

Left Ventricular Remodeling and Myocardial Recovery on Mechanical Circulatory Support

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ABSTRACT

Background: Myocardial recovery after ventricular assist devices (VAD) is rare but appears more common in nonischemic cardiomyopathies (NICM). We sought to evaluate left ventricular (LV) end diastolic diameter (LVEDD) for predicting recovery after VAD.

Methods and Results: NICM patients receiving long-term mechanical support between 1996 and 2008 were reviewed. Subjects were divided into 3 groups: mild, moderate, and severe dilation (Group A: LVEDD <6.0 cm [n = 22]; Group B: 6.0-7.0 cm [n = 32]; Group C: >7.0 cm [n = 48], respectively). Overall, recovery (successful explant without transplantation) occurred in 14 of 102 subjects (14%). Of these, 2 died and 2 required transplantation within 1 year. Recovery was more common in patients without LV dilation (Groups A/B/C = 32%/22%/0%, $P < .001$), as was sustained recovery (alive and transplant free 1 year after explant; A/B/C = 27%/10%/0%, $P = .001$). Of the recovery patients in Group A, 6/7 (86%) had sustained recovery versus 3/6 (50%) in Group B.

Conclusions: Recovery occurred in 32% of NICM patients without significant LV dilation at time of VAD, the majority of whom experienced significant sustained recovery. Recovery was not evident in those with severe LV dilation. Routine echocardiography at the time of implant may assist in targeting patients for recovery after VAD. (*J Cardiac Fail* 2010;16:99–105)

Key Words: Heart-assist device, heart failure, remodeling, cardiomyopathy.

Although ventricular assist devices (VAD) play a vital and well-defined role as bridges to transplant and destination therapy for patients with severe chronic heart failure (CHF), their utility as temporary support to facilitate

recovery of native cardiac function has been reported, but is less well understood.¹⁻¹² The hemodynamic unloading with VAD support results in significant alteration in myocardial histology,⁸ protein levels,¹¹ and gene expression.^{13,14} Mechanical support induces reductions in markers of neurohormonal activation,^{15,16} improvement in myocyte calcium handling,^{17,18} and improvement in the proinflammatory cytokine milieu.¹⁹⁻²¹ Although reverse remodeling, less extensive fibrosis, and a decrease in myocyte size have been reported after VAD support,^{11,19,22-24} very few VAD-supported patients have recovery, which allows VAD explantation with an overall frequency of approximately 5%.^{9,25,26} This may be in part due to the difficulties and risks involved in weaning patients that make many clinicians reluctant to pursue weaning strategies. The ability to identify subjects with a greater probability of recovery, would allow a greater percentage of subjects to be successfully recovered.

Recovery on VAD support is more common in nonischemic cardiomyopathy than in ischemic cardiomyopathy. We have previously reported an incidence of VAD explantation due to recovery of 11% in patients with nonischemic cardiomyopathy (NICM) compared with 3% in ischemic

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patients and further observed that the majority of the non-ischemic recovered patients had a recent onset to their cardiomyopathy.²⁵ The history of symptoms onset is a notoriously unreliable marker of acuity, and the extent of ventricular remodeling may be a more reliable predictor of the probability of recovery. We hypothesized that recovery after VAD would be more prevalent in those with acute NICM without left ventricular (LV) remodeling at the time of implant, compared with those subjects with more significant remodeling. This study was designed to investigate the ability of preimplant echocardiography as a simple clinical measure of LV remodeling, LV end-diastolic diameter (LVEDD), to predict the likelihood of subsequent recovery.

Methods

Study Design and Data Collection

Data from the University of Pittsburgh Medical Center Cardiothoracic Transplantation Program's Transplant Patient Management System was reviewed retrospectively. The Transplant Patient Management System is a password-protected, HIPAA-compliant, web-based prospective data collection for all patients who receive mechanical circulatory support and is approved by the University of Pittsburgh Institutional Review Board. Patients were included in the present study if they had a NICM and were implanted with a VAD at the University of Pittsburgh Medical Center between 1996 and 2008. Exclusion criteria included: known ischemic or valvular cardiomyopathy; congenital heart disease; age <17 years; and support with a right ventricular assist device only. LV end-diastolic diameters were determined from the 2-dimensional echocardiographic parasternal long-axis view using the internal dimension perpendicular to the LV long-axis at the level of the papillary muscle insertion, or the maximal dimension.

