advanced

cardiomyopathy. To date, there are no definitive therapies to effectively induce reverse cardiac remodelling and improve overall cardiac function within DMD patients. However, we do have advanced heart failure therapies to improve the morbidity and mortality of DMD patients. Here, we present a case of implantation of a left ventricular assist device (LVAD) as a long-term support for a DMD patient with advanced cardiomyopathy who had presented to our institution in cardiogenic shock greater than 3 years ago.

Case Report

An 18-year-old male with DMD presented to the UT Southwestern Neuromuscular Cardiomyopathy Clinic with

advanced heart failure for evaluation and consideration of advanced heart failure therapies (November, 2013). This patient was diagnosed with DMD at the age of 6 years and genetic testing revealed a deletion of Exons 49 to 52 of the dystrophin gene. The patient's past medical history includes DMD-associated cardiomyopathy, a prior transient ischaemic attack, moderate restrictive lung physiology, and mild scoliosis. Although the patient's pulmonary function testing [forced vital capacity: 2.16 L or 40% predicted, forced expiratory volume: 2.03 L or 45% predicted, mean inspiratory pressure: 60 cm H₂O, and mean expiratory pressure: 32 cm H₂O) revealed severe volume restriction and limited diaphragmatic muscle strength, the patient did not require any mechanical pulmonary support. The family history was unremarkable for muscular dystrophy or cardiac disease, and the social history revealed that the patient was a high school senior with no history of tobacco, alcohol, or recreational drug use. The patient was never prescribed steroids as a child, began using a wheelchair by age 11, and did not require bilevel positive airway pressure or ventilatory support. He developed a cardiomyopathy as a teenager, and despite optimization of standard heart failure medications, the patient's clinical condition declined in the preceding months requiring initiation of inotropic support.

Upon initial presentation to the clinic, the patient reported worsening dyspnoea, orthopnea, right upper quadrant abdominal pain with fullness, and increased leg oedema. His medications included milrinone (0.5 µg/kg/min), carvedilol 12.5 mg twice daily, spironolactone 25 mg daily, furosemide 20 mg twice daily, and warfarin. Of note, the patient's enalapril was discontinued because of persistent symptomatic hypotension. The physical exam was notable for sinus tachycardia, elevated jugular venous distention (10 cm above the sternal angle) with a positive hepatojugular reflux, an S3, left parasternal heave, laterally displaced point of maximal impulse, lukewarm extremities, and 1+ lower extremity

oedema. The clinical assessment was that the patient was in decompensated heart failure (INTERMACS Profile 2), and he was admitted for IV diuresis and consideration for advanced heart failure therapies.

Notable laboratory data on admission included evidence of hepatic congestion [alanine transaminase (ALT) = 1135 U/L, aspartate transaminase (AST) = 522 U/L, total bilirubin = 2.9 mg/dL, INR = 6.3], elevated N terminal pro brain natriuretic peptide (NT-proBNP) (10 408 pg/mL) and cardiac enzymes (creatinine kinase = 1555 U/L, creatine kinase-MB = 33 U/L, and troponin T = 0.15 ng/mL), acute renal injury, and moderately elevated serum lactate (2.3 mmol/L) (Table 1). A cardiac magnetic resonance imaging revealed severe bilateral chamber enlargement, severely depressed biventricular heart failure (right ventricle ejection fraction = 26%; left ventricle ejection fraction = 21%), and restrictive left ventricular filling (Tables 2, 3). Haemodynamic assessment on inotropic support revealed elevated right and left filling pressures [mean right atrial pressure = 15 mmHg, right ventricular pressure = 52/11 mmHg, pulmonary artery pressure = 54/35 (43) mmHg, and mean pulmonary capillary

Table 2. Pre-LVAD cardiac MRI parameters

	DMD Patient	Reference
LV EDV (mL)	411	136 ± 30
LV ESV (mL)	351	45 ± 14
LV EF (%)	15	67 ± 5
RV EDV (mL)	260	157 ± 35
RV ESV (mL)	197	63 ± 20
RV EF (%)	26	60 ± 7
LV Mass (g)	151	178 ± 31
Other	LV non-compaction present No late gadolinium enhancement	N/A

EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; DMD, Duchenne muscular dystrophy; LV, left ventricle; LVAD, left ventricular assist device; RV, right ventricle; MRI, magnetic resonance imaging; N/A, not applicable.

