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Chronic Unloading by Left Ventricular Assist Device Reverses Contractile Dysfunction and Alters Gene Expression in End-Stage Heart Failure

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Background—Left ventricular (LV) assist devices (LVADs) can improve contractile strength and normalize characteristics of the Ca\(^{2+}\) transient in myocytes isolated from failing human hearts. The purpose of the present study was to determine whether LVAD support also improves contractile strength at different frequencies of contraction (the force-frequency relationship [FFR]) of intact myocardium and alters the expression of genes encoding for proteins involved in Ca\(^{2+}\) handling.

Methods and Results—The isometric FFRs of LV trabeculae isolated from 15 patients with end-stage heart failure were compared with those of 7 LVAD-supported patients and demonstrated improved contractile force at 1-Hz stimulation, with reversal of a negative FFR after LVAD implantation. In 20 failing hearts, Northern blot analysis for sarcoplasmic endoreticular Ca\(^{2+}\)-ATPase subtype 2a (SERCA2a), the ryanodine receptor, and the sarcolemmal Na\(^{+}\)-Ca\(^{2+}\) exchanger was performed on LV tissue obtained before and after LVAD implantation. These paired data demonstrated an upregulation of all 3 genes after LVAD support. In tissue obtained from subsets of these patients, Western blot analysis was performed, and oxalate-supported Ca\(^{2+}\) uptake by isolated sarcoplasmic reticular membranes was determined. Despite higher mRNA for all genes after LVAD support, only SERCA2a protein was increased. Functional significance of increased SERCA2a was confirmed by augmented Ca\(^{2+}\) uptake by sarcoplasmic reticular membranes isolated from LVAD-supported hearts.

Conclusions—LVAD support can improve contractile strength of intact myocardium and reverse the negative FFR associated with end-stage heart failure. The expression of genes encoding for proteins involved in Ca\(^{2+}\) cycling is upregulated (reverse molecular remodeling), but only the protein content of SERCA2a is increased.

Key Words: heart failure □ sarcoplasmic reticulum □ calcium □ genes □ heart-assist device

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hearts were unsuitable for transplantation because of hepatitis B, extensive atrial damage during harvest, and high creatine phosphokinase levels with subsequently normal MB fraction, respectively. For LVAD patients, insertion and operation of the device (Thermo Cardio Systems Inc.) were performed as previously described. Inflow to the LVAD is provided through a conduit inserted into the LV via an ~1-in hole in the apex. Tissue removed in making this hole was immediately frozen in liquid nitrogen and subsequently used for pre-LVAD biochemical and molecular analyses and/or immersed in iced Krebs’ solution for measurement of trabecular force production and the force-frequency relationship (FFR, detailed below).

Heart Explantation and LV Pressure-Volume Relationships

At the time of transplantation, all hearts were perfused with 4°C hypocalcemic hyperkalemic cardioplegia solution, and tissue samples were obtained with the heart cold. Before tissue harvest in 3 nonfailing, 8 CHF, and 10 CHF+LVAD patients, the hearts were subjected to analysis of static LV pressure-volume relationships as described previously. Briefly, with the heart kept cold, pressure within a compliant water-filled latex balloon in the LV chamber was measured with a high-fidelity micromanometer while volume was within a compliant water-filled latex balloon in the LV chamber. The heart was subjected to electrophoresis, transferred to nitrocellulose membranes, and then hybridized with cDNA for rat SERCA2a (1.18-kb EcoRI fragment), the human Na+-Ca2+ exchanger (0.659-kb EcoRIPstI fragment), rabbit RyR (0.55-kb EcoRI-BamHI fragment), and human GAPDH (1.3-kb PstI fragment). All cDNA probes were labeled with [32P]dCTP (3000 Ci/mmol, Amersham) to a specific activity of 1×106 cpm/μg by use of a multiprimer DNA labeling system (Amersham). The blots were exposed to X-Omat AR film, and autoradiograms were then analyzed by laser densitometry in the linear response range of the x-rays with GAPDH used as an internal standard. The relative expression of each gene was quantified as the ratio of target band intensity to GAPDH band intensity standardized to the average of nonfailing samples on the blot. The same nonfailing hearts were used for standardization with a value of 1 arbitrarily designated as normal.

