

## Cardiac Improvement During Mechanical Circulatory Support A Prospective Multicenter Study of the LVAD Working Group

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**Background**—Myocardial recovery after left ventricular assist device (LVAD) support has been reported. The LVAD Working Group Recovery Study was a prospective multicenter trial to assess the incidence of myocardial recovery in patients bridged to cardiac transplantation.

**Methods and Results**—After LVAD implantation, patients were evaluated with the use of rest echocardiograms with partial LVAD support and cardiopulmonary exercise testing. Dobutamine echocardiography with hemodynamic measurements was performed in those patients with left ventricular ejection fraction  $>40\%$  during resting studies. Histological analysis was performed on myocardial samples taken at LVAD implantation and explantation. Sixty-seven LVAD patients with heart failure participated in the study. After 30 days, significant improvement occurred in left ventricular ejection fraction ( $17\pm 7\%$  versus  $34\pm 12\%$ ;  $P<0.001$ ) and reductions in left ventricular end-diastolic diameter ( $7.1\pm 1.2$  versus  $5.1\pm 1.1$  cm;  $P<0.001$ ) and left ventricular mass ( $320\pm 113$  versus  $194\pm 79$  g;  $P<0.001$ ) compared with before LVAD. Thirty-four percent of patients had left ventricular ejection fraction  $>40\%$  with partial device support. Left ventricular ejection fraction decreased over time to pre-LVAD measurement by 120 days. Peak  $\dot{V}O_2$  improved with mechanical support ( $13.7\pm 4.2$  versus  $18.9\pm 5.5$  mL/kg per minute, 30 versus 120 days;  $P<0.001$ ). Tissue analysis revealed significant reductions in myocyte size, collagen content, and cardiac tumor necrosis factor- $\alpha$ . Six subjects (9%) underwent LVAD explantation for recovery.

**Conclusions**—Cardiac function improves significantly after device implantation. Although cellular recovery and improvement in ventricular function are observed, the degree of clinical recovery is insufficient for device explantation in most patients with chronic heart failure. (*Circulation*. 2007;115:2497-2505.)

**Key Words:** heart-assist device ■ heart failure ■ remodeling ■ transplantation

Left ventricular assist devices (LVAD) are an effective therapeutic option for end-stage heart failure (HF) patients as a bridge to cardiac transplantation in those who deteriorate despite maximal medical therapy or as destination therapy in those not eligible for transplantation. As the use of these devices increased, an important observation was the phenomenon of profound cardiac recovery in some patients supported with devices who were thought to have irreversible HF. Studies on isolated myocytes have demonstrated recovery of contractile function and  $\beta$ -adrenergic responsiveness,<sup>1</sup> as well as regression in cellular hypertrophy<sup>2,3</sup> and fibrosis.<sup>4</sup> Expression of genes that regulate calcium handling,<sup>5,6</sup> tumor

necrosis factor- $\alpha$  (TNF- $\alpha$ ),<sup>7</sup> and cytoskeleton proteins<sup>8</sup> also normalizes after prolonged mechanical support. Echocardiographic studies have found a reduction in left ventricular (LV) end-diastolic dimension<sup>9–11</sup> and LV mass.<sup>2</sup> Despite the encouraging molecular data, however, the rate of LVAD explantation for recovery in chronic HF patients is low.<sup>11,12</sup>

### Clinical Perspective p 2505

The LVAD Working Group was a multi-institutional consortium that studied the incidence of myocardial recovery in LVAD-supported patients, representing the first multicenter, prospective study to detail sequential changes in cardiac function

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with the use of echocardiographic, metabolic, and pharmacological stress testing during LVAD support. Serial echocardiography with full and partial device support, invasive hemodynamic assessment during pharmacological stress, and cardiopulmonary exercise testing were performed to assess cardiac recovery. Myocardial biopsies at the time of LVAD implantation and removal (with cardiac transplantation) were analyzed for histological regression of myocyte hypertrophy and fibrosis and for changes in cytokine expression.

## Methods

### Patient Sample

Our study design was a prospective, multicenter, observational study that sought to characterize the changes over time that occur in cardiac function and exercise capacity during mechanical support. HF patients undergoing LVAD implantation as a bridge to transplantation between August 2001 and October 2003 with at least 30 days of device support were eligible for study. Patients were recruited from the following centers: Baylor College of Medicine, Cleveland Clinic Foundation, Columbia University, University of Michigan, University of Minnesota, Temple University, and Texas Heart Institute. Patients with active infection or bleeding and those requiring parenteral inotropic support at 30 days were excluded. All subjects signed informed consent. The study was approved by the institutional review board at each participating center.

