Regression of Cellular Hypertrophy After Left Ventricular Assist Device Support

Andreas Zafeiridis, PhD; Valluvan Jeevanandam, MD; Steven R. Houser, PhD; Kenneth B. Margulies, MD

Background—Although multiple studies have shown that the left ventricular assist device (LVAD) improves distorted cardiac geometry, the pathological mechanisms of the “reverse remodeling” of the heart are unknown. Our goal was to determine the effects of LVAD support on cardiac myocyte size and shape.

Methods and Results—Isolated myocytes were obtained at cardiac transplantation from 30 failing hearts (12 ischemic, 18 nonischemic) without LVAD support, 10 failing hearts that received LVAD support for 75±15 days, and 6 nonfailing hearts. Cardiac myocyte volume, length, width, and thickness were determined by use of previously validated techniques. Isolated myocytes from myopathic hearts exhibited increased volume, length, width, and length-to-thickness ratio compared with normal myocytes (P<0.05). However, there were no differences in any parameter between myocytes from ischemic and nonischemic cardiomyopathic hearts. Long-term LVAD support resulted in a 28% reduction in myocyte volume, 20% reduction in cell length, 20% reduction in cell width, and 32% reduction in cell length-to-thickness ratio (P<0.05). In contrast, LVAD support was associated with no change in cell thickness. These cellular changes were associated with reductions in left ventricular dilation and left ventricular mass measured echocardiographically in 6 of 10 LVAD-supported patients.

Conclusions—These studies suggest that the regression of cellular hypertrophy is a major contributor to the “reverse remodeling” of the heart after LVAD implantation. The favorable alterations in geometry that occur in parallel fashion at both the organ and cellular levels may contribute to reduced wall stress and improved mechanical performance after LVAD support. (Circulation. 1998;98:656-662.)

Key Words: heart-assist device ▪ myocytes ▪ cardiomyopathy ▪ hypertrophy

Dilated cardiomyopathy is characterized by impaired cardiac contractile performance, left ventricular chamber dilation, and a relative thinning of the left ventricular myocardium.1,2 By allowing a preserved stroke volume despite reduced fractional shortening, this gross anatomic remodeling of the heart is, in some respects, an adaptive mechanism. However, the geometric distortion associated with DCM leads to increased myocardial wall stress, which may further depress cardiac performance.

Studies on isolated myocytes have reported changes in cardiac myocyte shape according to the stress imposed on the heart. Isolated human myocytes from hearts with end-stage ischemic and idiopathic DCM increase substantially in volume and length, with smaller increases in myocyte diameter.3,4 Similar findings have been reported in animal models of ischemic DCM.5 Conversely, animal studies have also shown a reduction in myocyte size when preload and/or afterload are decreased.5-9 If such 2-way plasticity of the cell to regulate its size in response to physical stress were observed in humans, it might represent 1 aspect of the potential for myocardial recovery in advanced DCM.

Because of the relative shortage of donor organs and increases in waiting times for cardiac transplantation, a growing number of patients with advanced DCM are receiving mechanical circulatory support with an LVAD as a bridge to cardiac transplantation. As part of the circulatory support provided by these devices, the recipient's heart experiences dramatic reductions in both preload and afterload,10 along with reduced exposure to circulating neurohumoral factors.11 Recent studies have demonstrated that LVAD support improves the distorted geometry of the heart.12-16 Although our previous study identified changes in a crude measure of cell diameter after LVAD support,16 the exact nature of LVAD-induced “reverse remodeling” of the left ventricular myocytes is still unknown.

With newly refined myocyte isolation techniques and sophisticated cell morphometry techniques, the goals of the present study were to determine the morphological features of isolated human cardiac myocytes from patients with advanced HF versus nonfailing control hearts and to determine

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the effects of LVAD support on isolated human myocyte size and shape in advanced HF. We hypothesized that distorted cardiac myocyte geometry in advanced DCM would be largely ameliorated by sustained LVAD support.

