Research Highlight

Impact of reverse remodeling on cardiac function

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Submitted Jun 25, 2014. Accepted for publication Aug 19, 2014.
doi: 10.3978/j.issn.2225-319X.2014.08.10
View this article at: http://dx.doi.org/10.3978/j.issn.2225-319X.2014.08.10

Introduction

Left ventricular assist devices (LVADs) have become the standard of care for treatment of patients with refractory end-stage heart failure (1-5). An LVAD results in decompression of the left ventricle, which promotes reverse remodeling, as manifested by decreased ventricular size, decreased mitral and tricuspid valve regurgitation and improved ventricular function. This process may play an important role in inducing left ventricular recovery with eventual explantation of the device.

Right ventricular function and right-sided hemodynamics are also improved with LVAD therapy. Along with unloading of the right ventricle, there is a substantial reduction in central venous pressure (CVP), pulmonary artery pressure (PAP) and tricuspid regurgitation (TR).

Consistent with the macroscopic changes seen on echocardiography as well as intracardiac pressures measured on right heart catheterizations, there are microscopic changes in the heart that are consistent with reverse remodeling after placement of an LVAD. These microscopic changes include changes in myocyte size, regression of fibrosis, cellular hypertrophy, collagen content, gene expression and various biomarkers of recovery, such as cardiac tumor necrosis factor-alpha (6-10).

Methods

We retrospectively analyzed our institutional experience with 100 consecutive CF LVADs. This included both HeartMate II (HM II) LVAD (Thoratec Corp., Pleasanton, CA, USA) recipients as well as HVAD (HeartWare Inc., Framingham, MA, USA) recipients for both bridge-to-transplant (BTT) and destination therapy (DT). Our primary objective was to determine the magnitude and durability of reverse remodeling seen with CF pumps, as assessed by the decrease in left ventricular end diastolic dimensions (LVEDD) and degree of mitral regurgitation (MR) when comparing pre-LVAD to post-LVAD parameters.

Single-institutional results with reverse remodeling using continuous glow

LVAD therapy

One hundred patients with advanced heart failure underwent implantation of a continuous flow LVAD at our institution from March 2006 to July 2011. This included 93 HM II LVADs and seven HVADs. Patients were implanted as BTT in 68 cases and as DT in 32 cases. Clinical records of these patients, including echocardiograms and right heart catheterizations, were retrospectively reviewed to determine how LVEDD and degree of MR were affected by CF-LVAD support at one and six months post-LVAD implantation. The procedures followed were in accordance with institutional guidelines and this review was performed with IRB approval.

Device management

Device speed was clinically adjusted to optimize flow, peripheral perfusion, organ function and LV decompression. Patients underwent periodic echocardiograms to evaluate the degree of LV decompression, aortic ejection, residual mitral regurgitation, position of the interventricular septum, RV function and severity of TR.

All patients were postoperatively anticoagulated on aspirin 81 mg daily as well as warfarin with a target INR of 1.8-2.5. Heart failure medications typically included a beta blocker, ACE inhibitor and diuretics, as well as sildenafil if

Table 1 Baseline clinical characteristics of LVAD patients

Characteristics	Variable (%)
Mean age (years)	52.8±11.9[1]
Gender	
Male	73 (73.0)[2]
Female	27 (27.0)[2]
Race	
Caucasian	60 (60.0)[2]
African American	38 (38.0)[2]
Etiology of HF	
Ischemic CM	34 (34.0)[2]
NIDCM	66 (66.0)[2]
Height (cm)	164.7±29.9[1]
Weight (kg)	95.2±37.5[1]
BSA	2.0±0.3[1]
BMI	28.7±5.4[1]
Albumin	3.3±0.5[1]
DM	45 (45.0)[2]
HTN	87 (87.0)[2]
CRI*	30 (30.0)[2]
Creatinine	1.4±0.5[1]
COPD*	19 (19.0)[2]
Mechanical ventilation	5 (5.0)[2]
Reoperation	29 (29.0)[2]
SGOT	44.7±88.5
SGPT	45.8±85.3[1]
Inpatient**	55 (55.0)[2]

[1], mean ± SD; [2], absolute number (percentage of overall); *, as per patient's history in clinical records; **, in the hospital for longer than 1 day prior to surgery; LVAD, left ventricular assist device.

there was significant residual pulmonary hypertension.