VAD Systems

Patients received one of 6 VAD systems: Thoratec PVAD (Thoratec Corp, Pleasanton, CA) for left or biventricular support; Thoratec IVAD, Novacor LVAS (World Heart Corporation, Oakland, CA); Heartmate LVAS XVE (Thoratec Corp, Pleasanton, CA); HeartMate II (Thoratec); and the VentrAssist (Ventricor, Ltd, Chatswood, New South Wales, Australia).

Clinical Management and Evaluation of Recovery

It is our standard practice to give patients on VAD support angiotensin-converting enzyme inhibitors and β -blockers at the highest tolerated doses, whereas diuretics are administered as clinical needed. Our protocol for evaluation of myocardial recovery while on VAD support has been previously published.⁵ Briefly, 3 methodologies are used in each patient at full support and then with reduced support: echocardiography, exercise physiology, and hemodynamics assessed by right heart catheterization. In pulsatile VAD systems, the flow is lowered by one half. If this is tolerated for 3 minutes, then 5000 units of heparin are administered by intravenous bolus and the VAD flow is further decreased to single strokes every 10 seconds. In the HeartMate II, the revolutions per minute (rpm) is turned down to halfway between the current operating speed and 8000 rpm. If this is tolerated for 3 minutes, then the speed is further reduced to 8000 rpm. We first start to assess for recovery 2 to 4 weeks after implant, depending on clinical

course after the implantation surgery. Our criteria for recovery is >40% increase in fractional area change or preload-adjusted maximal power >4.0 mW/cm⁴ by echocardiography; maximal oxygen consumption >16 mL·kg·min by cardiopulmonary exercise test; and pulmonary capillary wedge pressure <20 mm Hg and pulmonary arterial saturation >60% by invasive hemodynamics (5).

Analysis

The purpose of the study was to examine the association between preimplant LVEDD and subsequent recovery. Because gender and body surface area have known associations with LVEDD, we conducted multivariable logistic regression analyses to control for these characteristics.

Patients were then divided into 3 groups based on pre-VAD LVEDD as assessed by transthoracic echocardiography: minimal dilation (Group A: LVEDD <6.0 cm), moderate dilation (Group B: 6.0 to 7.0 cm), and severe dilation (Group C: >7.0 cm). These simple break points (6 cm and 7 cm) were chosen in an effort to develop an easily applicable clinical guideline based on a recent report in subjects with recent-onset cardiomyopathy.²⁷ Given differences in LVEDD by gender, this analysis was then repeated using gender specific tertiles derived from the current cohort. The gender-adjusted tertiles were constructed by dividing subjects into 3 equal groups based on LVEDD while stratifying for gender. For men, cutoffs between Group A/B and Group B/C were 6.6 cm and 7.7 cm, respectively, which divided all men in the study into 3 equal groups of equal numbers. For women, however, cutoffs between Group A/B and Group B/C were 6.2 cm and 6.9 cm, respectively, to yield 3 equal groups. Groups A, B, and C for men and women were then combined to yield gender-adjusted tertiles (Group A for men combined with Group A for women) such that the groups were of equal size and consistent numbers of men and women. We then examined baseline characteristics among the 3 primary groupings (ie, not gender-adjusted). For these analyses, *P* values were determined using chi-square tests for categorical variables (such as gender) and analysis of variance for continuous variables (such as age).

We then used Fisher's exact test to examine associations between LVEDD and our primary outcome variable "recovery," defined as explant of LV assist devices without transplantation. Because cardiomyopathy can recur after recovery and result in death or the need for cardiac transplantation soon after removal of mechanical support, we also used Fisher's exact test to assess the association between LVEDD and our secondary outcome variable "sustained recovery"—defined as survival at 1-year postexplant without transplantation. We conducted these analyses using both traditional and gender-based tertiles to test the robustness of our results. Survival at 1 year among recovered patients was then confirmed by Kaplan-Meier analysis, censoring patients without events, and comparison between LVEDD groups was made by log-rank test.

All tests were 2-tailed. A *P* value < .05 was considered statistically significant. Statistical analyses were performed using SPSS for Windows, version 14 (SPSS, Inc, Chicago, IL) and Stata, version 9.2 (Statacorp, College Station, TX).

