Disease-Specific Remodeling of Cardiac Mitochondria After a Left Ventricular Assist Device

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Background. **Failing hearts can exhibit elements of structural and molecular "reverse remodeling" after support with a left ventricular assist device (LVAD). The present study examined LVAD-induced remodeling of cardiac mitochondria.**

Methods. **Left ventricular tissue from 20 failing and 21 LVAD-supported hearts, catagorized as ischemic (ICM) or dilated (DCM) cardiomyopathy and four nonfailing hearts were studied. Myocyte mitochondrial ultrastructure was assessed by high-performance liquid chromatography determination of cardiolipin, a specific lipid component of the inner membrane, and its three major molecular species: L_4, L_3O, and L_2O_2.**

Results. **Both failing and LVAD-supported hearts exhibited a reduction in cardiolipin content that was independent of the type of cardiomyopathy. However, in failing/ICM hearts, there was a 25% increase in the L_4/L_3O ratio and a 70% increase in the L_4/L_2O_2 ratio, indicating a change in cardiolipin composition. These alterations were normalized by LVAD support. In sharp contrast, molecular species ratios in DCM hearts were the same as those in nonfailing hearts regardless of whether LVAD support had been used or not.**

Conclusions. **These data demonstrate LVAD-induced reverse remodeling of myocyte cardiolipin composition in ICM but not DCM hearts.**

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Mechanical support of the failing human heart with a left ventricular assist device (LVAD) can lead to some degree of structural and functional "recovery" [1–4], which, in a subset of patients, may be sufficient for removal of the device without subsequent transplantation [5]. Previous studies have indicated that LVAD support can reverse abnormalities in the myocyte calcium (Ca^{2+}) transient, normalize pressure-volume and force-frequency relationships, restore the contractile response to β-adrenergic agonists, upregulate endothelin A receptors and genes regulating calcium cycling proteins, and modulate antiapoptotic genes [6–10]. As a whole, these observations support the concept that LVAD support can normalize aspects of cardiac structure and function, a process termed "reverse remodeling."

LVAD support also improves indices of myocyte mitochondrial function [11]. The specific lipid component of mitochondrial membranes is cardiolipin (diphosphatidylglycerol), the presence of which is essential for oxidative ATP formation and substrate transport [12–14]. Other data suggest that in addition to total cardioplipin content, the relative concentrations of the molecular species tetralinoleoyl-cardiolipin (L_4, approximately 80% of total), trilinoleoyl-oleoyl-cardiolipin (L_3O, approximately 15% of total), and dilinoleoyl-dioleoyl-cardiolipin (L_2O_2, 3% of total) are related to mitochondrial ultrastructure (ie, density of cristae membranes) [15]. We hypothesized that the reverse remodeling produced by LVAD-induced reductions in LV pressure and volume load may lead to alterations in myocyte mitochondrial ultrastructure. To test this hypothesis, cardiolipin content and composition were measured in myocardium harvested from patients with chronic heart failure, from LVAD-supported patients, and nonfailing control hearts. To assess the influence of underlying disease, data were subdivided by the etiology of failure broadly categorized as ischemic (ICM) or dilated (DCM) cardiomyopathy based upon clinical history.

Material and Methods

Tissue Harvest and Cardiolipin Assay

Under a protocol approved by the Institutional Review Board of the New York Presbyterian Hospital, myocardium harvested from four nonfailing, 20 failing (eight ICM, 12 DCM), and 21 LVAD (eight ICM, 13 DCM) hearts was used for the study. The nonfailing hearts were unsuitable for transplant due to hepatitis B, extensive atrial damage during harvest, high CK levels with subsequently normal MB fraction, and subclinical coronary artery disease without history of infarction or ischemia. For LVAD patients, insertion of the device [Thermo Cardio Systems Inc [TCI], Woburn, MA] was performed as previously described [16]. At the time of transplantation, all hearts were perfused with 4°C hypocalcemic/hyperkalemic cardioplegia solution. All tissue samples

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were obtained from the LV free wall of explanted hearts and did not contain areas of gross scarring or evidence of recent infarction. After immersion in liquid nitrogen, tissue was stored at –70°C until analysis. Total cardiolipin concentration along with L_4, L_3O, and L_2O_2 were determined in each sample by HPLC with precolumn derivatization as previously described [15]. Briefly, cardiolipin extracted from myocardium was converted to a fluorescence-labeled derivative (2-[naphthyl-1′-acetyl]-cardiolipin dimethyl ester) and then resolved by reverse-phase high-performance liquid chromatography (HPLC) into well-defined molecular species determined by the size and double bonds of the fatty acyl group. Data were then standardized to protein content of each sample as determined by the Lowry technique.

