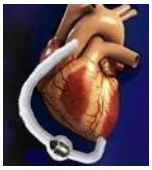

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Peer-Reviewed Original Research

Left Ventricular Assist Device is a Viable Therapy in End Stage Hypertrophic Cardiomyopathy

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Abstract

Left Ventricular Assist Device (LVAD) therapy use is increasing rapidly in advanced heart failure (HF). Little data exists on the application of this therapy in patients with advanced HF due to hypertrophic cardiomyopathy (HCM). Altered ventricular geometry, thickened septum and reduced LV end-diastolic diameter (LVEDD) in HCM may lead to increased suction events, arrhythmias and inflow cannula malfunction.

We hypothesized that patients with end stage HCM benefit from LVAD therapy and have a similar rate of complications to those with ischemic or dilated CM.

Between 2009 and 2014, 5 patients with end stage HCM (HCM and EF <50%), were implanted with either a HeartMate II ® (80%) or HVAD® (20%) device, as a bridge-to-transplant (BTT) (80%) or destination therapy (DT) (20%). We compared baseline characteristics, surgical, and long-term clinical outcomes between these patients and those receiving an LVAD for end stage dilated and ischemic CM (n=214) during that time frame. The HCM cohort had a smaller LVEDD (5.2 versus 6.9 cm, p=0.001) and a higher LVEF (28% v 18%, p=0.002).

Cardiopulmonary bypass time was similar between the groups (72min vs 69min). Post-operative length of stay was also similar at 21 days. Operative mortality for HCM patients was 0. All 4 BTT patients survived to transplant. LVAD therapy resulted in improved LVEDD (5.2 cm to 3.9 cm), PASP (58.8 mmHg to 30.8 mmHg), and cardiac index (1.5 to 2.82L/min/m^2) in patients with HCM, without an increased incidence of postoperative complications. Median duration of LVAD support in the HCM group was 14 months and 10 months for the control.

We conclude that select patients with end stage HCM may benefit from LVAD therapy with a similar rate of complications compared to traditional candidates. Additional study is warranted to further evaluate durable mechanical support in this population.

Keywords: hypertrophic cardiomyopathy, left ventricular assist device, heart failure

Introduction

Hypertrophic cardiomyopathy (HCM) is a common genetically inherited cardiovascular disease, affecting at least 1 in 500 people world-wide (1). It is caused by an autosomal dominant mutation in the genes that encode sarcomere proteins or sarcomere-associated proteins (2), leading to left ventricular hypertrophy of varying morphologies. The pathophysiology of HCM is complex and consists of multiple interrelated abnormalities, including left ventricular outflow obstruction, diastolic dysfunction, mitral regurgitation, arrhythmias, and myocardial ischemia (3). The clinical diagnosis is usually made by 2D echocardiogram imaging or cardiac MRI and it is based on the presence of a hypertrophied and non-dilated left ventricle in the absence of another cardiac or systemic disease that could explain the degree of hypertrophy (≥ 15mm wall thickness in an adult or equivalent indexed to body surface area in a child)(4). Most patients with HCM have normal systolic ejection fraction throughout the disease process. However, some progress into a phase characterized by systolic dysfunction, LV dilatation, and wall thinning, often referred to as end-stage or “burned-out” HCM (5). Dilated-hypokinetic HCM develops in 5-15% of these patients, resulting in rapid progression of heart failure symptoms, arrhythmia and ultimately death, and is the single most frequent indication for heart transplantation among patients with HCM (4,6,7).

In recent years, left ventricular assist devices (LVAD) have become a standard therapeutic option for patients with advanced heart failure (HF) due to dilated or ischemic cardiomyopathy, with trials showing benefit in mortality compared to medical therapy (8). Patients with HCM present unique challenges for mechanical support with smaller LV cavities and increased wall thickness and thus are not represented in these trials. In this study we report the characteristics, surgical and long term outcomes of patients with burned out HCM who received LVAD therapy

in our institution compared with those who received LVAD as treatment for dilated or ischemic cardiomyopathy.