Results

Between 1996 and 2008, 348 patients underwent VAD implantation at the University of Pittsburgh for planned

long-term support. Of these, 241 were excluded, largely because of an etiology of ischemic cardiomyopathy (Fig. 1). Of the remaining 107 VAD implants, 102 had LVEDD measured before implantation and were included in this analysis. There were 22 patients in Group A (LVEDD <6.0 cm), 32 patients in Group B (LVEDD 6.0 to 7.0 cm), and 48 patients in Group C (LVEDD >7.0 cm). Baseline characteristics across the 3 groups are presented in Table 1. Ejection fraction and preimplant hemodynamics were similar among all 3 groups. Age was also similar among groups. However, there were more women with lower LVEDD (Groups A/B/C = 50%/41%/21%, $P = .03$). Duration of support was 146 ± 156 days overall and was not significantly different between LVEDD groups (111 ± 100 , 115 ± 114 , 182 ± 192 days, respectively for Groups A, B, C, $P = .09$). Devices used are presented in Table 2. Because subjects with lower body size are more likely to receive extracorporeal support, a greater proportion of subjects in Group A received support with Thoratec LV assist devices than in Groups B or C.

Multivariable Analysis

By multivariable logistic regression controlling for gender and body size, each 1-cm increase in LVEDD was associated with a 61% decrease in the odds of recovery (OR 0.39, 95% CI: 0.21-0.71, $P = .002$); individual contributions of gender and body size were not statistically significant. Therefore, further analysis focused on LVEDD.

Recovery by LVEDD

Of the 102 subjects, there were 14 patients (13.7%) in whom recovery of ventricular function permitted device removal without cardiac transplantation. In the 14 recovered patients (10 female/4 male), mean age was 32 ± 14 , LVEF was $18 \pm 8\%$, and LVEDD was 5.7 ± 1.2 cm. Evidence of myocardial inflammation by histology was seen in only 3 patients and etiology was divided between myocarditis ($n = 3$), peripartum cardiomyopathy ($n = 4$), and idiopathic dilated cardiomyopathy ($n = 7$). Duration of support

before device explant for myocardial recovery ranged from 41 to 263 days, with the majority being explanted by 120 days ($n = 10$).

Recovery was more evident in Group A with minimal LV remodeling (7 of 22 subjects [32%]), less evident in Group B with moderate LV dilatation (7 of 32 subjects [22%]), and not evident in Group C (0 of 48 subjects). According to Fisher's exact test, smaller LV size was significantly associated with recovery (prevalence by groups 32%/22%/0%, Fig. 2, $P < 0.001$). Results by gender adjusted tertiles were similar (prevalence of recovery by groups 29%/12%/0%, Fig. 3, $P = 0.002$). LVEDD for all patients, stratified by recovery or not, is presented in Fig. 4.

Sustained Recovery by LVEDD

Of the 14 recovered subjects, 4 had events (death or cardiac transplant) within 1 year after explantation. Two patients died, 1 suddenly in the setting of recurrent heart failure 2 months after explant and 1 of sepsis 4 months after explant, whereas 2 were transplanted within 1 year after explant. Three of the 4 patients dying or transplanted within 1 year had borderline recovery studies and 2 of these patients had extenuating circumstances further prompting explant (device infection). All events were early and for the patients alive at 1-year follow-up, LV recovery was maintained in all with no further events (follow-up 1 to 8 years, median 5 years). Of recovered subjects, overall survival was 85% at 1 year after explant, and transplant-free survival was 69% by Kaplan-Meier survival analysis (censoring patients without events). One subject in Group A had an event versus 3 in Group B (1 year transplant-free survival by Kaplan-Meier survival analysis: 86% vs. 50% respectively, $P = .2$). Sustained recovery (transplant-free survival greater than 1 year after explant) occurred in 27%, 10%, and 0% of subjects in Groups A, B, and C, respectively, $P = .001$ using Fisher's exact test (Fig. 2) with slightly more pronounced differences using gender adjusted tertiles (prevalence of sustained recovery by groups 24%/3%/0%, Figure 3, $P = .001$).

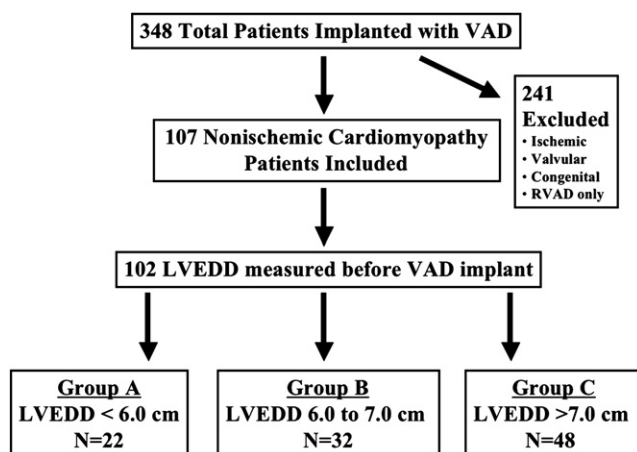


Fig. 1. Patient cohort summary.