Analysis of Myocyte Diameter

For a subset of hearts (four nonfailing, nine failing, 11 LVAD), tissue samples were fixed in 10% buffered formalin, embedded in paraffin, and mounted on glass slides. As previously described [8], samples were then prepared with Masson's Trichrome stain and images viewed on a Nikon microscope with a MTI 3CCD digital camera at 20× magnification. Digitally acquired images were analyzed using Image Pro Plus V3.0 by an examiner blinded to the heart condition. For diameter measurements, two orthogonal diameters were obtained per myocyte and then averaged. Only sections containing fibers cut in cross-section were analyzed. The diameters of 50 myocytes per slide were measured and then averaged. For ICM hearts, only regions remote from gross infarct zones were analyzed.

Data Anlaysis

To determine differences between nonfailing, failing, and LVAD groups, data were first compared by analysis of variance and the Newman-Keuls test without regard to the etiology of failure. Analysis was then repeated with data subdivided by ICM or DCM. To lessen the potentially confounding variable of time dependence [17], nonfailing and failing heart data were compared with LVAD data obtained in patients supported for ≥ 40 days, as previously described [8, 17]. Correlation between cardiolipin content/composition and patient age or duration of LVAD support was determined by regression analysis after application of curve-fitting techniques as required (Igor Pro; Wavemetrics, Inc, Eugene, OR). For all comparisons, p less than or equal to 0.05 was considered significant. Data are presented as mean ± standard error.

Results

Demographic data are shown in Table 1. Within the LVAD group, the DCM patients tended to be slightly younger than ICM patients and exhibited a wider range in duration of LVAD support. There was no difference in the mean duration of LVAD support between groups (p = 0.53), with a median value of 124 days for ICM patients and 119 days for DCM patients. Pharmacotherapy of non-LVAD patients was extensive and included positive inotropic agents and vasoactive agents (milrinone, dobutamine, norepinephrine, dopamine, vasopressin, nitroglycerin, nitroprusside), diuretics (furosemide, bumetanide), digoxin, and antiarrhythmic drugs (lidocaine, amiodarone). In contrast, LVAD patients were primarily receiving angiotensin-converting enzyme inhibitors (captoril, lisinopril) alone or in combination with furosemide or amiodarone.

Table 1. Patient Characteristics

	ICM		DCM	
	Failing	LVAD	Failing	LVAD
Age (years)	60 ± 1	59 ± 3	44 ± 2	48 ± 5
Gender	7M, 1F	7M, 1F	10M, 2F	10M, 3F
Mean duration of LVAD support (days)	—	138 ± 23	—	166 ± 30
Range of LVAD support (days)	—	(60–246)	—	(61–379)

Data are presented as mean ± standard error.

ICM = ischemic cardiomyopathy; DCM = dilated cardiomyopathy; failing = chronic heart failure; LVAD = left ventricular assist device.

Total Cardiolipin and Cell Size

Figure 1 depicts a representative chromatogram of cardiolipin species from human heart and demonstrates the relative preponderance of the L_4 component. Table 2