Methods

Between 2010 and 2014, five patients with end stage or burned-out HCM, defined as patients with a history of HCM and systolic dysfunction with EF <50%, were implanted with either a Heart Mate II ® (Thoratec Corp., Pleasanton, CA) or HVAD® (HeartWare Corp., Framingham, MA) device as a bridge to transplant (BTT) or destination therapy (DT) in our institution. We compared baseline characteristics, surgical and long-term outcomes between these patients and non-HCM patients who received an LVAD for end stage dilated and ischemic cardiomyopathy during the same time frame (n=214). Baseline demographics, laboratory values, echocardiographic and catheterization data, operative and post-operative clinical variables were obtained via review of the medical record.

Statistical Methods

Patient characteristics were summarized by the mean ± standard deviation for continuous variables and by frequency counts (percent) for categorical variables. Student's two sample t-test for independent groups and Fisher's exact test were used to compare between HCM and non-HCM groups for continuous and categorical data, respectively. All non-normal and ordinal variables were summarized by the median (1st quartile, 3rd quartile) and compared using Mann-Whitney U test.

Comparisons of pre and post LVAD implantation data among HCM patients were done using paired t-tests for normally distributed continuous variables or Wilcoxon matched-pairs signed-ranks test for non-normal and ordinal variables.

All analysis conducted in SAS v9.4. (SAS Institute Inc., Cary, NC)

Results

Baseline characteristics

There was no difference in baseline demographic characteristics (age, gender, BMI) between the patients who received an LVAD for end stage HCM compared to non-HCM patients (Table 1). All HCM patients were experiencing NYHA class III-IV symptoms and were on positive ionotropic agents pre-operatively (versus only 14% of the control patients), however none received temporary mechanical support. There was no significant difference in pre-operative hemoglobin, renal function tests, liver function tests (LFTs), platelets or INR between the groups (table 2).

We found that the HCM cohort had a significantly smaller LV end diastolic diameter than the non-HCM cohort (5.2 vs 6.9cm, p=0.001) and a higher LV EF (28% vs 18%, p=0.002) (Table 2). There were no significant differences in MR or TR severity between groups. The HCM cohort had a higher pulmonary artery wedge pressure than the control group (32 vs 27mmHg, p=0.006); however RA pressure, PA systolic pressure and cardiac index values were not significantly

different. Additionally, there was no between group difference in incidence of pre-operative arrhythmia (ventricular tachycardia or atrial fibrillation) (Table 1).

Table 1. Baseline Patient characteristics

	Control (n=241)	HCM (n=5)	p-value
Age	57.19 ± 11.79	56.00 ± 13.00	0.82
Gender			
Male	195 (81%)	4 (80%)	1.00
BMI	29.07 ± 5.85	26.00 ± 3.32	0.24
History of VT			
Yes	77 (47%)	1 (20%)	0.37
History of A Fib			
Yes	113 (47%)	4 (80%)	0.19
Pre-op vasopressor			
Yes	33 (14%)	5 (100%)	<0.001
Pre-op temporary MCS*			
Yes	65 (27%)	0 (0%)	0.33
LVAD type			0.53
Heartmate II	208 (86%)	4 (80%)	
HVAD	33 (14%)	1 (20%)	

Table 1: All values reposted as n (%), mean ± SD, or median (25% percentile, 75% percentile).

A fib = atrial fibrillation; BMI = Body mass index; VT = ventricular tachycardia;

*temporary mechanical circulatory support = impella, balloon pump, or ECMO

Table 2: Baseline Laboratory and hemodynamic characteristics

Pre-VAD	Control (n=241)	HCM (n=5)	p-value
Hb (g/dL)	10.98 ± 1.73	11.48 ± 1.81	0.52
BUN (mg/dL)	36 ± 20.46	41.60 ± 9.07	0.55
Creatinine (mg/dL)	1.58 ± 0.81	1.96 ± 0.64	0.29
Platelets (k/uL)	199.29 ± 85.2	150.2 ± 50.51	0.20
Albumin (mg/dL)	3.5 (3.2, 4.0)	3.4 (3.4, 3.7)	0.74
INR	1.4 (1.3, 1.7)	1.6 (1.4, 2.2)	0.19
AST (U/L)	40.0 (27.0, 76.0)	48.0 (36.0, 65.0)	0.73
BNP (pg/dL)	1090.42 ±700.98	1366.60 ± 862.48	0.39
LVEDD (cm)	6.89 ± 1.16	5.18 ± 0.76	0.001
LV EF (%)	18.46 ± 6.72	28.00 ± 8.15	0.002
Severe MR (n, %) **Yes**	51 (22%)	0 (0%)	0.59
Severe TR (n, %) **Yes**	17 (7%)	0 (0%)	1.00
RA pressure (mmHg)	14.68 ± 6.67	14.60 ± 7.06	0.98
PA systolic pressure (mmHg)	57.50 ± 13.27	58.80 ± 11.01	0.83
PVR (Wood units)	4.03 ± 2.69	4.49 ± 2.04	0.71
Wedge pressure (mmHg)	27.23 ± 7.78	32.00 ± 2.35	0.006
Cardiac Index (L/min/m^2)	1.84 ± 0.55	1.50 ± 0.22	0.17