Discussion

Although myocardial recovery may remain an uncommon event among VAD-supported patients, this study demonstrated that for subjects with NICM and minimal remodeling, device explant for recovery occurred in 32%. For the majority of these subjects recovery was maintained with an event-free survival at 1 year of 86%. Recovery was also experienced in 22% of subjects with moderate LV dilatation, although the 1-year transplant-free survival in this cohort was only 50%. These findings suggest preimplant echocardiography is predictive of the potential for VAD-supported myocardial recovery, and that small LV chamber size indicative of the absence of remodeling delineates a group in which recovery is not only possible but should be a primary goal of VAD therapy.

Table 1. Baseline Characteristics

	Group A	Group B	Group C	<i>P</i> *
	LVEDD <6.0 cm	LVEDD 6.0 to 7.0 cm	LVEDD >7.0 cm	
n	22	32	48	
Age	44 ± 16	41 ± 15	48 ± 14	NS
Male gender [n (%)]	11 (50%)	19 (59%)	38 (79%)	.03
Etiology [n (%)]				
Alcoholic cardiomyopathy	0 (0%)	3 (9%)	1 (2%)	
Familial cardiomyopathy	0 (0%)	1 (3%)	2 (4%)	
Hypertrophic cardiomyopathy	1 (5%)	0 (0%)	0 (0%)	
Idiopathic cardiomyopathy	15 (68%)	18 (57%)	41 (86%)	
Myocarditis ¹	5 (22%)	2 (6%)	3 (6%)	
Peripartum cardiomyopathy	1 (5%)	8 (25%)	1 (2%)	
Left ventricular ejection fraction (%)	16 ± 4	15 ± 7	13 ± 4	NS
Inotrope/pressor support [n (%)]	16 (73%)	25 (78%)	41 (87%)	NS
IABP support [n (%)]	16 (73%)	26 (81%)	39 (81%)	NS
Cardiac index (L/min/m ²)	1.8 ± 0.5	1.8 ± 0.6	1.9 ± 0.4	NS
PCWP (mm Hg)	26 ± 8	27 ± 9	29 ± 8	NS
Serum sodium (mEq/L)	132 ± 6	135 ± 6	132 ± 6	NS
Total bilirubin (mg/dL)	1.2 ± 1.1	2.0 ± 3.2	1.6 ± 1.1	NS
Serum albumin (mg/dL)	3.0 ± 0.9	3.1 ± 0.6	3.5 ± 0.6	NS
Serum creatinine (mg/dL)	1.6 ± 0.9	1.4 ± 0.7	1.5 ± 0.7	NS
Blood urea nitrogen (mg/dL)	36 ± 26	25 ± 13	31 ± 16	NS

LVEDD, left ventricular end-diastolic diameter; NYHA, New York Heart Association; IABP, intraaortic balloon pump; PCWP, pulmonary capillary wedge pressure; NS, not significant.

Values are mean ± SD.

**P* values were determined using chi-square tests or Fisher's exact test for categorical variables (such as gender) and analysis of variance for continuous variables (such as age).

¹Myocarditis was defined clinically although only 2 had evidence of inflammation on biopsy.

Hetzer described their experience in chronic idiopathic dilated cardiomyopathy in which patients had LVEDD at the time of implantation averaging >70 mm.¹⁰ They noted that patients with lasting recovery (defined as freedom from cardiac death or transplantation at 1 month to 5.5 years of follow-up) had significantly smaller LVEDD at time of device explant (51 vs. 57 mm). Although the Berlin group excluded subjects with acute cardiomyopathies and focused on chronic idiopathic dilated cardiomyopathy, its finding that an LVEDD >55 mm before device removal was a risk factor for early recurrence of HF²⁸ mirrors the results of the current study. Importantly, although their group also investigated intricate assessments of cardiac function and weaning as an important part of the evaluation for recovery, the distinctly different populations of our groups suggest that the most important predictor of the likelihood of

successful long-term recovery is the simple measurement baseline preimplant LVEDD.