### Clinical Protocol

Patients were evaluated monthly after LVAD implantation. Evaluations were performed until time of transplantation or for the duration of the study. Pre-LVAD clinical data were collected retrospectively. Use of angiotensin-converting enzyme inhibition and  $\beta$ -blockade after device implantation was encouraged, but there was no protocol-proscribed medical regimen during LVAD support. At the time of the inception of our study, no uniform consensus could be reached among the participating centers on the optimal medical regimen for patients during mechanical support. All patients were kept with the LVAD in auto mode, except when there was a clear clinical indication for use of the fixed mode in high-flow states (eg, aortic insufficiency). Monthly assessments included the following: medication review, resting echocardiogram at full and reduced LVAD support, and cardiopulmonary exercise testing in ambulatory patients. Patients with LV ejection fraction (LVEF)  $>40\%$  at reduced device support underwent dobutamine echocardiography with simultaneous hemodynamic monitoring. The decision for LVAD explantation for recovery was made by clinicians at the individual centers, and there were no protocol-specified criteria for explantation.

Echocardiography and exercise studies were interpreted locally in a blinded fashion. Echocardiographic measurements were made at full (LVAD in auto mode) and reduced support (15 minutes after reducing LVAD flow to 4 L/min). Complete 2-dimensional studies were recorded from standard views as previously described.<sup>12</sup> Because echocardiographic measures of right ventricular (RV) function are limited, RV area shortening was chosen to compare changes over time. Exercise testing at full LVAD support included measurement of peak  $\dot{V}O_2$  and LVAD flow at rest and peak exercise recorded from the LVAD power base unit.

Dobutamine stress echocardiography with hemodynamic measurements was performed in those patients with LVEF  $>40\%$  at reduced LVAD flow. A Swan-Ganz catheter was inserted, and LVAD data were recorded from the power base unit. Baseline hemodynamic and echocardiographic data were obtained with the LVAD in auto mode. Repeat measurements were recorded with the LVAD weaned to 2 L/min or at the lowest tolerated flow. Dobutamine was infused in 5-minute dose increments from 5 to 20  $\mu\text{g/kg}$  per minute with ECG and echocardiographic monitoring. Infusion rate was increased to 40  $\mu\text{g/kg}$  per minute if 85% of predicted maximum heart rate was not achieved. Hemodynamic and echocardiographic data were recorded after 3 minutes at each infusion rate.

## Data Management

Clinical data were entered directly into a preformatted ACCESS PC database at each center. Each month, the updated database was mailed electronically to the data-coordinating center (Columbia University). The central database was maintained by a dedicated data manager.

## Myocardial Tissue Analysis

Myocardial tissue was obtained from the apical core at LVAD implantation and from the surrounding apical area at the time of cardiac transplantation. Approximately 40 mg of myocardial tissue was collected at each time point. Myocardial tissue samples were fixed and stored in alcohol as described previously.<sup>11</sup> Samples were shipped in dry ice to the tissue core laboratory (Baylor College of Medicine). Tissue samples were then dehydrated, cleared in xylene, and embedded in paraffin with the use of standard protocols. Five-micrometer sections were cut, collected on slides, and rehydrated. Measurements of myocyte size, collagen content and myocardial TNF- $\alpha$  content were performed as described previously.<sup>3,7</sup>

## Data Analysis

Statistical analyses were performed with the use of SPSS version 11.5 (SPSS, Chicago, Ill). Continuous variables are expressed as mean  $\pm$  SD. Differences over time were evaluated with repeated-measures ANOVA with Tukey ad hoc tests for comparisons among specific time points. This analysis was implemented by a regression approach that accounted for missing data points. Paired  $t$  tests were used for comparisons between pre-LVAD and explant data for tissue analysis. In an analysis to screen for markers of recovery, tissue parameters were correlated with echocardiographic measures with the use of Spearman (nonparametric) correlation coefficients. Because of the small number of patients undergoing dobutamine testing, independent  $t$  tests were used in comparisons of explanted and nonexplanted patients. All probability values were obtained with the use of 2-sided analyses. A probability value  $<0.05$  was considered statistically significant for all analyses.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

## Results

### Baseline Characteristics

Data submission concluded in May 2004. Sixty-seven patients were enrolled (Table 1). Thirty-seven subjects had nonischemic cardiomyopathy, and 30 had ischemic cardiomyopathy. The majority of subjects ( $n=46$ ) had chronic HF (duration  $>6$  months). LVEF was  $17 \pm 7\%$ , with 37 patients demonstrating moderate or severe RV dysfunction. All patients had New York Heart Association class IV symptoms, and all required either inotropic support or temporary mechanical support (intra-aortic balloon pump, extracorporeal LVAD, or extracorporeal membrane oxygenation) before LVAD implantation. Most of the devices used were Heart-Mate VE LVADs (Thoratec Corporation, Pleasanton, Calif;  $n=59$ ), with a small number receiving Novacor LVADs (World Heart, Oakland, Calif;  $n=5$ ), Thoratec extracorporeal assist devices ( $n=2$ ), or DeBakey LVADs (MicroMed, Houston, Tex;  $n=1$ ). Two patients required biventricular support with the Thoratec. Duration of LVAD support averaged  $134 \pm 109$  days.