Table 2: All values reported as n (%), mean ± SD, or median (25% percentile, 75% percentile). Hb = Hemoglobin; LVEDD = Left ventricular end diastolic diameter; LVEF = Left ventricular ejection fraction; MR= mitral regurgitation; TR=tricuspid regurgitation; RA= right atrium; PVR= pulmonary vascular resistance

Operative and post-operative outcomes

80% (n=4) of the HCM patients received a Heart Mate II ® and 20% an HVAD®. This was similar to the control group (85% Heart Mate II ® and 15% HVAD®) (table 1). 80% of the HCM were implanted as bridge to transplant (BTT), with only one implantation as destination therapy (DT). The median post-operative length of stay was similar between groups at less than 30 days for both. Median duration of LVAD support was also similar at roughly 14 months for both groups. There was no difference in post-operative complications including bleeding, stroke, and hemolysis between groups. One-year mortality for the HCM patients was zero (Table 3).

Table 3: Post-VAD Outcomes

Post-VAD	Control (n=241)	HCM (n=5)	p-value
RVAD need (n, %) Yes	19 (8%)	0 (0%)	1.00
Peri-op pRBCs	7.0 (4.0, 14.0)	2.0 (0.0, 4.0)	0.007
LOS* (days)	29 (21.0, 43.0)	21.0 (14.0, 33.0)	0.37
Time to Rehospitalization (days)	39 (15.0, 99.0)	28 (24.0, 280.0)	0.35
LOS > 30 days Yes	106 (44%)	1 (20%	0.37
Rehospitalization (1yr) Yes	154 (72%)	5 (100%)	0.33
Hemolysis (1yr) Yes	30 (12%)	0 (0%)	1.00
GI bleed (1yr) Yes	71 (29%)	1 (20%)	1.00
Stroke (1yr) Yes	27 (11%)	0 (0%)	1.00
Death (1yr) Yes	68 (28%)	0 (0%)	1.00
Implant to death or transplant (months)	13.7 (3.8, 25.4)	14 (11.0, 16.0)	0.99

Table 3: All values reposted as n (%), mean ± SD, or median (25% percentile, 75% percentile).

pRBC = packed red blood cells; GI = gastrointestinal, LOS=length of stay

In the patients with HCM, LVAD therapy resulted in a significant improvement in LV end diastolic diameter (from 5.2 cm to 3.9cm), PASP (from 58.8mmHg to 30.8mmHg), and cardiac index (from 1.5 to 2.82 L/min/m^2) after 3 months of support (Table 2). 80% of the HCM patients had a baseline history of atrial fibrillation compared to 47% in the control group, and all of them experienced post-operative atrial fibrillation (Table 4). The only HCM patient with a history of pre-operative VT experienced post-operative VT. The HCM cohort received a combined average of 2.2 units of RBCs post-operatively (Table 3). None of the HCM patients required post-operative temporary mechanical support (Extra Corporeal Membrane Oxygenation, Impella, Intraortic Balloon Pump or Right Ventricular Assist Device). The HCM patients required between 5 and 7 days of inotropic support post-operatively, without echo evidence of post-operative right ventricular failure or dysfunction.

Table 4: Pre and post VAD comparisons among HCM patients

Variable	Pre (N=5)	Post (N=5)	P-value
Cardiac Index (L/min/m^2)	1.50 ± 0.22	2.82 ± 0.57	0.005
RV dysfunction (1=mild, 2=moderate)	1.0 (1.0, 2.0)	0.0 (0.0, 1.0)	0.13
PA systolic pressure (mmHg)	58.80 ± 11.01	30.80 ± 7.05	<0.001
LVEDD (cm)	5.18 ± 0.76	3.96 ± 0.49	0.020
LVESD (cm)	4.23 ± 0.71	3.08 ± 0.77	0.002
Mitral regurgitation (1=mild, 2=moderate)	1.0 (1.0, 2.0)	0.0 (0.0, 0.0)	0.06

Table 4: All values reposted as n (%), mean ± SD, or median (25% percentile, 75% percentile). RV=right ventricle; PA=pulmonary artery; LVESD=left ventricle end systolic dimension

Overall, there was no increased incidence of post-operative arrhythmias, right ventricular dysfunction, dialysis, bleeding or CVA in the HCM cohort. All 4 BTT HCM patients were successfully transplanted, with one of them receiving a heart-kidney transplant.