Echocardiography

Preoperative echocardiograms were reviewed and compared to echocardiograms at 1 and 6 months postoperatively. All echocardiograms were performed by staff cardiologists at Henry Ford Hospital. LVEDD, and the severity of MR based on a graded system was recorded for each patient. A graded qualitative system for RV function, as well as severity of TR was used for each patient. Additionally, RVEF and RVEDD were recorded. Finally, echocardiograms were reviewed for tricuspid annular plane systolic excursion (TAPSE) measurements preoperatively, at one and six months post-LVAD.

Hemodynamic variables

Hemodynamic variables were analyzed pre-LVAD implantation and compared to one and six months post-LVAD implantation values. These variables included CVP, PAP, pulmonary capillary wedge pressure (PCWP) and cardiac index (CI). Perioperative RV failure was defined as the need for intravenous inotropes for greater than 14 days postoperatively or a right ventricular assist device (RVAD).

Statistical analysis

Statistical analysis was conducted by a statistician from the Department of Biostatistics at Henry Ford Hospital. Data were represented as frequency distributions and percentages. Values of continuous variables were expressed as a mean ± standard deviation (SD). Continuous variables were compared using independent samples t-tests. Categorical variables were compared by means of Chi-square tests. For all analyses, a P value of <0.05 was considered statistically significant. Kaplan-Meier analysis was used to calculate survival along with a log-rank P value when comparing groups. Actuarial survival at one, three and five years post-implant were calculated by constructing life tables. All data were analyzed using SPSS 11.5 (SPSS Inc., Chicago, Illinois, USA).

Results

Demographics

There were 73 male and 27 female LVAD patients with a mean age of 52.8±11.9 years. Etiology of heart failure was coronary artery disease (ischemic cardiomyopathy) in 34 patients and non-ischaemic dilated cardiomyopathy in 66 patients. Median LVAD support time was 378.3 days, 371.5 days for BTT patients and 422.2 days for DT patients. Additional preoperative clinical characteristics of the patients are listed in *Table 1*.

Echocardiographic data

LVEDD significantly decreased at one month post-LVAD implantation from 71.6±12.4 to 58.3±13.8 mm (P<0.001). The severity of MR was moderate or severe in 76.0% of

Table 2 LVEDD and severity of MR pre-LVAD compared to 1 and 6 months post-LVAD

Factors	Pre-LVAD	One month postop	Six months postop	P value for pre-LVAD *vs*. one month	P value for pre-LVAD *vs*. six months
LVEDD	71.6±12.4	58.3±13.8	60.6±17.3	<0.001	0.769
Severity of MR					
None, trace or mild	24.0%	92.0%	89.0%	<0.001	0.371
Moderate	51.0%	6.0%	8.0%	<0.001	0.808
Severe	25.0%	2.0%	3.0%	0.003	0.315
Moderate or severe	76.0%	8.0%	11.0%	<0.001	0.371

LVEDD, left ventricular end diastolic dimensions; LVAD, left ventricular assist device.

Table 3 Hemodynamics pre- and post-LVAD implantation

Factors	Pre-LVAD[1]	One month post-LVAD[1]	Six months post-LVAD[1]	P value
CVP (mmHg)	12.4±5.9	8.7±4.5	7.4±5.2	<0.001
PAPs (mmHg)	52.3±14.1	36.8±11.3	35.5±10.4	<0.001
PAPd (mmHg)	24.9±9.3	16.7±7.0	15.3±7.1	<0.001
PAPm (mmHg)	35.5±10.7	24.5±8.0	22.8±7.6	<0.001
PCWP (mmHg)	23.0±9.4	12.9±8.0	11.1±6.5	<0.001
TPG (mmHg)	12.3±7.7	11.7±4.9	11.6±4.0	0.723
CI (L/min/m^2)	1.8±0.5	2.4±0.5	2.4±0.5	<0.001
RVSWI (L/min/m^2)	408.6±144.6	614.4±196.2	616.0±181.1	<0.001