Because the duration of HF may significantly affect myocardial recovery, an analysis of patients with acute onset ( $<6$  months) and chronic HF was performed. The baseline characteristics of these groups are also shown in Table 1. Patients

**TABLE 1. Study Sample Baseline Characteristics**

	All (n=67)	Acute HF (<6 mo) (n=21)	Chronic HF (>6 mo) (n=46)	P
Age, y	50±13	48±14	51±13	0.354
Cause of HF, n (%)	37 DCM (55), 30 CAD (45)	8 DCM (38), 13 CAD (62)	29 DCM (63), 17 CAD (37)	0.057
Duration of HF, mo	58.3±68.7	0.67±1.43	85.8±68.0	<0.001
Cardiac index, L/(min · m <sup>2</sup> )	2.0±0.7	2.13±0.70	1.96±0.67	0.550
LVEF, %	17±7	17±9	17±7	0.978
Significant RV dysfunction, n (%)	37 (55)	10 (48)	27 (59)	0.398
Inotropic dependence, n (%)	58 (87)	19 (90)	39 (85)	0.526
Inotropic dose, µg/(kg · min)				
Dobutamine	6.72±3.50	6.94±4.51	6.62±2.98	0.809
Milrinone	0.42±0.17	0.48±0.20	0.40±0.16	0.191
IABP/Abiomed/ECMO, n (%)	26 (39)	11 (52)	19 (41)	0.398
Ventilator, n (%)	27 (40)	15 (71)	12 (26)	<0.001
Device, n				
HeartMate	59	19	40	...
Novacor	5	1	4	
DeBakey	1	...	1	
Thoratec	2	1	1	
Duration of support, d	134±109	132±102	135±114	0.943

DCM indicates dilated cardiomyopathy; CAD, ischemic cardiomyopathy; IABP, intra-aortic balloon pump; and ECMO, extracorporeal membrane oxygenation.

with acute-onset HF more frequently had coronary artery disease and required mechanical ventilation.

### Clinical Follow-up

At the time of data analysis, 11 patients (16%) were still supported with devices, 44 (66%) had undergone transplantation, 6 (9%) had died, and 6 (9%) underwent device explantation for recovery. Of the 6 patient mortalities, all 6 patients suffered from nonischemic cardiomyopathy, and 5 patients suffered from chronic HF. The causes of death included fulminant sepsis (n=2), cerebral bleed after a fall (n=1), a cerebral vascular accident (n=1), encephalopathy of unclear origin (n=1), and hepatic failure (n=1). Heart rate was significantly lower at all time points after LVAD support (Table 2). In contrast, blood pressure was significantly higher throughout LVAD support. Mean resting LVAD flow was unchanged during the period of support. In the post-LVAD period, 70% of patients were treated with a  $\beta$ -blocker or angiotensin-converting enzyme inhibitor by the 60-day visit.

### Echocardiographic Data

Echocardiographic parameters before and serially after LVAD implantation with partial device support are shown in Table 2 and Figure 1. LVEF increased at 30 days (17±7% versus 34±12%;  $P<0.001$ ), with 32% of patients having LVEF >40%. LVEF decreased over time such that at 120 days, LVEF was comparable to the pre-LVAD measurement. LVEDD also decreased at 30 days ( $P<0.001$ ). After 30 days, there was mild but sustained increase in LVEDD. LV mass decreased by 30 days after LVAD implantation ( $P<0.001$ ) but stabilized thereafter. In contrast to the changes in LV function, RV function underwent persistent improvement.

RV area shortening was improved at 120 days compared with after 30 days of LVAD support.

### Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing with full LVAD support was performed monthly in ambulatory patients. The LVEF of this group was similar to the LVEF of the nonambulatory patients. Peak  $\dot{V}O_2$  progressively improved throughout the study period despite no change in peak LVAD flow and a progressive reduction in resting LVEF (Table 2).

### Dobutamine Testing

Twenty-three patients (34%) had a LVEF >40% at some time point and were approached about dobutamine testing with invasive hemodynamic monitoring. Fifteen patients consented to the test (Figure 2), and 6 patients underwent device explantation for recovery. Comparison of hemodynamic parameters during dobutamine testing for this small cohort of explanted and nonexplanted patients was performed in a secondary analysis. Explanted patients had lower pulmonary capillary wedge pressure at lowest LVAD flow than those not explanted (8.5±4.5 versus 15±5.7 mm Hg;  $P<0.05$ ). At peak dobutamine, there was a trend toward a higher blood pressure (132±21 versus 111±16 mm Hg;  $P=0.06$ ) and LVEF (60±10 versus 40±13%;  $P=0.05$ ) in patients selected for explantation. No other differences existed between the 2 groups.

### Patients Explanted for Cardiac Recovery

Of the 6 explanted patients, 4 had acute presentations (2 acute myocarditis, 1 acute myocardial infarction, and 1 recent-onset cardiomyopathy). The pre-LVAD LVEF for these explanted patients ranged from 10% to 26%, with a mean of 16±7%.