Western Blot Analysis

In 4 patients, sufficient myocardium was obtained from the pre-LVAD apical core to allow for both mRNA isolation and Western blot analysis for target proteins. These data were then compared with similar analysis of post-LVAD free wall from the same hearts. For Western blot, ~1 g of tissue was homogenized in 1.0 mL of ice-cold buffer containing 20 mmol/L Na-HEPES, pH 7.4, 4.0 mmol/L EGTA, 1.0 mmol/L dithiothreitol, and EDTA-free complete protease inhibitors (Boehringer-Mannheim). Samples were centrifuged, and protein concentration of the supernatant was determined before SDS-PAGE by use of 6% gels to detect RyR and 7.5% gels to detect SERCA2a and the Na+-Ca2+ exchanger (1.3-kb PstI fragment). All cDNA probes were labeled with [32P]dCTP (3000 Ci/mmol, Amersham) to a specific activity of 1×106 cpm/μg by use of a multiprimer DNA labeling system (Amersham). The blots were exposed to X-Omat AR film, and autoradiograms were then analyzed by laser densitometry in the linear response range of the x-rays with GAPDH used as an internal standard. The relative expression of each gene was quantified as the ratio of target band intensity to GAPDH band intensity standardized to the average of nonfailing samples on the blot. The same nonfailing hearts were used for standardization with a value of 1 arbitrarily designated as normal.

Northern Blot Analysis

In 20 patients, tissue was obtained both before LVAD (apical core) and after LVAD (free wall) for Northern blot analysis. Apical and free wall tissue samples obtained from 8 non-LVAD CHF hearts were also analyzed to determine whether regional differences in gene expression exist. For all samples, tissue without gross evidence of infarction or scarring was analyzed. Total RNA was extracted from myocardium with guanidinium thiocyanate, followed by centrifugation in cesium chloride solutions. Aliquots of total RNA were then separated by electrophoresis, transferred to nitrocellulose membranes, and then hybridized with cDNA for rat SERCA2a (1.18-kb EcoRI fragment), the human Na+-Ca2+ exchanger (0.659-kb EcoRIPstI fragment), rabbit RyR (0.55-kb EcoRI-BamHI fragment), and human GAPDH (1.3-kb PstI fragment). All cDNA probes were labeled with [32P]dCTP (3000 Ci/mmol, Amersham) to a specific activity of 1×106 cpm/μg by use of a multiprimer DNA labeling system (Amersham). The blots were exposed to X-Omat AR film, and autoradiograms were then analyzed by laser densitometry in the linear response range of the x-rays with GAPDH used as an internal standard. The relative expression of each gene was quantified as the ratio of target band intensity to GAPDH band intensity standardized to the average of nonfailing samples on the blot. The same nonfailing hearts were used for standardization with a value of 1 arbitrarily designated as normal.
TABLE 1. Patient Data

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<th>EF, %</th>
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<th>LVAD Function</th>
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<td>Normal</td>
<td>DOB, MIL, TNG, amidarone</td>
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</table>

Mean ± SEM: 50 ± 3 18 ± 1 88 ± 9

EF indicates ejection fraction; DOB, dobutamine; DA, dopamine; NE, norepinephrine; MIL, milrinone; VASOP, vasopressin; bivad, biventricular assist device; TNG, trinitroglycerine; IABP, intra-aortic balloon pump; and LD0, lidocaine.