[1], mean + SD; LVAD, left ventricular assist device; CVP, central venous pressure; PAPs, pulmonary artery pressure-systolic; PAPd, pulmonary artery pressure-diastolic; PAPm, pulmonary artery pressure-mean; PCWP, pulmonary capillary wedge pressure; TPG, transpulmonary gradient; CI, cardiac index; RVSWI, right ventricular stroke work index.

patients preoperatively. At one month, only 8.0% had moderate or severe MR (P<0.001) and this was maintained at six months post-LVAD implantation (*Table 2*).

Improvement in right ventricular function and right-sided hemodynamics

From March 2006 to June 2012, 130 patients with chronic heart failure underwent implantation of a CF-LVAD at our institution. This included 122 HM II LVADs and eight HVADs. Patients were implanted as BTT in 76 cases and as DT in 54 cases. Patients with preoperative long-term LVADs (n=4) as well as patients who underwent concomitant tricuspid valve repairs during their LVAD implant (n=21) were not included in the analysis. Clinical records of the remaining 105 patients, including right heart catheterizations and echocardiograms, were retrospectively reviewed to determine how RV size and function were affected by CF-LVAD support at one and six months post-LVAD implantation.

Hemodynamic data

At one month post-LVAD implantation, CVP decreased from 12.4±5.9 to 8.7±4.5 mmHg (P<0.001), systolic PAP decreased from 52.3±14.1 to 36.8±11.3 mmHg (P<0.001) and PCWP decreased from 23.0±9.4 to 12.9±8.0 mmHg (P<0.001). Additionally, CI increased from 1.8±0.5 to 2.4±0.5 L/min/m^2 (P<0.001) and RVSWI improved from 408.6±144.6 to 614.4±196.2 mmHg mL/m^2 (P<0.001) (*Table 3*).

Echocardiographic data

Right ventricular function

RVEF increased from (33.1±4.9)% preoperatively to (40.4±6.2)% (P<0.001) at 1 month postoperatively, with

Table 4 RV function pre-LVAD compared to 1 and 6 months post-LVAD

RVF	Normal (%)	Mildly reduced (%)	Moderately or severely reduced (%)	P value
Pre-LVAD	4.8	38.1	57.1	
One month postop	6.7	60.0	33.3	0.008
Six months postop	11.4	57.1	31.4	0.442

LVAD, left ventricular assist device.

Table 5 TR pre-LVAD compared to 1 and 6 months post-LVAD

TR	Mild (%)	Moderate or severe (%)	P value
Pre-LVAD	88.6	11.4	
One month postop	95.2	4.8	<0.001
Six months postop	94.3	5.7	<0.766

LVAD, left ventricular assist device.

a reduction in RVEDD from 36 to 31 mm (P=0.020). Qualitatively, RV function was moderately or severely reduced in 57.1% of patients preoperatively. At 1 month, only 33.3% had moderately or severely reduced RV function, and this improvement was maintained at 6 months post-LVAD implantation (P=0.008) (*Table 4*).

Qualitative assessment of severity of tricuspid regurgitation

The severity of TR was moderate or severe in 11.4% of patients preoperatively. At 1 month, only 4.8% had moderate or severe TR and this improvement was also maintained at 6 months post-LVAD implantation (P<0.001) (*Table 5*).

Tricuspid annular plane systolic excursion (TAPSE)

TAPSE measurements were recorded for 92 (87.6%) patients. Mean TAPSE for patients was 1.1±0.4 cm preoperatively. This increased significantly to 1.9±0.4 cm at 1 month (P=0.004) and was maintained at 2.0±0.5 cm at 6 months post-LVAD implantation.

Right ventricular failure

Postoperative RV failure occurred in 11 patients. This included six patients who were treated with milrinone for an extended period of time and five patients who underwent RVAD placement. Among the six patients who required prolonged milrinone therapy, three were INTERMACS category IA preoperatively on inotropic support and an intra-aortic balloon pump. Milrinone was weaned off in five patients at 17 days, 18 days, 3 months in two patients and 4.5 months. One patient was transplanted on milrinone at 9 months. Among the five patients who required an RVAD, two were INTERMACS category IA preoperatively.