TABLE 2. Serial Echocardiography and Cardiopulmonary Exercise Testing

	Pre-LVAD (n=67)	30 Days (n=41)	60 Days (n=34)	90 Days (n=21)	120 Days (n=16)
Heart rate, bpm	95±16	84±18*	79±18*	78±14*	77±18*
Blood pressure, mm Hg	99±18	115±16*	119±20*	120±15*	118±13*
Inotropes, %	87	12	2	0	0
ACE-I or ARB, %		47	59	57	68
β-Blockers, %		35	53	49	56
LVAD flow, L/min		5.8±1.2	5.6±1.3	5.8±1.2	5.6±1.0
Echocardiography					
LVEDD at 4 L/min, cm	7.1±1.2	5.1±1.1*	5.2±0.9*	5.4±0.9*	5.6±1.5*
LVEF at 4 L/min, %	17±7	34±12*	32±13*	30±13*	24±7‡§
LVEF >40% at 4 L/min, %	0	32	27	19	6
LV mass at 4 L/min, g	320±113	194±79*	183±73*	193±75*	187±64*
RV area shortening at 4 L/min		0.24±0.11	0.22±0.12	0.25±0.12	0.35±0.11†
RV systolic pressure at 4 L/min, mm Hg		39±10	35±9	39±9	33±6
Exercise testing, n		20	19	12	11
Peak $\dot{V}O_2$ , mL/(kg · min)		13.7±4.2	16.1±4.2‡	17.4±4.9‡	18.9±5.5‡
Exercise duration, min		8.7±3.2	11.3±4.1‡	13.4±3.5‡	15.2±3.3‡
Peak LVAD flow, L/min		8.1±1.3	7.7±2.1	8.8±1.4	8.7±1.5

ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensinogen receptor blocker; LVEDD, LV end-diastolic diameter; and  $\dot{V}O_2$ , oxygen consumption.

\* $P<0.001$  vs pre-LVAD.

† $P<0.05$ , ‡ $P<0.01$  vs 30 days.

§ $P<0.05$ , || $P<0.01$  vs 60 days.

Two explanted patients with chronic HF had nonischemic cardiomyopathy. The 4 patients with acute HF have maintained stable LVEFs 1 year after device explantation. Both patients with chronic HF exhibited a decline in LVEF by 6 months without clinical sequelae.

### Myocardial Tissue Analysis

In a subgroup analysis, 22 patients had paired apical histological samples (Figure 3) from the time of LVAD implant and explant. Paired tissue was not available from the 6 subjects who underwent device explantation without transplantation because myocardial tissue was not available. Myocyte size was reduced from  $52\pm 8.6$  at implantation to  $37\pm 7.1$  pixels at explantation ( $P<0.001$ ). Total collagen deposition decreased from  $2.3\pm 0.76\%$  at implant to  $1.3\pm 0.60\%$  at explant ( $P<0.001$ ). Myocardial TNF- $\alpha$  content was also reduced from  $3.8\pm 1.8\%$  to  $1.6\pm 0.99\%$  ( $P<0.001$ ). Tissue parameters were correlated with functional measures to screen for markers for recovery. Duration of device support did not affect changes in any of the 3 parameters measured. Larger myocyte size at LVAD implantation correlated weakly with a lower LVEF before transplantation ( $r=-0.5$ ,  $P<0.05$ ) and tended to correlate with increased LV mass before transplantation ( $r=0.4$ ,  $P=0.06$ ). No other relationships were found between changes in the myocardial samples and echocardiographic measures.