SR Preparation

Ca²⁺ uptake by SR membranes isolated from 2 nonfailing, 5 CHF, and 4 CHF+LVAD hearts was directly assayed by use of the suction filtration method¹ adapted to eliminate the regulatory effects of phospholamban by providing a relative excess of Ca²⁺. Briefly, after tissue homogenization, membrane vesicles enriched in SR were isolated by sequential centrifugation, resuspended in sucrose/histidine, and placed in uptake medium (50 mmol/L histidine, 3 mmol/L MgCl₂, 100 mmol/L KCl, 5 mmol/L potassium oxalate, and 0.05 mmol/L CaCl₂ with tracer ⁴⁵Ca²⁺). After incubation, Ca²⁺ uptake was initiated by the addition of 3 mmol/L ATP. Before and 5 minutes after ATP administration, aliquots were removed and analyzed for protein and ionized Ca²⁺ by spectrophotometry with 1,2-bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid as the Ca²⁺ indicator. Aliquots were then suctioned through a 0.45-μm filter and washed with KCl, imidazole, EGTA, and MgCl₂. Radioactivity of the filtrate and the filter was then counted, and Ca²⁺ uptake was measured in both the absence and presence of 1 mmol/L ryanodine, and the difference between measurements was used to index the contribution of RyR to Ca²⁺ influx across the membrane.

Statistical Analysis

All pre- and post-LVAD data from the same patient were compared by paired t test, as were apical and free wall mRNA data from the same heart. Comparisons between groups were made by ANOVA. For all tests, a value of P < 0.05 was considered significant.

Results

Hemodynamic Effects of LVAD Support

Characteristics of patients from whom pre- and post-LVAD tissue samples were obtained are shown in Table 1, with patients subdivided under the broad categories of dilated (DCM) or ischemic (ICM) cardiomyopathy. The duration of LVAD support ranged from 24 to 151 days. Two patients exhibited echocardiographic evidence of LVAD valvular malfunction: one with inflow obstruction (patient 7) and the other with inflow regurgitation (patient 18). Hemodynamic variables, which were obtained with the patients anesthetized and mechanically ventilated before LVAD implantation and with the patients receiving full LVAD support immediately before heart transplant, are shown in Table 2.

Static LV Pressure-Volume Relationships

Ex vivo pressure-volume relationships are shown in Figure 2. A marked difference between the nonfailing and CHF hearts is evident, with the curve derived from the CHF+LVAD hearts falling between these 2 extremes. Mean V₃₀ values for the nonfailing and CHF+LVAD hearts were not significantly different (96 ± 10 and 138 ± 11 mL, respectively), whereas the mean V₃₀ value for the CHF hearts (267 ± 20 mL) was greater than the values for the others (P < 0.001). Consistent with a previous report,¹⁷ the pressure-volume relationships of the 2
hearts with LVAD inflow valve dysfunction (patients 7 and 18) were similar to those of the CHF hearts not receiving LVAD support.

Trabecular FFRs
Trabecular dimensions were similar among all groups, as was developed force at 1 Hz in trabeculae from pre-LVAD core samples and the free wall of non-LVAD hearts (Table 3). In contrast, developed force at 1 Hz in trabeculae isolated from the LV free wall of post-LVAD hearts tended to be higher than that measured in pre-LVAD core trabeculae, although with the small sample size, this difference did not achieve statistical significance. Developed force was reduced similarly by increasing stimulation frequency in the pre-LVAD core and non-LVAD transplant samples but, on average, did not decline in the post-LVAD samples (Figure 2A). Representative force tracings from individual hearts are shown in Figure 2C. The effects of increased stimulation frequency on developed force in the 3 paired pre-LVAD and post-LVAD trabeculae are summarized in Figure 2B, which suggests that in individual hearts, LVAD support converts the FFR from negative to positive.

Northern Blot Analysis
In non-LVAD-supported CHF hearts (Figure 3), apical SERCA2a mRNA levels were, on average, greater than in the free wall, whereas RyR and the Na\textsuperscript+–Ca\textsuperscript{2+} exchanger mRNA were not different. A representative Northern blot depicting pre- and post-LVAD samples obtained from the same hearts is shown in Figure 4. The normalized pre- and post-LVAD mRNA values for all patients are shown in Figure 5. mRNA levels of SERCA2a, RyR, and the Na\textsuperscript+–Ca\textsuperscript{2+} exchanger were higher in the post-LVAD free wall than in the pre-LVAD apex. Statistical analysis failed to show any correlation between post-LVAD mRNA values for any of the genes and the duration of LVAD support, patient age, the value of any hemodynamic parameter, or V\textsubscript{50}.

