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Circulation 2001;104;670-675
DOI: 10.1161/hc3101.093903
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

Comparison of Right and Left Ventricular Responses to Left Ventricular Assist Device Support in Patients With Severe Heart Failure

A Primary Role of Mechanical Unloading Underlying Reverse Remodeling

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Background—Left ventricular assist devices (LVAD) reverse ventricular, myocardial, and systemic abnormalities characteristic of severe heart failure (reverse remodeling). The relative contributions of hemodynamic unloading and normalized biochemical milieu to reverse remodeling are unknown.

Methods and Results—Structural and functional characteristics were measured from 53 hearts of patients undergoing transplantation without LVAD support (medical support) and 33 hearts from patients receiving a median of 46 days of LVAD support (range, 8 to 360 days). Compared with medical support alone, patients receiving LVAD support for ≥30 days had higher central venous pressures (11±6 versus 8±5 mm Hg, $P=0.04$), lower pulmonary artery diastolic pressures (14±9 versus 21±9 mm Hg, $P=0.01$), and higher cardiac outputs (5.1±1.6 versus 3.7±1.0 L/min, $P<0.001$). In LVAD versus transplantation hearts, V_{30} (ex vivo volume yielding ventricular pressure of 30 mm Hg) was decreased in the left ventricle (LV) (179±75 versus 261±118 mL, $P=0.005$) but not in the right ventricle (RV) (140±59 versus 148±52 mL, P=NS). LV myocyte diameter decreased more significantly after LVAD support (17%, $P=0.05$) than in the RV (11%, P=NS). Compared with transplantation, LVAD support increased normalized SERCA2a content in the LV (0.51±0.26 versus 1.04±0.34, $P<0.001$) but not in the RV (0.48±34 versus 0.67±0.55, P=NS). Finally, LVAD support improved force-frequency relations of isolated superfused LV trabeculae ($P=0.01$) but not RV trabeculae.

Conclusions—Reduction of hemodynamic load is a primary factor underlying several important features of reverse remodeling. These findings do not preclude a possible primary role of neurohormonal factors underlying other facets of reverse remodeling during LVAD support. **(*Circulation*. 2001;104:670-675.)**

Key Words: mechanics ■ remodeling ■ hemodynamics

When used to bridge critically ill patients with heart failure to heart transplantation, left ventricular mechanical assist devices (LVAD) reverse many of the ventricular structural and intrinsic myocardial abnormalities characteristic of end-stage disease.[1–9] This multifaceted process of reverse remodeling has been associated with recovery of LV contractile performance in some patients to a degree that the device could be explanted without the need for transplantation.[10–12] Although this recovery does not appear to be uniform and may not be permanent in most patients undergoing LVAD explantation,[10–14] an understanding of the mechanisms underlying the unprecedented degree and scope of reverse remodeling could lead to development of less invasive means of achieving the same goal.

LVADs provide profound volume and pressure unloading of the left ventricle. At the same time, they restore systemic blood pressure and flow to near normal levels.[15] With this comes normalization of the neurohormonal[4,16] and local cytokine milieu,[8] which may, in and of itself, contribute to myocardial recovery. An important, heretofore unanswered question is the relative contributions of reduced physical stress (hemodynamic unloading) and normalized biochemical milieu to the process of reverse ventricular remodeling.

The right and left ventricles mainly share a common biochemical milieu, but the hemodynamic effects of LVADs are different in the two chambers. Whereas the LV may be profoundly unloaded, the right ventricle (RV) generally does not receive such benefits.[17] In the present study, we took advantage of this difference to test the hypothesis that hemodynamic load is an important factor responsible for specific, readily assayable aspects of structural and molecular

Received March 16, 2001; revision received May 23, 2001;accepted May 31, 2001.

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reverse remodeling by comparing the process in the right and left ventricles.

Methods

Heart Harvest and Pressure-Volume Relations

Between January 1999 and February 2001, 87 human hearts from patients with end-stage heart failure were studied under a protocol approved by the Institutional Review Board of the New York Presbyterian Hospital. Fifty-three of the hearts were from patients undergoing transplantation without the need for LVAD support, whereas the other 34 hearts were from patients requiring LVAD support (HeartMate, Thermo Cardio Systems Inc) before transplantation. Four normal donor hearts unsuitable for transplantation were also obtained.