### Subgroup Analysis

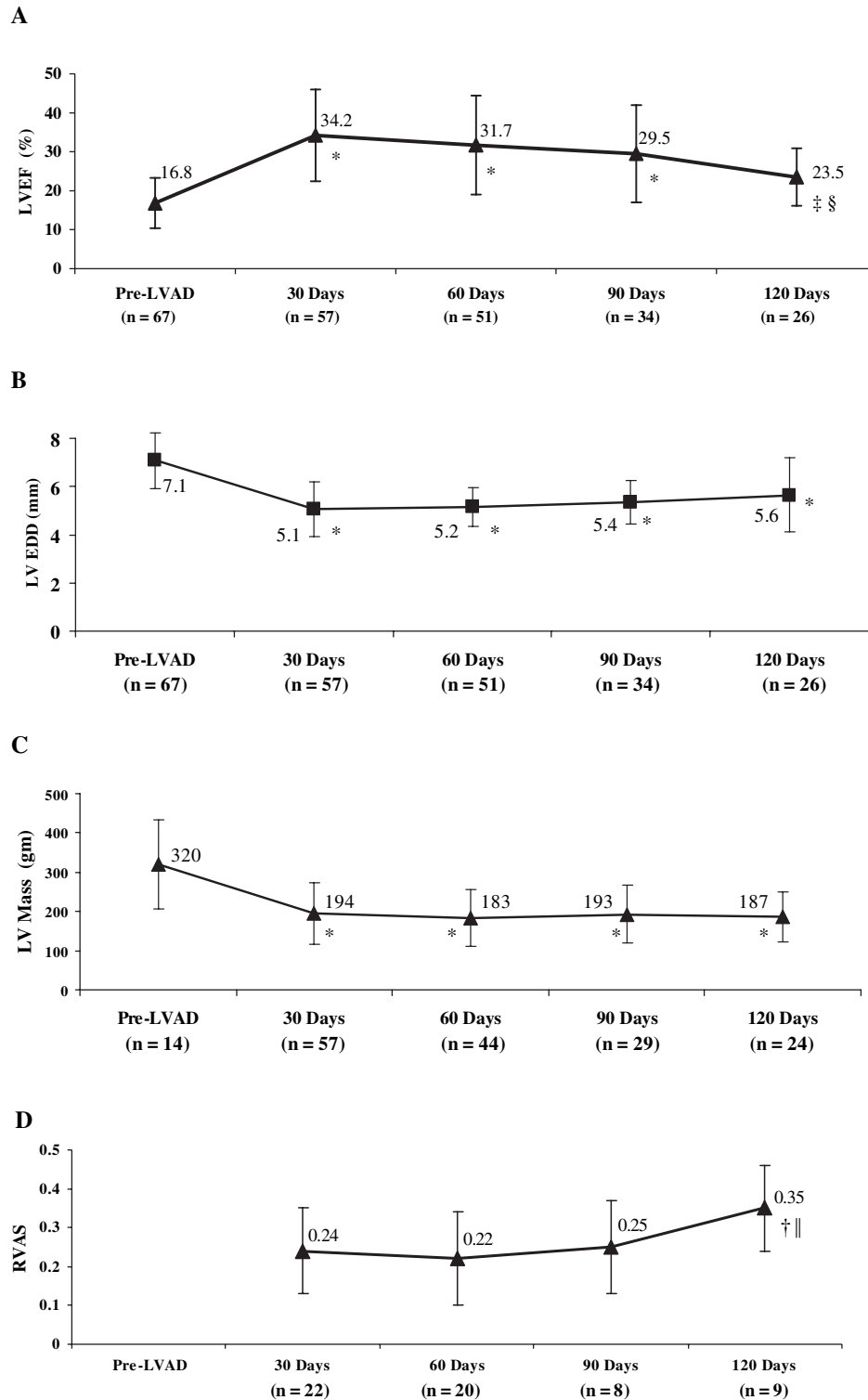
Several factors may affect myocardial recovery, including duration of HF, medical regimen during device support, and etiology of HF. Accordingly, subgroup analysis was per-

formed. Echocardiographic data in patients with acute ( $n=21$ ) and chronic HF ( $n=46$ ) revealed that although acute and chronic patients had similar baseline LVEF (acute,  $17\pm 10\%$ ; chronic,  $17\pm 5\%$ ;  $P=NS$ ), acute patients subsequently had a higher LVEF than chronic patients at all time points ( $P=0.02$ ). The greatest discrepancy was at 90 days, when the LVEF for the acute HF group was  $38\pm 12\%$  versus  $25\pm 11\%$  for the chronic group ( $P<0.05$ ). However, at 30 days, the percentage of patients with LVEF >40% was similar for the 2 groups. No differences between groups were observed for LV end-diastolic diameter, RV area shortening, and LV mass. Paired myocardial tissue analysis for the 7 acute and 15 chronic HF patients revealed improvements for both patient groups in regard to myocyte size, collagen deposition, and cardiac TNF- $\alpha$  (Figure 3).

No echocardiographic differences were observed between those subjects with ischemic and nonischemic etiologies of HF. Similarly, no echocardiographic differences were seen at reduced LVAD flow at any time point in patients receiving an angiotensin-converting enzyme inhibitor and/or  $\beta$ -blocker versus those who did not.

### Discussion

The important findings of this study are as follows: (1) LVEF significantly improved after LVAD implantation in almost all patients, with 34% of patients exhibiting an LVEF >40% with reduced support. (2) Longer duration of LVAD support appeared to deleteriously affect LV function. (3) Significant regression of myocyte hypertrophy was observed, with echocardiographic reduction in myocardial mass and histological decrease in myocyte size and



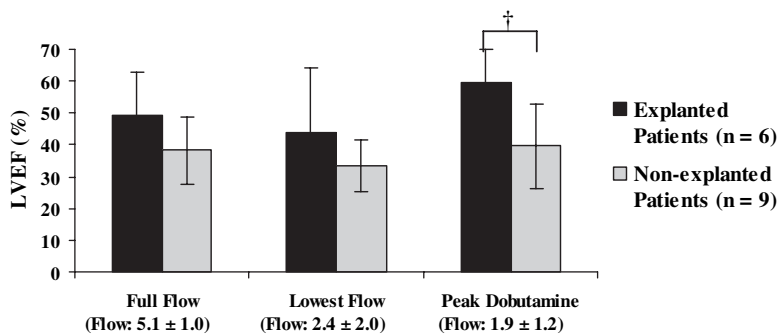
**Figure 1.** Serial echocardiographic changes. LVEF (A), LV end-diastolic diameter (EDD) (B), and LV mass (C) were significantly improved vs pre-LVAD. RV area shortening (RVAS) was improved at 120 days vs measurements at 30 days and 60 days of support. Comparisons with pre-LVAD: \* $P < 0.001$ . Comparisons with 30-day values: † $P < 0.05$ , ‡ $P < 0.01$ . Comparisons with 60-day values: § $P < 0.05$ , || $P < 0.01$ .