### Methods

**Patient Population**

Left ventricular myocardial tissue was obtained at the time of orthotopic transplantation from 30 patients with severe HF without LVAD support (HF group), 10 patients who required LVAD support for refractory HF before cardiac transplantation (HF/LVAD group), and 6 nonfailing human hearts. Patients designated as having ischemic cardiomyopathy had no history of myocardial infarction and were free of significant coronary stenoses. Of 10 patients receiving LVADs, 6 required preoperative insertion of an intra-aortic balloon pump, and all met established clinical criteria for LVAD support, consisting of PCWP ≥20 mm Hg with either systolic blood pressure ≤80 mm Hg or cardiac index ≤2.0 L·min⁻¹·m⁻² despite maximal oral and intravenous medical therapy. In all HF/LVAD patients, the LVAD used was the Thermo Cardio-systems vented electric or pneumatically driven HeartMate device (Thermo CardioSystems, Inc) before subsequent cardiac transplantation. The nonfailing group included 4 unused normal donor hearts, 1 pulmonary artery catheter (American Edwards Laboratories, AHS del Caribe, Inc), right atrial pressure (RAP), PA, and PCWP were measured directly. Cardiac output was measured by thermodilution, and cardiac index was expressed as the ratio of cardiac output to body surface area. Arterial pressure was measured invasively.

### Hemodynamics

Right-sided heart catheterization was performed in the HF/LVAD and HF groups at the time of LVAD placement and immediately before orthotopic heart transplantation. With a balloon-tipped pulmonar y artery catheter (American Edwards Laboratories, AHS del Caribe, Inc), right atrial pressure (RAP), PA, and PCWP were measured directly. Cardiac output was measured by thermodilution.

### Echocardiography

Resting echocardiographic studies were performed by a trained technician using a Sonos 1000 machine and a 2.5-MHz phased-array transducer (Hewlett Packard). From parasternal short-axis views, M-mode images at the level of the papillary muscles were recorded, and measurements of LVEDD, LVESD, septal thickness (VST), and posterior wall thickness (PWT) were made according to the guidelines of the American Society of Echocardiography. Left ventricular mass was calculated by use of the following formula previously validated by Devereux et al: Left ventricular mass (g) = 1.04 × (LVEDD + IVS + PWT)² - LVESD² + 10. 

### Myocyte Isolation

Immediately after aortic cross clamping, the aortic root was perfused with cold, blood-buffered cardioplegia solution in vivo. Then, 10 to 30 minutes after cross clamping, hearts were explanted and transported to the laboratory, where a coronary artery or vein was cannulated to allow cell isolation from the lateral free wall of the left ventricle. The perfused area of myocardium was excised and rinsed for 30 minutes with a nonrecirculating, nominally Ca²⁺-free solution containing Krebs-Henseleit buffer with 10 mmol/L taurine. Next, the myocardial segment was perfused for 30 minutes with a recirculating digestion solution containing type III collagenase (180 U/mL), 0.2 mmol/L CaCl₂, 0.05 mmol/L CaCl₂, and 0.2 mmol/L CaCl₂. The tissue was then exposed to a nonrecirculating rinsing for 10 minutes with Krebs-Henseleit solution containing 10 mmol/L taurine, 20 mmol/L 2.3-butandienone oxime, and 0.2 mmol/L CaCl₂. The tissue was then removed from the cannula, and the midmyocardial area was minced in the rinse solution. The resulting cell suspension was filtered and centrifuged (25g). Isolated myocytes were resuspended in a Krebs-Henseleit solution containing 1% w/vol bovine albumin, 10 mmol/L taurine, and 0.2 mmol/L CaCl₂. All solutions were equilibrated with 95% O₂ and 5% CO₂. The temperature was kept at 37°C throughout the isolation procedure. Initial yields of rod-shaped myocytes ranged from 10% to 50%.

- Freshly isolated myocytes were fixed in an iso-osmotic solution containing 1.5% glutaraldehyde in 0.06 mol/L phosphate buffer. As previously described by Gerdes et al, this fixation method does not alter myocyte volume. Fixed cells were centrifuged through a Ficoll gradient to remove unwanted debris and cell fragments as described. Final cell suspensions from all hearts contained an average of 36% rod-shaped myocytes.