Hearts were preserved with cold (4°C) hypocalcemic, hyperkalemic cardioplegia solution at explantation. The passive ventricular pressure-volume relations were measured in the right and left ventricles as described previously.[2,7] Briefly, the aortic root, proximal pulmonary artery, and, for LVAD-supported hearts, the inflow cannula, were clamp-occluded. Compliant water-filled latex balloons (unstressed volume >400 mL) were placed in each chamber. Intraventricular pressures were measured as volumes were progressively increased. Chamber size was indexed by the volume yielding an intraventricular pressure of 30 mm Hg (LVV_{30} and RVV_{30}).

Histologic Assessment of Myocyte Diameter and Collagen Content

For a subset of hearts, tissue samples were obtained from the LV and RV free walls, fixed in 10% buffered formalin, embedded in paraffin, mounted on glass slides, and prepared with Masson's trichrome stain. Images were viewed on a Nikon microscope with an MTI 3CCD digital camera at ×20 magnification. Digitally acquired images were analyzed with Image Pro Plus V3.0 by an examiner blinded to whether or not the heart was normal, failing, or LVAD-supported and whether the sample was obtained from the right or left ventricle. For diameter measurements, two orthogonal diameters were obtained per myocyte and then averaged, and only sections containing fibers cut in cross section were analyzed. The diameters of 50 myocytes per slide were measured and then averaged. Myocardial collagen content was assessed with the use of a software filter set to capture the blue-stained collagen. The number of pixels included in this color range was divided by the total number of pixels occupied by the myocardial sample on the fields. Ten optical fields per slide were analyzed and then averaged. For ischemic cardiomyopathic hearts, only regions remote from gross infarct zones were analyzed.

TABLE 1. Patient Demographics and Hemodynamics at Time of Transplantation (for Medically Supported Patients) or LVAD Insertion (mean±SD)

	Medical Support	LVAD Support
No. of Patients	53	34
Age, y	54.1±11.2	49.7±13.3
Sex, male/female	41/12	29/5
ICM/DCM	33/20	15/19
CVP, mm Hg	7.9±5.1	18.8±5.9
PAP, mm Hg	30.5±13.7	37.2±8.4
Mean arterial pressure, mm Hg	80±11	90±14
Cardiac output, L/min	3.8±1.0	3.7±0.96
Receiving inotropic support, n (%)	29 (67)	34 (100)*
IABP, n	0	8*
Duration of LVAD support, d	NA	77±71 (46, 8–360)†

Values are mean±SD unless otherwise indicated. ICM indicates ischemic cardiomyopathy; DCM, idiopathic dilated cardiomyopathy; CVP, central venous pressure; PAP, pulmonary artery pressure; IABP, intra-aortic balloon pump; NA, not applicable.

*$P<0.001$ vs medical support (Fisher's exact test).

†Numbers in parentheses are median values and ranges.

SERCA2a Western Blot Analysis

Approximately 180 mg of tissue was homogenized in 1.0 mL ice-cold buffer containing 20 mmol/L Na-HEPES, pH 7.4, 4.0 mmol/L EGTA, and 1.0 mmol/L DTT and EDTA–free complete protease inhibitors (Boehringer-Mannheim). Samples were centrifuged, and supernatant protein concentration was determined by Bradford assay before SDS-PAGE with 10% gels to detect SERCA2a. Proteins were immediately transferred to nitrocellulose and verified by staining with Coomassie blue and then blocked by incubation with 2.5% nonfat dry milk in PBS-T buffer (0.0.5% Tween-20). After washing with PBS-T, blots were incubated with primary antibody for 2 hours at room temperature. Primary antibodies were diluted in 2.5% nonfat dry milk in PBS-T buffer and included mouse monoclonal antibodies against SERCA2a (Calbiochem, diluted 1:2500) and actin (Oncogene Research Products, diluted 1:20 000). After washes with PBS-0.05% Tween-20, membranes were incubated with peroxidase-conjugated goat anti-rabbit or goat anti-mouse IgG antiserum (Boehringer-Mannheim) diluted 1:4000, washed with PBS-0.05% Tween-20, and developed by enhanced chemiluminescence (Amersham Pharmacia Biotech).