Table 1. Patient characteristics and laboratory data

	Baseline 6 months prior to LVAD	Pre-LVAD	Post-LVAD (~12 months)	Post-LVAD (~38 months)
Height (cm)	180	180	180	180
Weight (kg)	84	95	91	79
Body surface area (m ²)	2.05	2.18	2.14	1.99
Na (mmol/L)	134	136	139	140
Cr (mg/dL)	0.1	0.44	0.10	<0.10
Hgb (g/dL)	13.9	9.3	14.2	16.0
ALT (U/L)	92	1135	86	47
AST (U/L)	51	522	57	45
Total bilirubin (mg/dL)	0.4	2.9	1.1	1.3
Total CK (U/L)	1005	1555	871	447
Troponin I (ng/mL)	<0.015	Not measured	Not measured	Not measured
Troponin T (ng/mL)	Not measured	0.15	<0.01	<0.01
NT-proBNP (pg/mL)	3130	10 408	530	457
C-reactive protein	Not measured	36.5	<5.0	<5.0
LDH (U/L)	Not measured	608	268	244

ALT, alanine transaminase; AST, aspartate transaminase; CK, creatine kinase; LDH, lactate dehydrogenase; LVAD, left ventricular assist device; NT-proBNP, N terminal pro brain natriuretic peptide.

Table 3. Echocardiographic parameters

	LVEDD (cm)	LVESD (cm)	LVEF (%)	RVEDD (cm)	RVEF (%)	Mitral filling
Pre-LVAD	6.2	5.8	<35	4.0	Moderate dysfunction	Grade III
Post-LVAD ~1 year	6.0	5.9	<35	Could not be quantified because of image quality, but the RV is dilated with moderately reduced function.		
Post-LVAD ~3 years	6.2	5.7	<35	Could not be quantified because of image quality, but the RV is mildly dilated with mildly reduced function.		

LVAD, left ventricle assist device; LVEDD, left ventricle end-diastolic dimension; LVEF, left ventricle ejection fraction; LVESD, left ventricle end-systolic dimension; RVEDD, right ventricle end-diastolic dimension; RVEF, right ventricle ejection fraction.

wedge pressure = 31 mmHg] with low cardiac output (cardiac output/index by assumed Fick were 3.4 L/min and 1.6 L/min/m², respectively). The patient remained in cardiogenic shock, and additional pressor support with vasopressin, dopamine, and dobutamine was initiated. A multidisciplinary assessment of the patient for either an LVAD and/or heart transplantation was initiated. Specific input was obtained from nutrition, physical therapy, and the neurology and pulmonary teams with experience caring for muscular dystrophy patients. On the basis of a comprehensive assessment of the patient, the Heart Transplant and LVAD Committee recommended implantation of an LVAD as destination therapy. Of note, there has been precedence for the implantation of a Food and Drug Administration-approved LVAD into a DMD patient as has recently been reported.¹

To avoid disruption of the diaphragm and preserve the patient's residual diaphragmatic muscle strength, an active decision was made to recommend implantation of an intrapericardial centrifugal continuous-flow LVAD. Insurance approval was obtained, and subsequently, the patient underwent successful implantation of a centrifugal continuous-flow LVAD in December of 2013. He tolerated the procedure very well, was extubated on post-operative day (POD) #1, and was transferred out of the intensive care unit on POD #3. The patient had some post-LVAD right-sided heart failure, which resolved within 1 month post-surgery. This right-sided heart failure likely was secondary to decompensated LV systolic dysfunction, and it resolved with up-titration of the LVAD speed. His hepatic and renal function returned to baseline levels, and cardiac congestion as indicated by NT-proBNP dramatically improved (Table 1). All inotropic support was weaned off by POD #6, and he was discharged home on POD #14.

The patient has been hospitalized for four brief hospitalizations since implantation of the LVAD. Three of the hospitalizations were for supratherapeutic INR, while one of the hospitalizations was for dizziness secondary to hypovolemia. His course has been otherwise unremarkable, and he is alive and doing very well 38 months post-LVAD implantation. He remains independent of ventilatory and nutritional support. The LVAD parameters have remained relatively stable over the past 3 years (Table 4). The patient successfully graduated from high school and is enjoying quality time with his family, including several long distance family vacations.

Discussion

Duchenne muscular dystrophy is an X-linked recessive disorder that results from mutations in the dystrophin gene. This debilitating neuromuscular disease affects 1 in 5000 boys, usually presenting before age 5 when motor development milestones are missed. Most boys are wheelchair dependent by their teenage years. Respiratory muscle strength progressively declines leading to respiratory complications, although the use of respiratory therapy and ventilatory support have significantly prolonged survival.² Cardiac disease in DMD patients often presents with progressive cardiomyopathy and/or arrhythmias. Current medical therapy for DMD-associated cardiomyopathy is derived from small clinical trials coupled with established chronic heart failure regimens.^{3–5} Initiation of angiotensin-converting enzyme inhibitor and steroid therapy in childhood has been shown to reduce mortality, and the addition of eplerenone was recently shown to reduce decline in left ventricular systolic function.^{4–6} Unfortunately, nearly all DMD patients will develop progressive cardiac dysfunction despite maximal medical therapy, necessitating the search for additional therapies. Without medical intervention, the mean age of death is in the 20s; although with modern medical management, the lifespan can be prolonged into the 30–40 year range. In 2017, because of advances in respiratory management, end-stage cardiomyopathy is now the primary mode of death among DMD patients.^{3,7}