### Cell Volume Measurements

The complex shape of cardiac myocytes makes the measurement of cell volume challenging. Previous reports suggest that Coulter Channelyzer analysis can rapidly provide accurate volume measurements for a large number of cardiac myocytes. In the present studies, we used the Coulter Channelyzer analysis and shape factor adjustment as previously derived and validated by other investigators to derive the final median myocyte volume for each isolated cell preparation. To examine the possible influence of the percent rod-shaped cells on the myocyte volumes measured with the Coulter Channelyzer, we performed subgroup analyses within the HF group. Previous studies indicate that the inclusion of round cells does not significantly alter the final cell volume.

### Light Microscopic Morphometry

Images of randomly selected rod-shaped myocytes with normal striations and no membrane blebs or granularity were obtained with CCD camera, frame grabber, and Olympus M801 microscope (n=35 myocytes per heart). Previous studies have demonstrated that this sample size adequately represents the population at the 95% CI.
The length and profile surface area of myocytes were measured with the public-domain NIH Image software, version 1.59. Myocyte length was measured as the longitudinal axis of the best-fitting ellipse. The average width of each myocyte was calculated by the ratio of the profile surface area to the length of the cell. In addition, after hematoxylin staining, the number of nuclei per cell was evaluated in 100 cells per heart in 10 unsupported failing hearts, 10 failing hearts with antecedent LVAD support, and 4 nonfailing hearts.

Statistical Analysis
All data are expressed as mean ± SEM. To compare the morphological characteristics of myocyte preparations from each of the 3 groups, 1-way ANOVA for independent groups was performed by use of the SAS mainframe software program. In case of statistical significance, Tukey post-hoc analysis was used to locate the significantly different means. Paired Student’s t test was used to compare the morphodynamic data before and after LVAD placement in the HF/LVAD group. Two-way ANOVA was performed to compare the percent of mononucleated and binucleated cells in the 3 experimental groups, 1-way ANOVA for independent groups was performed by use of the SAS mainframe software program. In case of statistical significance, Tukey post-hoc analysis was used to locate the significantly different means. Paired Student’s t test was used to compare the morphodynamic data before and after LVAD placement in the HF/LVAD group. Two-way ANOVA was performed to compare the percent of mononucleated and binucleated cells in the 3 experimental groups. A P value of < 0.05 was considered statistically significant for all hypothesis testing.

Results
Clinical Characteristics
The clinical characteristics of the subjects from whom myocytes were obtained are summarized in Table 1. Average age, body weight, heart weight, congestive heart failure duration, and sex distribution did not differ between the HF and HF/LVAD groups. There was a greater proportion of subjects with nonischemic cardiomyopathy in the HF/LVAD compared with the HF group. In the HF/LVAD group, the average duration of LVAD support was 75 ± 15 days (range, 24 to 156 days). The strong male predominance in both groups of failing hearts was not present in the nonfailing group. Overall, the use of pharmacotherapy was similar among patients in the HF and HF/LVAD groups, except for the higher average inotropic requirements in the LVAD group before device placement. However, patients in the HF/LVAD group received far less medical therapy after the device was implanted than they had been receiving before implantation. Intravenous inotropic therapy, including both dobutamine and milrinone in most patients, was weaned within 1 week of LVAD placement in all patients. In addition, the use of converting enzyme inhibitors decreased from 90% to 10%, the use of digoxin decreased from 70% to 10%, and the use of diuretics decreased from 60% to 20% after LVAD support. Ten percent of patients received β-blocker therapy, and 20% received a calcium channel antagonist both before and after LVAD placement.

Echocardiography
As shown in Table 2, echocardiographic studies revealed no differences in left ventricular morphology between the HF and HF/LVAD groups before device implantation. Specifically, similarities in LVEDD, LVESD, left ventricular mass, and LVEF indicate overall equivalence of cardiac hypertrophy before mechanical support. Paired echocardiographic data, obtained before and after LVAD support, were available for 6 of the 10 LVAD-supported patients. In these 6 individuals, LVEDD decreased from 7.5 ± 0.5 to 5.5 ± 0.3 cm (P < 0.01), and LV mass decreased from 347 ± 63 to 193 ± 23 g (P < 0.05).