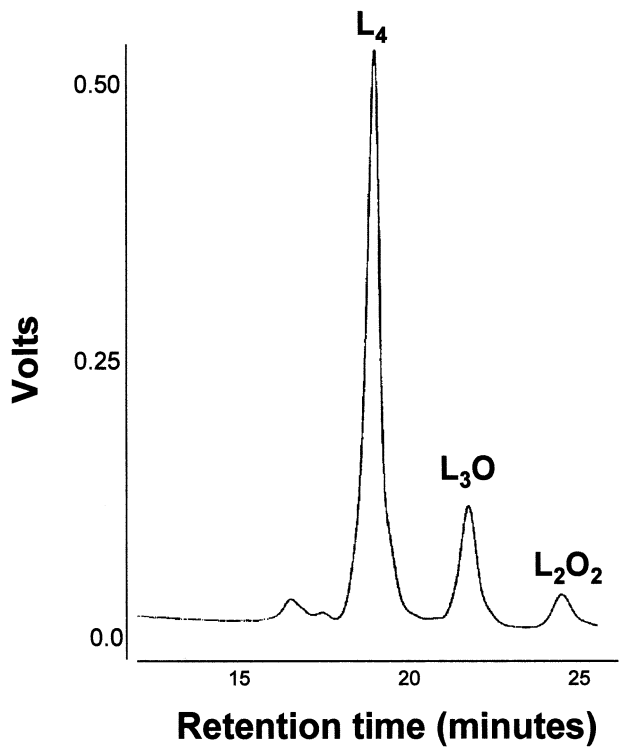

Fig 1. Representative chromatogram for cardiolipin molecular species.(L_4 = tetralinoleoyl-cardiolipin; L_3O = trilinoleoyl-oleoyl-cardiolipin; L_2O_2 = dilinoleoyl-dioleoyl-cardiolipin.)

Table 2. Absolute Cardiolipin Values

	All Hearts			ICM		DCM	
	Nonfailing (n=4)	Failing (n=20)	LVAD (n=21)	Failing (n=8)	LVAD (n=8)	Failing (n=12)	LVAD (n=13)
Total cardiolipin	13.9 ± 0.5	10.7 ± 0.5[a]	8.2 ± 0.6[a,b]	10.5 ± 0.9[a]	8.3 ± 1.0[a]	10.5 ± 0.7[a]	7.9 ± 0.7[a,b]
L_4	10.8 ± 0.3	8.3 ± 0.4[a]	6.2 ± 0.4[a,b]	8.6 ± 0.7	6.0 ± 0.8[a,b]	8.0 ± 0.6[a]	6.1 ± 0.6[a,b]
L_3O	2.2 ± 0.1	1.4 ± 0.09[a]	1.4 ± 0.14[a]	1.2 ± 0.1[a]	1.6 ± 0.3	1.5 ± 0.1[a]	1.2 ± 0.2[a]
L_2O_2	0.70 ± 0.09	0.49 ± 0.05	0.43 ± 0.04	0.42 ± 0.09[a]	0.53 ± 0.08	0.50 ± 0.1	0.35 ± 0.05[a,b]

Data are in nmol/mg protein.

DCM = dilated cardiomyopathy; ICM = ischemic cardiomyopathy; L_4 = tetralinoleoyl-cardiolipin; L_3O = trilinoleoyl-oleoyl-cardiolipin; L_2O_2 = dilinoleoyl-dioleoyl-cardiolipin.

[a] Difference from non-failing; [b] difference failing vs LVAD.

Data are presented as mean ± standard error.

shows absolute values for total cardiolipin and L_4, L_3O, and L_2O_2. In general, heart failure produced lower levels of total cardiolipin and the L_4 and L_3O species that were accentuated by LVAD support for 40 days or more. A similar pattern was evident when hearts were subdivided by ICM and DCM, although in LVAD-supported DCM hearts, L_2O_2 content was also reduced relative to nonfailing, failing, and ICM LVAD. There was no correlation between absolute values of any of the molecular species and patient age or LVAD duration of 40 days or more regardless of disease. To determine the influence of simultaneous changes in myocyte size on total cardiolipin, values from individual hearts were normalized to cell diameter. As shown in Figure 2, within this subset of hearts, myocyte diameter in failing hearts was increased relative to nonfailing but normalized after LVAD support. Accordingly, despite absolute cardiolipin values that were lower in LVAD-supported than failing hearts, when normalized to cell diameter, the value was nearly identical for both groups. However, normalized total cardiolipin for both failing and LVAD-supported hearts was markedly lower than that for nonfailing hearts.