fibrosis. (4) Functional capacity, as evidenced by peak  $\dot{V}O_2$ , improved throughout LVAD support despite no change in peak LVAD flow or LVEF, suggesting that peripheral factors may account for much of the long-term

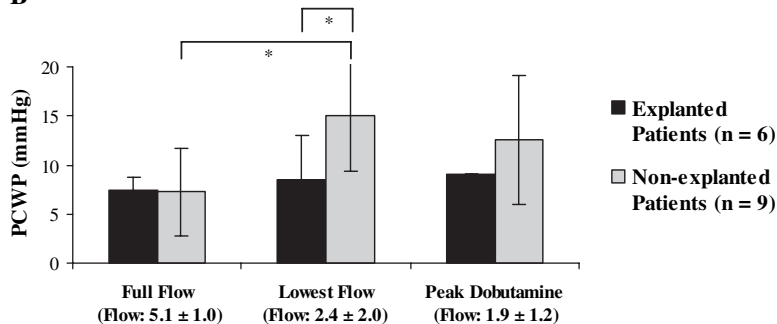
improvement. (5) Finally, complete recovery leading to LVAD explantation was rare, occurring in 9%, with the majority of recovered patients having acute presentations and nonischemic origins of HF.



A



B



**Figure 2.** Dobutamine testing. Dobutamine stress testing with invasive hemodynamic monitoring revealed a higher ejection fraction at peak dobutamine in patients explanted for recovery (A). In contrast, patients not suitable for explantation had an increase in pulmonary capillary wedge pressure (PCWP) with reduction of LVAD flow (B). \* $P < 0.05$ ; † $P = 0.05$ .

## Recovery

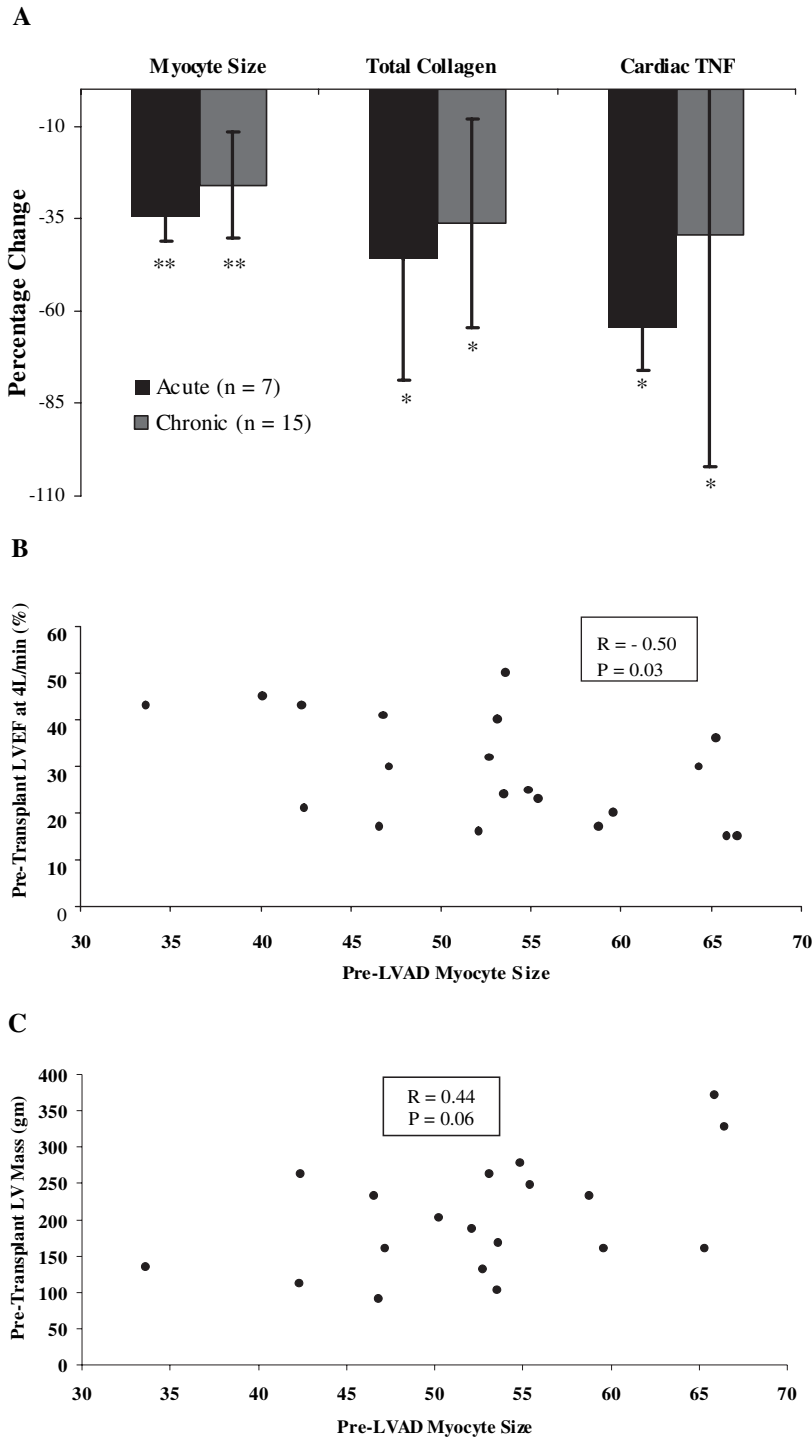
Many studies have reported myocardial recovery at the cellular and clinical levels. Studies of myocardial tissue from explanted hearts with device support described recovery of gene expression,<sup>6,13</sup> regression of cellular hypertrophy,<sup>2–4</sup> and improvement in calcium cycling,<sup>5,6</sup> in vitro contractile function,<sup>1,14</sup>  $\beta$ -receptor density and myocyte oxygenation,<sup>1,15</sup> as well as decreased deposition of cytokines such as TNF- $\alpha$ ,<sup>7</sup> interleukin-6,<sup>16</sup> interleukin-8,<sup>16,17</sup> and complement C3a.<sup>17</sup> There have been conflicting reports on the impact of device support on the extracellular matrix, with some studies reporting an increase<sup>18,19</sup> and others a decrease in collagen deposition.<sup>4,11,20</sup> Many studies were performed in the absence of clinical correlation, but in the few studies in which clinical parameters were analyzed, the cellular improvement was more impressive than the clinical impact.<sup>11,21</sup> In this study, paired myocardial tissue analysis revealed reduction in myocyte size, collagen deposition, and myocardial TNF- $\alpha$  expression consistent with some previous reports. The improvement in the tissue parameters appears greater than the modest changes observed in cardiac function.