Morphology of Human Ventricular Myocytes
As shown in Table 3 and the Figure, myocytes from the HF group exhibited marked hypertrophy compared with myo-
cytes from nonfailing control hearts. This hypertrophy was characterized by an almost doubling of median cell volume, a 48% increase in cell length, and a 20% increase in cell width without any change in myocyte thickness. Among the nonfailing control hearts, the volume and shape of left ventricular myocytes from the 2 hearts with right ventricular disease did not differ from those obtained from the 4 normal donor hearts.

LVAD implantation significantly reduced the size of left ventricular myocytes. Specifically, antecedent LVAD support was associated with a 28% reduction in cell volume, 20% reduction in cell length, 20% reduction in cell width, and 36% reduction in cell profile area. In contrast, LVAD support was associated with no change in cell thickness, and these disproportionate changes in cell dimensions resulted in a significant 32% reduction in the length-to-thickness ratio of myocytes from LVAD-supported failing hearts. Comparisons between the HF/LVAD and nonfailing groups did not reveal significant differences within any morphometric parameter.

As shown in Table 3, advanced cardiomyopathy was associated with a higher proportion of binucleated myocytes compared with nonfailing hearts. Specifically, while only 25% of myocytes from nonfailing hearts were binucleated, 48% of myocytes from the HF group were binucleated (P<0.05), with 0.6% having >2 nuclei. In advanced cardiomyopathy with antecedent LVAD support, the 50% rate of binucleation was greater than that observed in nonfailing controls (P<0.05) but not different from that observed in the HF group.

**Cell Preparation and Cell Volume**

The proportion of isolated cardiac myocytes with a rod-shaped morphology varied from preparation to preparation. To assess a possible influence of the proportion of rods on the cell volume measured by the Coulter Channelizer, we performed a subgroup analysis within the 30 patients in the HF experimental groups. These plots demonstrate that the distribution of myocyte lengths is shifted to the right and is broader in the HF group compared with the nonfailing controls. An intermediate location and shape of the frequency distributions for length and profile area were observed in the HF/LVAD group. Such differences in the frequency distributions between groups were not observed for average cell width. Further analysis of frequency distributions reveals that only 20% of cells in the HF group have maximum length <150 μm, whereas the respective value in HF/LVAD group is 40%.

**Table 3. Human Cardiac Myocyte Morphometric Data**

<table>
<thead>
<tr>
<th>Variable</th>
<th>HF</th>
<th>HF/LVAD</th>
<th>Nonfailing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rods, %</td>
<td>30±3</td>
<td>24±5</td>
<td>27±8</td>
</tr>
<tr>
<td>Volume, μm³</td>
<td>51 888±2067</td>
<td>37 443±3307*</td>
<td>27 947±1980*</td>
</tr>
<tr>
<td>Length, μm</td>
<td>201±6</td>
<td>161±7*</td>
<td>136±4*</td>
</tr>
<tr>
<td>Width, μm</td>
<td>31.5±0.9</td>
<td>25.1±1.5*</td>
<td>26.2±1.3*</td>
</tr>
<tr>
<td>Thickness, μm</td>
<td>10.9±0.7</td>
<td>11.8±0.7</td>
<td>10.1±1.0</td>
</tr>
<tr>
<td>Length-to-thickness ratio</td>
<td>21.0±1.7</td>
<td>14.2±1.3*</td>
<td>14.0±1.3</td>
</tr>
<tr>
<td>Mononucleated cells, %</td>
<td>48±3</td>
<td>50±2</td>
<td>75±2</td>
</tr>
<tr>
<td>Binucleated cells, %</td>
<td>51±3</td>
<td>50±2</td>
<td>25±2</td>
</tr>
</tbody>
</table>

All data are mean±SEM.
*P<0.05 vs HF.