Influence of ICM and DCM on Cardiolipin Composition

As shown in Table 3, calculating relative (percent of total) values for L_4, L_3O, and L_2O_2 revealed that in comparison with nonfailing hearts, ICM/failing hearts exhibited only a trend toward an increase in L_4 at the expense of L_3O and L_2O_2. A similar trend was not evident in the DCM hearts. In contrast, although total cardiolipin in LVAD-supported hearts was the same for both the ICM and DCM groups (8.3 ± 1.0 versus 7.9 ± 0.7), relative to failing hearts, LVAD support produced a significant shift away from L_4 and toward L_3O and L_2O_2 in ICM but not DCM hearts (Table 3). To more precisely characterize LVAD-induced alterations in cardiolipin composition and determine if the modest trend toward a relative increase in L_4 within ICM/failing hearts was an artifact, the ratio of individual species within each heart was also determined. This approach improves accuracy and fidelity of analyzing species shifts from heart-to-heart because unlike absolute cardiolipin content, the measurement is independent of auxiliary measurements such as protein content. Furthermore, the L_4/L_3O ratio in particular has emerged as a tissue-specific indicator of mitochondrial

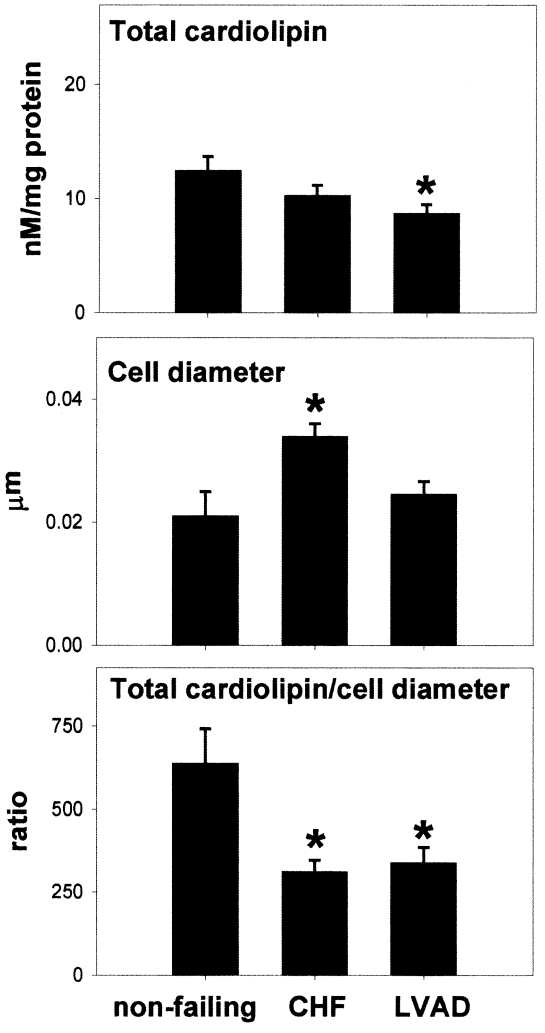

*Fig 2. Total cardiolipin content and myocyte diameter in four nonfailing, nine failing (CHF), and 12 left ventricular assist device (LVAD)-supported hearts. *Difference from nonfailing. Data are presented as mean ± standard error.*

Table 3. Cardiolipin Species Relative to Total

	All hearts			ICM		DCM	
	Nonfailing	Failing	LVAD	Failing	LVAD	Failing	LVAD
L_4	78 ± 1	78 ± 1	75 ± 1	82 ± 1	72 ± 2[a,b]	76 ± 2	77 ± 2
L_3O	15 ± 1	13 ± 0.6	17 ± 0.9[ab]	12 ± 1	20 ± 2[a,b]	14 ± 1	15 ± 1
L_2O_2	5.0 ± 0.5	4.7 ± 0.4	5.2 ± 0.3	3.9 ± 0.7[a]	6.6 ± 0.5[b]	5.1 ± 0.5	4.3 ± 0.4

Data are percent.

DCM = dilated cardiomyopathy; ICM = ischemic cardiomyopathy; L_4 = tetralinoleoyl-cardiolipin; L_3O = trilinoleoyl-oleoyl-cardiolipin; L_2O_2 = dilinoleoyl-dioleoyl-cardiolipin.

[a] Difference from non-failing; [b] difference failing vs LVAD.

Data are presented as mean ± standard error.

ultrastructure [15]. As shown in Figure 3, when data from all hearts are pooled, no significant effects of failure or LVAD support on any of the molecular species ratios were evident. However, when subdivided according to ICM or DCM, failure produced clear elevations in L_4/L_3O and L_4/L_2O_2 within ICM hearts that were reversed by LVAD support. In contrast, neither failure nor LVAD support altered any molecular species ratios in the DCM hearts.