Discussion

In this small case series, LVAD was employed in 5 HCM patients with clinical success. Additionally, all four BTT HCM patients were successfully supported to orthotopic heart transplant. Our report adds to a small body of literature

demonstrating that, despite difficulties related to the nature of the disease, LVAD can be used successfully in selected HCM patients.

This is one few, and largest, series to report that LVAD therapy can be used in patients with end stage HCM, without added morbidity and mortality. The first reported case series included four patients with dilated HCM implanted with axial continuous flow devices, and showed LVAD therapy did not result in increased morbidity or mortality (9). Another case series with three patients showed that patients with HCM benefited from LVAD therapy with centrifugal continuous flow devices in the short to medium term (10). Our findings are in agreement with the previous reports and add evidence to support use of this technology when and if necessary in this population.

Patients with end stage HCM represent a different cohort than those with dilated and ischemic cardiomyopathy. As mentioned, the pathophysiology of HCM is complex and is characterized by left ventricular outflow obstruction, diastolic dysfunction, mitral regurgitation, increased burden of arrhythmias, and myocardial ischemia. The ventricular geometry is also different, with small cavities, thicker walls, and redundant mitral valve leaflets, which is a potential technical concern for LVAD placement and function. They are at a high risk of sudden death due to heart failure and arrhythmias; a risk that increases markedly with increase in NYHA class (4). Medical therapy for these patients remains limited due to different pathophysiology than those with dilated or ischemic cardiac disease. Afterload reduction and diuresis is often poorly tolerated, resulting in increased outflow obstruction, hypotension and renal injury, while ionotropic agents can increase the risk of arrhythmias (11). LVAD therapy has been shown to improve outcomes in patients with advanced dilated or ischemic cardiomyopathy who are failing maximal medical therapy (12, 13). However patients with HCM have not been represented in the LVAD trials. There is concern for increased suck down events and arrhythmias due to smaller LV cavity size in these patients, as well as RV dysfunction post LVAD implantation.

Progression to end stage dilated-hypokinetic stage occurs in ~10-15% of patients with HCM (14). Once LV dilatation is established, the evolution toward severe heart failure and death is often rapid, with reported refractoriness to medical therapy and more severe symptoms than those with idiopathic dilated CM, despite overall better EF (6). Duration from onset of end-stage HCM to death or transplantation was reported to be only ~2.7 years in one report by Harris, et al. (15). This is consistent with our data, showing that all of the HCM patients were experiencing NYHA class IV symptoms requiring ionotropic support prior to LVAD implantations, despite a significantly higher EF than the control group. A combination of altered ventricular geometry with smaller cavity size, resulting in similar or even reduced effective stroke volume despite higher EF, as well as severe combined diastolic and systolic dysfunction in HCM likely contribute to this discrepancy.

Cardiac transplantation remains the optimal treatment option for end-stage HCM patients. However, the numbers of patients needing transplantation and, as a result, the transplant wait times are increasing. Consequently, end-stage HCM patients are at risk of progressing to irreversible pulmonary hypertension,

refractory heart failure and ultimately death without further advanced HF therapy options. The use of LVAD therapy has markedly increased over the recent years, with overall transplant numbers remaining the same. As a result, the proportion of patients transplanted after VAD therapy continues to increase. In the last year, approximately 90% of patients undergoing heart transplant in our center had previously received an LVAD. Given high morbidity and mortality associated with end-stage HCM and the scarcity of the ideal therapy, heart transplantation, LVAD placement is a reasonable next step. This is the largest case series reporting that selected patients with end stage HCM can benefit from LVAD therapy without increased morbidity and mortality, similarly to those with dilated and ischemic cardiomyopathy. LVAD therapy appears to be a viable therapy for selected patients with end stage hypertrophic cardiomyopathy awaiting cardiac transplantation.

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