Albeit limited, advanced heart failure therapies (primarily heart transplantation) have been utilized for the management of cardiomyopathy secondary to neuromuscular disease. Patients with muscular dystrophy (most commonly Becker muscular dystrophy) who received a heart transplant exhibit similar overall survival at 1 and 5 years compared with a matched non-ischaemic cardiomyopathy heart transplant patient cohort.⁸ However, heart transplantation in DMD patients remains highly controversial. Recently, an axial continuous-flow LVAD was implanted into a 30-year-old male with DMD, whose post-LVAD course was prolonged and complicated by multiple medical issues.¹ To the best of our knowledge, this current case represents the first report of a centrifugal continuous-flow LVAD in a DMD patient and represents the longest surviving DMD patient in the world

Table 4. LVAD parameters

	Post-LVAD (Hospital Discharge)	Post-LVAD (~12 months)	Post-LVAD (~38 months)
LVAD power (Watts)	3.6	4.2	4.4
LVAD speed (RPM)	2600	2660	2680
LVAD flow (L/min)	4.2	4.1	4.4

LVAD, left ventricle assist device.

with a permanent LVAD with minimal post-implant complications.

In our current case, there are key points that highlight the beneficial effects of the LVAD on end-organ perfusion in this patient. First, the patient did have acute renal injury, as evident by a creatinine level of 0.44 mg/dL. DMD patients often have low creatinine levels because of their low muscle mass; however, an increase in this patient's creatinine level from 0.10 to 0.44 mg/dL is a mark of significant renal dysfunction. One year post-LVAD, the creatinine level dropped to 0.10 mg/dL, suggesting recovery of the renal function. Second, at baseline, the patient has a mild transaminitis (ALT>AST) that is often observed in DMD patients and presumably was secondary to the skeletal muscle breakdown. However, at the time of decompensation, this patient had a significant increase in the ALT and AST values suggesting liver congestion from decompensated heart failure. One year post-LVAD, the liver enzymes were back to baseline levels. Finally, marked reduction in the NT-proBNP level is a strong indicator that the LVAD improved the patient's overall volume status.

The long-term success in the management of this patient can be attributed to multiple key factors, which are listed below:

- (1) Use of a multidisciplinary team pre-LVAD and post-LVAD implantation.
- (2) Appropriate candidate selection. While moderate restrictive pulmonary physiology was present, the patient did not require any mechanical ventilatory support either pre-LVAD or post-LVAD.
- (3) Recognition of end-organ dysfunction. DMD patients have very low baseline serum creatinine because of low muscle mass and even mild elevations are indicative of renal dysfunction. Conversely, liver function tests may be borderline elevated, although further elevation, especially with evidence of volume overload, suggest right-sided heart failure in DMD patients.
- (4) An experienced cardiothoracic surgeon with significant expertise implanting LVADs into critically ill patients with advanced cardiomyopathy.
- (5) Selection of a LVAD that would not disrupt the diaphragm and thus further weaken the diaphragmatic muscle strength. We believe this is perhaps the most important factor that has allowed this patient to live for an extended period of time without any major medical complications. To date, this patient remains free of any mechanical ventilatory support.

- (6) Early extubation with aggressive pulmonary toilet.
- (7) Aggressive care provided by physical, occupational, and respiratory therapy teams post-LVAD.
- (8) Very supportive and involved family.

In conclusion, we present a case of treatment of advanced DMD-associated cardiomyopathy with the successful implantation of a centrifugal continuous-flow LVAD. In DMD patients, placement of LVADs that do not require disruption of the diaphragm should be encouraged to minimize pulmonary complications post-LVAD. As pulmonary therapies continue to improve the morbidity and mortality within this patient population, the impact of advanced cardiomyopathy will continue to increase. This case demonstrates the feasibility of successfully implanting LVADs into DMD patients with long-term survival and decreased morbidity. Further studies are needed to investigate the optimal selection of DMD patients with advanced end-stage cardiomyopathy, who may derive a morbidity and mortality benefit from implantation of centrifugal continuous-flow LVADs.

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Conflict of interest

None declared.

Disclosures

Pradeep P.A. Mammen MD has the following disclosures to declare:

American Heart Association: Co-Chair of the AHA Innovative Research Grant Committee (Basic Science 2).
 California Institute of Regenerative Medicine: Member of the CIRM Grant Review Committee.
 CareDx Inc.: Consultant and Site PI for the OAR Registry.
 Catabasis: Consultant
 HeartWare: Consultant
 PhaseBio: Consultant and Research Grant.

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