SERCA2a, RyR, and Na\textsuperscript+–Ca\textsuperscript{2+} Exchanger Protein
A Western blot of protein obtained from 4 paired pre- and post-LVAD samples and 1 nonfailing heart is shown in Figure 6. Semiquantitative densitometric analysis with values standardized to those measured in the nonfailing heart demonstrated, on average, no change in RyR (71±3% versus 91±6%, P=0.06) and the Na\textsuperscript+–Ca\textsuperscript{2+} (116±16% versus 112±12%, P=0.6) exchanger protein but an ~4-fold increase (15±14% versus 62±8%, P=0.001) in SERCA2a.

SR Ca\textsuperscript{2+} Uptake
The amount of oxalate-supported Ca\textsuperscript{2+} uptake over 5 minutes was 394±42 nmol/L per milligram protein for nonfailing hearts, 296±20 nmol/L per milligram protein for CHF hearts, and 372±51 nmol/L per milligram protein for CHF+LVAD hearts. The addition of ryanodine to the incubation medium to block concomitant release via the RyR increased Ca\textsuperscript{2+} uptake by 25% in nonfailing membranes but only by 10% in SR membranes from both CHF and CHF+LVAD hearts.

Discussion
In some patients, LVAD support leads to sufficient improvement in global pump function for explant of the device.\textsuperscript{7,18} Although long-term outcome has been poor in many patients,\textsuperscript{18,19} the concept that LVADs may have a role as a “bridge to recovery” has developed, in part, because of studies demonstrating reversal of chamber enlargement, reduction in LV mass, and regression of myocyte hypertrophy.\textsuperscript{1,4,5,20} In addition, recent data showing an increased rate of unloaded myocyte shortening,\textsuperscript{3} an enhanced inotropic response to \( \beta \)-adrenergic stimulation,\textsuperscript{3,21} and improved cytosolic Ca\textsuperscript{2+} transients (increased peak, accelerated decay)\textsuperscript{3} after LVAD serve to underscore the multitude of abnormalities that may undergo recovery, even in severely diseased myocardium.

The finding of LVAD-induced improvement in isolated myocyte Ca\textsuperscript{2+} metabolism is of particular interest because under most circumstances of severe heart failure, myocardial systolic and diastolic contractile dysfunction are associated with abnormal excitation-contraction coupling.\textsuperscript{8,9} Recent data have demonstrated increased SERCA2a protein after LVAD support,\textsuperscript{22} but whether the contractile strength of intact myocardium also improves remained unknown. Consistent with prior studies,\textsuperscript{14,23} the present study revealed a negative FFR in trabeculae isolated from failing hearts. Importantly, the behaviors of free wall tissue obtained from non-LVAD transplant hearts and apical tissue obtained at the time of LVAD implantation were similar, thus excluding the possibility that regional factors contributed to differences between these pre- and post-LVAD data. After LVAD support, force at all stimulation rates tended to increase, and the FFR in individual hearts was converted from negative to positive.
We hypothesized that upregulated expression of genes encoding for proteins involved in Ca\(^{2+}\) handling would occur in conjunction with LVAD-induced recovery of force and FFR. Inasmuch as SERCA2a activity has been linked to the FFR, downregulation of the gene encoding for SERCA2a in heart failure appears to be associated with the negative FFR. Indeed, recent studies demonstrating that overexpression of SERCA2a in failing human myocytes normalizes their force generation.