The high likelihood of recovery in the absence of remodeling may reflect the higher prevalence of transient myocardial inflammation in this subset. VAD support in acute fulminant myocarditis must sustain the patient until inflammation can subside and the ventricle can recover, but support does not have to induce reverse remodeling or eliminate long standing molecular pathologies. Subjects with biopsy proven myocarditis (n = 2) and peripartum cardiomyopathy (n = 10) were more likely to recover in our analysis (6 of 12). However, when they were excluded from analysis, small LV size remained highly predictive of recovery (overall recovery incidence 9%; recovery by LVEDD groups 21%, 17%, 0%, respectively for Groups A, B, and C, *P* = .007). Indeed, LV size may of greatest use as a predictor of recovery when myocardial histology is unremarkable and the etiology of the primary cardiomyopathy remains uncertain.

Of note, although recovery was evident in moderately dilated group B patients, it was less durable, suggesting hemodynamic support induced reversal of the molecular changes and remodeling was only a temporary victory and not sustainable after support was removed. As an initiating receptor of the apoptosis pathway and programmed cell death in cardiac myocytes, high myocardial Fas expression predicts less recovery in recent-onset NICM.²⁹ Recently investigation of cytokines and apoptosis on VAD support found the effects of support to be highly variable.¹⁴ Fas expression is markedly elevated in subjects with heart failure receiving VAD support and was not reliably reduced

Table 2. Devices

	Group A LVEDD <6.0 cm	Group B LVEDD 6.0 to 7.0 cm	Group C LVEDD >7.0 cm
HeartMate XVE	1 (4%)	1 (3%)	8 (17%)
HeartMate II	0 (0%)	4 (13%)	3 (6%)
Novacor	3 (14%)	4 (13%)	15 (31%)
Thoratec PVAD BiVAD	12 (55%)	10 (31%)	11 (23%)
Thoratec PVAD LVAD	2 (9%)	7 (21%)	7 (15%)
Thoratec IVAD LVAD	1 (4%)	2 (6%)	1 (2%)
VentrAssist	3 (14%)	4 (13%)	3 (6%)

PVAD, paracorporeal ventricular assist device; BiVAD, biventricular assist device; LVAD, left ventricular assist device.

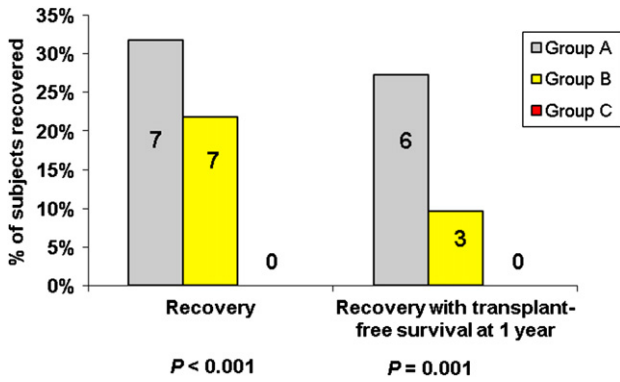


Fig. 2. Incidence of recovery and transplant-free survival at 1 year across the 3 left ventricular end-diastolic diameter (LVEDD) groups. Groups defined as follows: Group A, LVEDD <6.0 cm; Group B, 6.0 to 7.0 cm; Group C, >7.0 cm. *P* values were computed using Fisher’s exact test because of small cell sizes.

by the hemodynamic unloading of VAD support.³⁰ This suggests that hemodynamic unloading may not be enough for clinical recovery in subjects whom have experiences even moderate remodeling without adjunctive therapy to reverse the molecular changes of end-stage heart failure. Aggressive medical therapy to promote reverse remodeling and recovery while on VAD support has been reported¹² and seems very likely to be of benefit. Given the retrospective nature of this analysis, most patients reported herein were not treated with an aggressive remodeling regimen.