**Table 4. Comparison of Cardiac Myocyte Morphometry in Ischemic Versus Nonischemic Cardiomyopathy Without Prior LVAD Support**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ischemic Cardiomyopathy</th>
<th>Nonischemic Cardiomyopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume, μm³</td>
<td>51 731±3677</td>
<td>51 993±2511</td>
</tr>
<tr>
<td>Length, μm</td>
<td>196±10</td>
<td>204±7</td>
</tr>
<tr>
<td>Width, μm</td>
<td>31.5±1.3</td>
<td>31.5±1.2</td>
</tr>
<tr>
<td>Thickness, μm</td>
<td>11.2±1.0</td>
<td>10.8±0.9</td>
</tr>
<tr>
<td>Length-to-thickness ratio</td>
<td>19.6±2.4</td>
<td>21.9±2.4</td>
</tr>
</tbody>
</table>

All data are mean±SEM.
*P<0.05 vs ischemic cardiomyopathy.
group without LVAD support. In this analysis, we compared the cell volume measurements between the 3 tertiles of percent rod-shaped cells and found that the median cell volume was 50,901 ± 3,196 μm³ in the 10 patients with >40% rod-shaped cell, 52,075 ± 4,324 μm³ in the 10 patients with 20% to 40% rod-shaped cells, and 52,688 ± 3,491 μm³ in the 10 patients with <20% rod-shaped cells. There were no significant differences between tertiles, indicating that yield of rod-shaped myocytes did not affect measured cell volume.

Discussion

With the use of newly enhanced myocyte isolation techniques, the present study demonstrates that advanced DCM in humans is associated with distortions of normal cardiac myocyte size and shape compared with myocytes from nonfailing hearts. In addition, these studies indicate that there is no systematic difference in the changes in myocyte size and shape between isolated myocytes from hearts with nonischemic cardiomyopathy and those from noninfarcted zones in hearts with prior myocardial infarction. Despite equally advanced cardiomyopathy, circulatory support with an LVAD before transplantation results in regression of cellular hypertrophy and a tendency toward normalization of myocyte size and shape. Specifically, LVAD support for an average of 75 days significantly reduced the volume, length, average width, and length-to-thickness ratio of isolated human myocytes from patients with end-stage cardiomyopathy. We also observed that most of the change in myocyte volume after LVAD support is related to reduced myocyte length. In this context, the finding that LVAD support did not alter the increased proportion of binucleated myocytes in advanced HF indicates that reduced cell length after LVAD support is probably not attributable to induction of cell division or selective attrition of binucleated cells.

Myocyte Hypertrophy in HF

The methodology for characterization of myocyte size and shape used in this study exploits recent advances in human myocyte isolation techniques that allow us to obtain relatively high yields of rod-shaped cardiac myocytes from cardiectomy specimens at the time of transplantation. These isolated myocyte preparations, in turn, offer a unique opportunity to characterize the complex geometry and heterogeneity observed among cardiac myocytes. The importance of such characterization is underscored by previous studies demonstrating that the gross anatomic changes in the heart mirror the geometric changes at cellular level in humans and animals.2,23-24

With the use of isolated cardiac myocyte preparations from 30 subjects with advanced congestive HF and 6 nonfailing controls, our findings confirm and extend previous observations concerning changes in myocyte geometry in advanced cardiomyopathy.2,26-27,29 In the present studies, an almost doubling of myocyte volume was observed in the unsupported failing hearts. This large increase in cell volume is more than enough to account for the differences in heart weight observed between the 2 groups. Confirming previous studies,21,27,24 we observed no relationship between the proportion of rod-shaped myocytes and the measured cell volume within the HF group.

The results of our study also confirm previous findings that the distorted geometry of the left ventricle in hearts with DCM is due mainly to the longitudinal growth of the cell (47% increase in length and 20% increase in width with little or no change in thickness). In fact, previous studies on isolated human cardiac cells from end-stage ischemic cardiomyopathy have reported nearly identical 45% increase in length and 20% increase in average width compared with isolated myocytes from normal human hearts.2,24 Moreover, we observed particularly wide and flattened frequency distributions for cell length but not cell width among myocytes from the HF group compared with normal cardiac myocytes. Our findings may be reflecting an increased diversity of myocyte shape from the same heart preparation, as has been noted in some previous studies.29 In addition, our findings extend previous results4 by demonstrating that the changes in myocyte size and shape observed in advanced DCM do not differ between hearts with ischemic and nonischemic origins for their HF.