Comment

In the failing heart, disruption of energy metabolism may occur at all coupling sites, including oxidative phosphorylation (coupling of respiration to ATP formation), the phosphocreatine shuttle (coupling of ATP formation to utilization), and myosin activation (coupling of ATP utilization to contraction) [18, 19]. With ischemic myocardium in particular, changes in creatine kinase isoenzyme distribution may compromise energy transfer between mitochondria and the contractile apparatus [18]. Efficiency of mitochondrial coupling is largely determined by the functional status of the inner membranes, of which cardiolipin is the characteristic phospholipid. First isolated from lipid extracts of the bovine heart, cardiolipin has a significant impact upon respiration, substrate transport, and the electrochemical gradient of mitochondrial membranes [12–14, 20]. Recent data indicate that variations in the relative proportion of individual fatty acid side chains of cardiolipin influence morphology and density of the inner mitochondrial membrane, and that the L4/L3O ratio in particular correlates with tissue oxygen consumption and the degree of stacking of inner membranes [15]. Additional evidence for the functional significance of shifts in the cardiolipin molecular species ratios comes from recent data demonstrating a near absence of L4 in patients suffering from the cardiomyopathy associated with Barth Syndrome (M. Schlame, unpublished data).

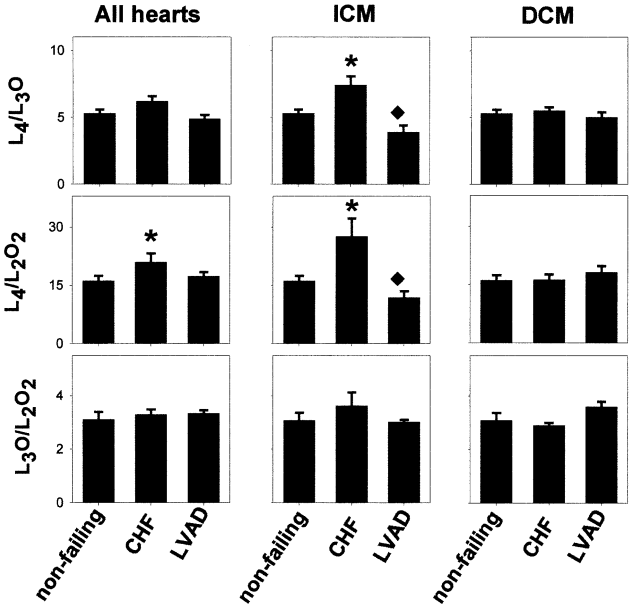

*Fig 3. Ratios of cardiolipin molecular species with all heart samples pooled or divided by underlying disease. Data are presented as mean ± standard error. (*CHF = *failing hearts;* DCM = *dilated cardiomyopathy;* ICM = *ischemic cardiomyopathy;* LVAD = *left ventricular assist device-supported hearts;* L_4 = *tetralinoleoyl-cardiolipin;* L_3O = *trilinoleoyl-oleoyl-cardiolipin;* L_2O_2 = *dilinoleoyl-dioleoyl-cardiolipin. *Difference from nonfailing;* diamond = *difference between CHF versus LVAD.)*

In some heart failure patients, LVAD support leads to a reversal of chamber enlargement and reduction in LV mass that is accompanied by improvement in global pump function [1–3, 5]. Additional studies of isolated myocytes and intact isometric LV trabeculae have demonstrated increased contractile function and an enhanced inotropic response to β-adrenergic stimulation after LVAD [6–8], indicating that augmented LV pump function is not simply the result of changes in size and geometry. At the cellular level, isolated myocytes show LVAD-induced improvement in cytosolic Ca^{2+} transients (increased peak, accelerated decay) [6], and molecular studies have demonstrated an upregulation of SERCA2a mRNA, which is accompanied by increased protein production and enhanced SR Ca^{2+} uptake [7]. Previous data suggest that LVAD support can also improve mitochondrial coupling in CHF hearts [11]. We therefore hypothesized that hemodyanamic unloading of the failing human LV with a mechanical assist device would alter cardiolipin composition within the cardiomyocyte.