In prior retrospective clinical studies, the frequency of cardiac recovery and device explantation has varied.<sup>9,12,22</sup> Recent reports from the Harefield Hospital (UK) describe the use of clenbuterol, an oral  $\beta_2$  agonist, in combination with an aggressive pharmacological regimen consisting of lisinopril, carvediol, spironolactone, and losartan in LVAD patients to enhance myocardial recovery.<sup>23</sup> With this approach, 11 of 15 dilated cardiomyopathy patients (73%) demonstrated cardiac recovery sufficient to undergo successful device explantation, with 100% and 89% cumulative rates of freedom from recurrent HF at 1 and 4 years, respectively.<sup>23</sup> This intriguing report represents a rate of cardiac recovery significantly

higher than any other in the literature. The Harefield strategy will be tested in a US multicenter study that is due to commence recruitment in the near future. In contrast, the frequency of device explantation for complete recovery was only 9% in our cohort. Our study included both subjects with acute and chronic HF presentations and those with ischemic and nonischemic etiologies of HF. Medical therapy during LVAD support was variable and less aggressive, and there was no use of clenbuterol. The frequency of device explantation for the chronic HF patients was 4% (2/46), which is consistent with prior reports.<sup>12</sup> Importantly, explantation was not the end point of this observational study. The decision for device explantation was not based on uniform clinical criteria but on the individual center's clinical team consensus. However, we believe that these prospective data add to prior reports because all patients underwent uniform monthly evaluation of cardiac function, and only a small percentage of patients were found to have cardiac recovery sufficient to undergo LVAD explantation.

An important observation of this study is that the prevalence of partial recovery appears frequent and occurs early after LVAD implant. However, whether the increase in LVEF is related to partial recovery versus the marked unloading of the ventricle is unclear and cannot be determined from this study. The possibility of disuse atrophy during prolonged mechanical unloading has been raised,<sup>24–26</sup> and this hypothesis underlies the use of clenbuterol during LVAD support.<sup>22</sup> However, another report showed no myocyte atrophy with LVAD support.<sup>27</sup> In this study, neither continued decline in LV mass nor histological myocyte atrophy was observed.

The continued improvement of RV function differed from LV function, which deteriorated over time. With



**Figure 3.** Paired myocardial tissue analysis. Samples from 7 acute HF (<6 months) and 15 chronic HF (>6 months) patients were analyzed. Histological testing revealed significant improvements for both patient groups in myocyte size, collagen deposition, and cardiac TNF- $\alpha$  expression between myocardial specimens obtained at the time of cardiac transplantation compared with the time of LVAD implantation (A). No statistically significant differences existed in the histological parameters between the 2 patient groups. An exploratory analysis revealed an inverse relationship between myocyte size at the time of LVAD implantation and pretransplantation ejection fraction (B). A trend was also observed toward a direct association between myocyte size at the time of LVAD implant and pretransplantation LV mass (C). Comparisons with pre-LVAD: \* $P < 0.01$ ; \*\* $P < 0.001$ .