**Figure 2.** A, Normalized force (mean±SEM) developed at increasing stimulation frequency by isometric LV trabeculae from free wall of failing hearts (CHF free wall, n=15), from apex before LVAD placement (CHF apical core, n=5), and from free wall after LVAD support (LVAD free wall, n=7). *P<0.05 for CHF free wall vs LVAD free wall. B, Ratio between force developed at 2.5 and 1 Hz before and after LVAD support in 3 individual hearts. MI indicates myocardial infarction. C, Force tracings from isometrically contracting trabeculae isolated from 1 nonfailing (normal) and 2 DCM hearts. In 1 DCM heart, a negative FFR before LVAD support became markedly positive after LVAD support.

**Figure 3.** mRNA values from LV apex and free wall of individual CHF patients. Circles represent individual values; triangles, mean±SEM. *P<0.05.
frequency response support functional significance of SERCA2a downregulation. Consistent with these findings, our data suggest that improved force and FFR after LVAD were accompanied by SERCA2a upregulation. Our finding that SERCA2a expression in the apex of non-LVAD hearts was slightly higher than that of the free wall excludes regional heterogeneity as a confounding factor and suggests that the degree of LVAD-induced increase in free wall SERCA2a mRNA may in fact be underestimated. Complementing the gene expression data, the present data also identified a substantial increase in SERCA2a protein levels and increased oxalate-supported Ca\(^{2+}\) uptake by isolated SR membranes.

Although the relationship between SERCA2a and FFR has been more extensively studied, properties of the RyR, which regulates Ca\(^{2+}\) release to the myofilaments, also play a pivotal role in the ability of the SR to store and rapidly release Ca\(^{2+}\). We found upregulated expression of the gene encoding for RyR after LVAD support. However, there was little change in the protein content, a finding consistent with the fact that blockade of the RyR with an excess of ryanodine had the same effect on Ca\(^{2+}\) uptake by SR membranes isolated from both CHF and CHF+LVAD hearts. In a recent study, we showed that hyperphosphorylation of RyR in failing human myocardium disrupts the normal coupled gating of neighboring receptors, resulting in abnormal ensemble gating patterns, less coordinated SR Ca\(^{2+}\) release during excitation, and Ca\(^{2+}\) leak during diastole. After LVAD support, these abnormalities are reversed, possibly in response to normalization of the β-adrenergic signaling pathway. Thus, despite subtle changes in gene expression and/or protein content, it appears that channel or pump function may be more affected by posttranslational events.

Results of some studies have indicated that with decreased SERCA2a function in heart failure, a compensatory increase in the activity of the Na\(^{+}\)-Ca\(^{2+}\) exchanger occurs as this sarcolemmal protein assumes a greater role in extruding Ca\(^{2+}\) during diastole. Consistent with this process are data indicating upregulated myocardial expression of Na\(^{+}\)-Ca\(^{2+}\) exchanger mRNA in human heart failure. However, recent data indicate that levels of Na\(^{+}\)-Ca\(^{2+}\) exchanger protein are not necessarily changed in severe human heart failure, and animal studies have suggested that there can be decreased gene expression and reduced Ca\(^{2+}\) flux through the Na\(^{+}\)-Ca\(^{2+}\) exchanger in the setting of cardiac failure. Our data show that LVAD support leads to upregulated gene expression but no change in Na\(^{+}\)-Ca\(^{2+}\) exchanger protein content. Thus, as for RyR, isolated measurement of gene expression may not fully clarify pathophysiological or LVAD-induced changes of the Na\(^{+}\)-Ca\(^{2+}\) exchanger properties.

In summary, the present data provide evidence that in hearts that have undergone reverse structural remodeling, prolonged LVAD support also produces reverse molecular remodeling and improved myocardial contraction. Our data, in conjunction with other recent reports, suggest that upregulation of SERCA2a in particular may contribute to enhanced contractile function. Although we found increased expression of RyR and Na\(^{+}\)-Ca\(^{2+}\) genes after LVAD support, protein levels of both were not affected. Thus, their role in the pathophysiology of CHF in general and the effects of LVAD support in particular may be more fully clarified in functional studies that account for posttranslational modification.
References