Effects of LVAD Support on Myocyte Hypertrophy

The present studies demonstrate that circulatory support with an LVAD before transplantation results in regression of cellular hypertrophy and a tendency toward normalization of myocyte size and shape despite equally advanced cardiomyopathy. Specifically, we observed that LVAD support for an average of 75 days significantly reduced the volume, length, average width, and length-to-thickness ratio of isolated human myocytes from patients with end-stage cardiomyopathy. In early animal studies by Thompson et al5 and others,6,8,9 complete hemodynamic unloading of feline papillary muscles produced striking decreases in myocyte size and ultrastructural derangements. In more recent studies, hemodynamic support with an LVAD in subjects with DCM improved the distorted geometry of the heart.12-16 The present studies extend these previous observations by demonstrating substantial reductions in cell volume with nonuniform decreases in cell dimensions after LVAD support in association with reductions in left ventricular dilation and hypertrophy. Thus, although reductions in interstitial water content or fibrosis could occur after LVAD support, these studies indicate that changes in myocyte size account for a large proportion of the reductions in left ventricular mass and “reverse remodeling” of the heart during LVAD support. According to the Laplace relationship, such changes in myocyte and chamber shape will tend to decrease in myocardial wall stress after LVAD support.

We observed that reductions in myocyte volume after LVAD support are more closely related to decreases in myocyte length than to decreases in myocyte thickness. This disproportionate decrease in myocyte length suggests that LVAD support has its greatest impact on the cell dimension that is most distorted and most heterogeneous in dilated failing hearts. Our finding that LVAD support does not alter the increased proportion of binucleated cells...
associated with advanced HF suggests that the reduction in the length of cardiac myocytes after LVAD support is probably not attributable to induction of cell division or the selective attrition of larger binucleated cells. With respect to other physiological mechanisms, the relative contributions of changes in hemodynamic loading conditions, reductions in endogenous neurohormones, and/or altered pharmacotherapy to the regression of cellular hypertrophy after LVAD support cannot be determined from the present studies.

Study Limitations and Conclusions

Several potential limitations of the present studies deserve mention. First, the number of nonfailing hearts available for cell isolation is small. Nevertheless, high-quality morphologic data with low intragroup variability were obtained from 6 nonfailing hearts, and our findings were quite similar to those reported in previous investigations. Second, the HF/LVAD group had a higher proportion of subjects with nonischemic cardiomyopathy than the HF group. However, on the basis of the lack of origin-based differences in myocyte morphology within the HF group, it is unlikely that the unbalanced composition of the HF/LVAD group affected our findings. Because only myocytes from the midmyocardium of the lateral free wall of the left ventricle were used in this study, these studies provide no information about the potential for regional heterogeneity of myocyte size and shape. With respect to morphometric measurements, some investigators have suggested that cardiac myocytes may assume a more flattened shape after dissociation compared with their shape in intact tissue specimens. Although the present studies do not address this concern, it is unlikely that such potential distortion affected the clear-cut intergroup differences we observed. Finally, in the isolated cell preparations used in this study, the proportion of rod-shaped myocytes obtained varied between subjects. However, we observed no significant intergroup differences in the proportion of rod-shaped cells, and within the HF group, subgroup analysis confirmed that inclusion of round cells does not significantly alter the final cell volume with Coulter analysis.

In conclusion, our findings support our hypothesis that LVAD support can ameliorate the distorted cardiac myocyte geometry associated with advanced DCM and indicate that regression of cellular hypertrophy is a major contributor to left ventricular remodeling after LVAD implantation. Decreases in myocyte volume can likely account for reductions in cardiac mass after LVAD support, whereas disproportionate decreases in cell length appear to account for normalization of cardiac morphology with reduced chamber dilation and increased relative wall thickness. The unique ability of LVAD support to promote improvements in cardiac geometry also suggests an opportunity for future investigations to elucidate the basic molecular mechanisms involved in mediating changes in myocyte size and shape in response to changes in mechanical and neurohumoral stimulation.

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References

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