Whether device selection influences the potential for recovery remains unknown. Selection criteria, particularly in terms of device selection, are not standardized. Device use is highly variable based on institution and the marked progression of device development over time. There is some conflicting data that pulsatile pumps unload the LV more than continuous flow.³¹⁻³³ Although our study was not powered to see a difference between such devices, recovery

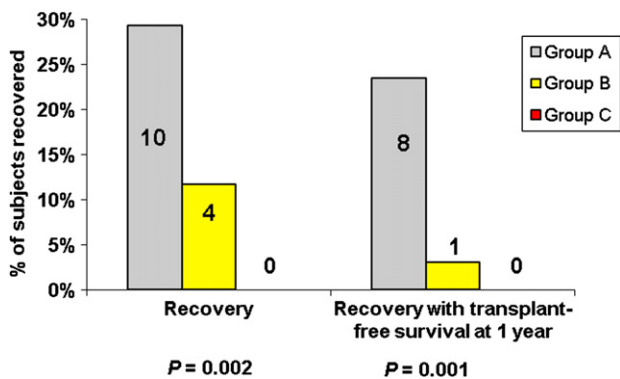


Fig. 3. Incidence of recovery and transplant-free survival at 1 year by gender-adjusted tertiles of left ventricular end-diastolic diameter (LVEDD). Groups defined as follows: Men: Group A, LVEDD <6.6 cm; Group B, 6.6 to 7.7 cm; Group C, >7.7 cm; Women: Group A, LVEDD <6.2 cm; Group B, 6.2 to 6.9 cm; Group C, 6.9 cm; n = 34 in each group. *P* values were computed using Fisher’s exact test because of small cell sizes.

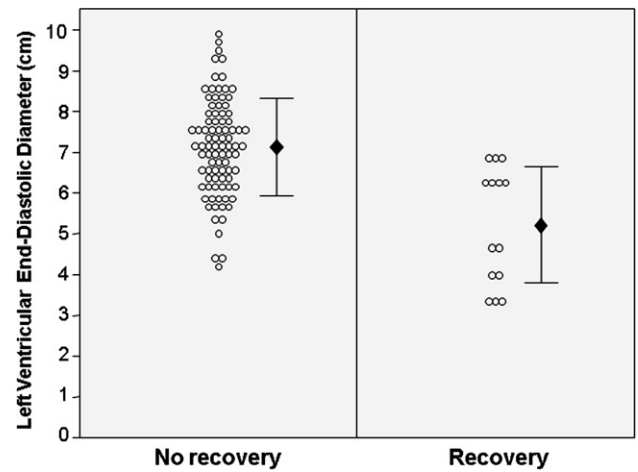


Fig. 4. Scatter plot of left ventricular end-diastolic diameter (LVEDD) separated by recovery (short-term recovery) or not. Open circles are individual patients. Closed diamonds represent means with standard deviation bars. Mean values were 7.1 ± 1.2 and 5.2 ± 1.4 cm for no recovery and recovery groups, respectively, *P* < .001.

occurred with several different systems, including biventricular support. One study does suggest that despite varying unloading of pulsatile versus continuous flow devices, there was similar improvement in tumor necrosis factor, total collagen, and myocyte size.³⁴

Limitations

The number of recovered patients in this retrospective single-center study is modest, and therefore the results must be interpreted with caution. The sample size is too small to determine optimal cut points for definitive clinical recommendations and therefore the raw LVEDD data stratified by recovery is presented in Fig. 4. Kaplan-Meier analysis of 1-year survival among recovered patients stratified by LVEDD was underpowered to detect differences, though a trend to improved survival in those with minimal remodeling. The study size precludes controlling for all potential confounders, such as ethnicity, medications, and different VAD systems. Although the purpose of this study was to identify patients with the highest likelihood of recovery, there may be selection bias. No subjects with marked LV dilatation (LVEDD >7.0 cm) were successfully recovered. However, because of their marked LV remodeling, these patients were not screened with the same vigor. Alternatively, recovery may have been more evident in subjects with only mild LV enlargement in part because recovery was anticipated and subjects screened aggressively. There are many factors yet to be elucidated to better understand the phenomenon of myocardial recovery with mechanical support, including effects of device type, gender, and protein and gene expression. Clinical conditions at the time of explant also likely play a role in sustained recovery that requires further investigation. Determination of the true clinical recovery potential requires a prospective study where all

subjects are screened aggressively. An NHLBI sponsored prospective multicenter study, the RECOVER trial, has been initiated with routine echocardiographic screening of all VAD subjects for recovery.

Conclusions

In patients with NICM without significant LV dilation at time of VAD, myocardial recovery sufficient for device explant occurred in 32% of subjects, the majority of whom experienced sustained recovery. In contrast, recovery did not occur in those with severe LV dilation. Routine transthoracic echocardiography at the time of implant may assist in targeting subjects appropriate intensive monitoring for recovery.

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