In relation to nonfailing hearts, failing hearts exhibited

an approximate 25% reduction in total cardioplipin content regardless of whether failure was from ICM or DCM. After LVAD support of more than 40 days, total cardiolipin in both ICM and DCM hearts was further reduced to roughly 60% of the level measured in nonfailing hearts. Given that there is an increase in myocyte size in failure that can regresses during LVAD support [2, 8, 16] and possibly complicate interpretation of total cardiolipin content due to simultaneous changes in mitochondrial size, in a subset of patients, total cardiolipin was normalized to myocyte diameter. This analysis magnified the impact of heart failure on total cardiolipin (normalized value less than half that of nonfailing hearts) but eliminated the further decline suggested by LVAD support. These data indicate that heart failure has a marked effect on cardiolipin content of myocytes and that this effect persists even when the heart is unloaded to the point where it is required to little, if any, work and myocyte size regresses. Whereas the present study does not shed light on the mechanism(s) behind abnormal mitochondrial ultrastructure in heart failure, our data suggest that the fundamental abnormality is not reversed by LVAD support and are consistent with the possibility of mitochondrial atrophy.

In contrast, assessment of mitochondrial membrane remodeling based upon alterations in cardiolipin composition (ie, shifts in the relative proportions of the individual cardiolipin molecular species) indicated an LVAD-induced change in ICM but not DCM hearts. Of particular note was the finding that in failing hearts with ICM, there was a 25% increase in the L_4/L_3O ratio and a 70% increase in the L_4/L_2O_2 ratio. These changes were not present after LVAD support, indicating normalization of cardiolipin composition. In sharp contrast, although total cardiolipin content in DCM hearts declined in a manner similar to that in ICM tissue, molecular species ratios in DCM hearts were the same as those in nonfailing hearts regardless of whether LVAD support had been used or not. These data suggest that elevation of the L_4/L_3O ratio in the ICM/failing hearts most likely represents a higher demand on oxidative ATP synthesis in those parts of the myocardium that survived the ischemic insult(s). Subsequent normalization of L4/L3O with LVAD treatment, therefore, appears to be the result of reduced myocardial energy demand and "relaxed" mitochondrial stress. Importantly, the marked differences between ICM and DCM hearts was apparent despite the relatively nonspecific differentiation of the pathologic states based entirely upon clinical history.

Although multiple changes in the structure and function of failing myocytes after LVAD have been described, to our knowledge, these are the first data demonstrating specific molecular alterations related more to the underlying disease than heart failure in general. This observation assumes particular importance in the context of the present study because when all failing hearts were pooled, changes in molecular species ratios within ICM hearts were masked by the lack of change in DCM hearts. However, results of the current study should be interpreted in the context of certain limitations. Of particular importance is the fact that although previous studies have provided data to firmly link mitochondrial cardiolipin to multiple aspects of cellular respiration, the specific relationships in failing myocardium remain to be established. In a previous study, Lee and colleagues [11] demonstrated a modest LVAD-induced improvement in mitochondrial respiratory function due to a decrease in state 4 respiration. Tissue samples from 7 LVAD-supported patients included in the study of Lee and colleagues were also analyzed for cardiolipin content and composition and suggested an association between shifts in molecular species ratios and oxidative function. However, because we do not have similar data in either nonfailing or failing hearts, we cannot conclude that LVAD-induced alterations in cardiolipin content or the ratios of individual molecular species reflect specific functional changes. Finally, the relatively small sample size and incomplete clinical history for the nonfailing hearts has potential impact. Although these hearts were not exhibiting clinical signs of failure at harvest, clearly, the circumstances leading to donor demise and the pharmacotherapy used to maintain viability until organ harvest may have influenced study results. Thus, whereas there was little variation in cardiolipin content and composition within the nonfailing group (as indicated by the small standard errors in Table 2), we cannot say with absolute certainty what the effects of failure or LVAD support are in relation to "normal." Nonetheless, the data clearly demonstrate differences between failing and LVAD-supported hearts.

In summary, the present study demonstrates that: (1) heart failure produces significant changes in myocardial cardiolipin content regardless of etiology but alters cardiolipin composition only in hearts with ischemic cardiomyopathy; and (2) LVAD support does not restore cardiolpin content of failing hearts but does normalize cardiolipin composition in those with ischemic cardiomyopathy. These data are consistent with disease-specific reverse remodeling of myocyte mitochondrial membranes after LVAD support.

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