LVAD support, the RV is unloaded indirectly through reduction in pulmonary artery pressures, and RV recovery may occur over a longer time trajectory than LV recovery. Similar time trends in RV recovery have been reported.<sup>3</sup>

### Assessment of Recovery

As the incidence of myocardial recovery has varied considerably, so too has the methodology to determine cardiac recovery. Echocardiographic parameters during full and

partial device support, hemodynamic measurements during exercise testing,<sup>12</sup> dobutamine stress testing,<sup>28</sup> and combinations of these have been used to gauge recovery. In our study, we designed a modified approach. Patients with reduced LVAD support who maintained an LVEF >40% were selected for dobutamine stress echo with hemodynamic monitoring. Patients who maintained low filling pressures and increased LVEF during dobutamine stress with partial support appear to be potential candidates for device explantation.

## Study Limitations

This study has a number of limitations. Because no uniformly accepted criteria exist for device explantation for recovery, criteria for explantation were determined by clinicians at the individual centers and not prescribed in the study protocol. In addition, the observational nature of this study precludes us from ascertaining the recovery rate without LVAD implantation. Because patients were removed from follow-up at the time of cardiac transplantation, some degree of selection bias may exist in the subjects followed up for longer periods of support. The timing of transplantation for LVAD patients, however, is based on time on the waiting list, blood type, and patient size and not related to cardiac function. All trends and associations reported here were similar when the analysis was done including only patients present for all time points (data not shown). Furthermore, a repeated-measures ANOVA was used to minimize the effects of missing data points. Because of the large number of statistical comparisons, however, overall type I error substantially exceeds the nominal 5% level. Also, no medical regimen during LVAD support was prescribed by protocol, although most patients received a  $\beta$ -blocker and/or angiotensin-converting enzyme inhibitor. Exercise and echocardiographic studies were not reviewed by core laboratories; however, the participating centers had considerable expertise in this testing.

Because not all centers were experienced with pump-off studies, echocardiographic measurements were made with partial LVAD support. This is a useful screening test and allows characterization of changes over time, although the comparison of pre- and post-LVAD measurements is limited by the different loading conditions. Calculations of LV mass are limited by the estimation and computation of 3-dimensional volumes by 2-dimensional measurements and may account for some measured variation. Finally, the participating centers decided to limit dobutamine stress testing with invasive hemodynamic monitoring to the patients who attained a LVEF >40% with reduced LVAD support. The possibility exists that more liberal use of dobutamine stress testing would have identified additional patients who had attained sufficient cardiac recovery for explantation. The small number of patients undergoing dobutamine testing (n=15) and myocardial tissue analysis (n=22) requires caution in the interpretation of these subgroup analyses.

In conclusion, we report the first large prospective study of cardiac function during LVAD support. Cardiac function and exercise capacity significantly improve after device implantation. Although cellular recovery and improvement in ventricular function are seen during LVAD support, the degree of clinical recovery is insufficient for device explantation in most patients. Future research will focus on the use of cell transplantation, genetic engineering, and/or novel pharmacological agents to promote cardiac recovery during LVAD support. This description of changes in cardiac function during mechanical unloading will be an important basis for these studies.

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## Disclosures

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### CLINICAL PERSPECTIVE

The LVAD Working Group Recovery Study is the first large prospective, multicenter trial of cardiac function during left ventricular assist device (LVAD) support and is the result of a collaborative effort by 7 of the largest US cardiac assist device centers. After LVAD implantation, patients were evaluated with the use of serial rest echocardiograms with partial LVAD support and cardiopulmonary exercise testing. Dobutamine echocardiography with hemodynamic measurements was performed in those patients with left ventricular ejection fraction >40% during resting studies. Sixty-seven LVAD patients participated in the study. After 30 days, significant improvement occurred in left ventricular ejection fraction and there was a reduction in left ventricular end-diastolic diameter and left ventricular mass. However, a progressive decrease occurred in left ventricular ejection fraction over time, with no difference from the pre-LVAD measurement by 120 days. Peak  $\dot{V}O_2$  progressively improved with mechanical support. Tissue analysis revealed significant reductions in myocyte size, collagen content, and cardiac tumor necrosis factor- $\alpha$ . Six subjects (9%) underwent LVAD explantation for recovery. We conclude that cardiac function improves significantly after LVAD implantation. Although cellular recovery and improvement in ventricular function are observed, the degree of clinical recovery is insufficient for device explantation in most patients with chronic heart failure. Future clinical research in this area will focus on the use of stem cell transplantation, genetic engineering, and/or novel pharmacological agents, such as clenbuterol, to promote cardiac recovery during LVAD support. We believe that our present work will be an important basis for these studies.

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