Discussion

Despite significant improvements in pump design and better short- and long-term outcomes with continuous flow pumps, LVAD therapy remains confined to very advanced, end-stage heart failure patients with severe functional limitations. Extension of this therapy to patients at earlier stages of disease is dependent on continued improvement in long-term outcomes as well as the potential for significant myocardial recovery with the option for device explantation. Left ventricular reverse remodeling is crucial to the concept of myocardial recovery. The clinical and pathologic sequelae of LV remodeling in heart failure are well defined and various options for intervention have been explored to slow or reverse the progression of the remodeling process. Passive constraint devices including the Acorn CorCap and the Myosplint have had experimental success in inducing LV reverse remodeling in heart failure patients but have not led to significant improvements in clinical outcomes (11,12). LVAD therapy, on the other hand, has significantly improved survival and quality of life in end-stage heart failure patients. However, there is little data concerning LV reverse remodeling with continuous flow device therapy. The ultimate goal of LV recovery, namely device explantation, remains a rare clinical event. Understanding LV reverse remodeling is an important precursor in being able to promote this recovery process.

Reductions in CVP and PAP with concomitant RV unloading are important goals of LVAD therapy because sustained RV function is crucial to good long-term outcomes. Our patients manifested considerable unloading of the RV, as demonstrated by significant reductions in CVP and PAP at 1 and 6 months post-implantation. There is the potential for these devices to induce RV dysfunction by causing leftward shifting of the interventricular septum (13). Our practice is therefore to obtain serial echocardiograms during the initial days and weeks of support to determine

the LVAD speed and ventricular loading conditions that will maximally decompress the LV without excessively shifting the interventricular septum and exacerbating RV dysfunction. These studies are performed at rest, although there may be additional benefits to performing them during activity as well. Device speed is increased until there is optimal decompression of the LV, with no bowing of the interventricular septum and either no residual or trivial MR. Additionally, we aim to have the aortic valve open several times per minute.

In conclusion, our results demonstrated that CF-LVAD support induced immediate and sustained reverse remodeling of the LV, as measured by significant reductions in LVEDD and severity of MR. Our data are consistent with similar studies with PF pumps and confirm the findings of smaller series with CF pumps (11-13). Given the substantial and consistent reduction in the severity of MR after LVAD implantation, we do not believe that concomitant mitral valve repair is necessary during the initial operation. To date, we have not performed any concomitant mitral valve procedures on patients undergoing LVAD implantation. Residual MR can generally be reduced by increasing the RPM's, which yields greater LV decompression. For the rare patient with symptomatic, refractory or severe residual MR, mitral valve repair may be warranted.

The engineering paradigm of CF will likely be the platform for future LVAD device development because of the associated advantages of CF pumps, namely improved survival, quality of life and decreased pump-related adverse events. While we have observed LV recovery leading to prolonged device explantation in only one of these patients, a more detailed examination of the reverse remodeling process, such as analysis of myocyte size, regression of fibrosis, cellular hypertrophy, collagen content, gene expression and various biomarkers of recovery, such as cardiac tumor necrosis factor-alpha, will extend our understanding of the remodeling process beyond just volume unloading of the LV and may allow for more focused attempts at long-term LV recovery. Additionally, it is possible that partial unloading of the LV may induce substantial reverse remodeling and promote myocardial recovery, although this hypothesis requires further preclinical and clinical analysis.

Study limitations

This is a retrospective review and limitations include potential inaccuracy of data retrieved from medical records. Additionally, the number of patients in this study was relatively small, thus limiting the statistical power of the analysis and conclusions. Further studies with more patients and longer follow-up will be useful.

Acknowledgements

Funding: This project was provided by Henry Ford Hospital.
Disclosure: The authors declare no conflict of interest.

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Cite this article as: Morgan JA, Paone G. Impact of reverse remodeling on cardiac function. Ann Cardiothorac Surg 2014;3(6):589-594. doi: 10.3978/j.issn.2225-319X.2014.08.10