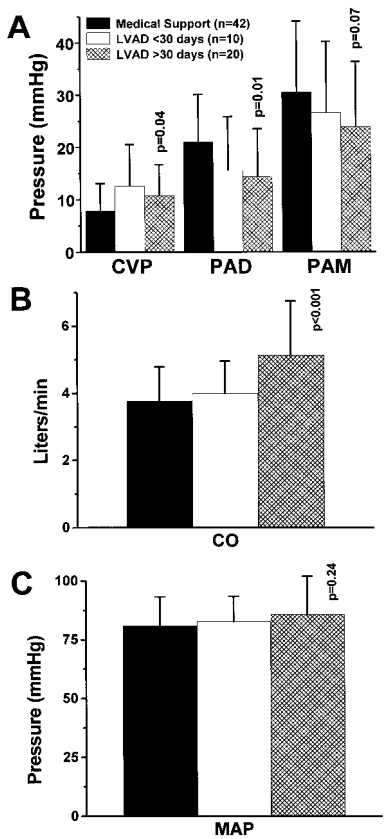

Figure 1. Central venous pressure (CVP), pulmonary diastolic and mean pressures (PAD and PAM, respectively), mean arterial blood pressure (MAP), and cardiac output (CO) measured under anesthesia at time of transplantation in medically supported patients and in patients requiring LVAD support with LVAD operational. Patients supported for <30 days or >30 days are shown separately. Probability values are for comparisons between transplantation and LVAD >30 days (unpaired *t* test).

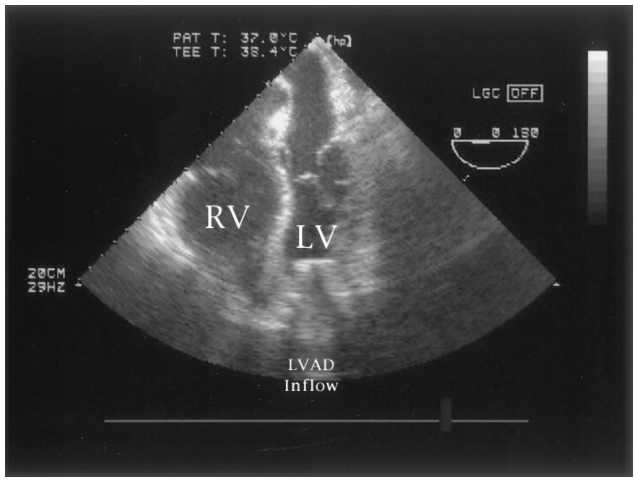

Figure 2. Typical transesophageal echocardiogram obtained from patient supported by LVAD showing LV volume unloading with continually loaded RV.

Myocardial Force Generation at Different Simulation Frequencies

Force-frequency relations were obtained from trabeculae isolated from right and left ventricles in a subset of hearts. Trabeculae <1 mm in diameter were excised from the respective free walls and immersed in ice-cold Krebs-Ringer solution with 30 mmol/L 2,3-butanedione monoxime before mounting in a bath with one end connected to a force transducer and the other to a micrometer. Two identical baths (one for the LV strip and one for the RV strip) were simultaneously perfused from the same warming flask with oxygenated Krebs-Ringer solution (37°C; flow rate, 1 mL/min; bath volume, 1 mL). Trabeculae were stimulated at 1 Hz and allowed to equilibrate for at least 1 hour at slack length. Trabeculae were then progressively stretched to L_{max}, the length of maximal force generation. After reequilibration, stimulation frequency was increased every 5 minutes at 0.5-Hz increments to a maximum of 2.5 Hz (150 beats/min). Adequate muscle oxygenation was ensured by stimulating at 3 Hz and switching perfusate from one with normal oxygenation (Po_2~600 mm Hg) to an identical solution with reduced oxygenated (Po_2~500 mm Hg). If muscle force dropped by >10%, the preparation was considered to be potentially limited by oxygenation of the muscle core and was excluded from further study.

Statistics

Data are expressed as mean±SD. Comparisons between groups were performed with unpaired *t* tests. Categoric demographic data were compared by Fisher's exact test. A value of $P<0.05$ was considered to be statistically significant.

Results

Patient Population

Patient demographics are summarized in Table 1. Patients requiring LVAD support tended to be younger (P=NS). There were more men in each group. Percentage-wise, there were more patients with ischemic cardiomyopathy (ICM) in the LVAD group. Mean arterial pressure and cardiac output before transplantation or LVAD insertion were not significantly different between groups. All of the LVAD patients were receiving intravenous inotropic support with dobutamine or milrinone before LVAD insertion, whereas this was used in ~67% of transplant patients. Eight patients required intra-aortic balloon pumping before LVAD insertion. The mean duration of the LVAD support was 77±71 days. Inotropic support was discontinued in all LVAD patients within 1 week of LVAD insertion. In ~60% of patients, other antineurohormonal therapy (mostly ACE inhibitors) was initiated during LVAD support; the rate of β-blocker and spironolactone use was low in both groups (<12%).

Hemodynamic Effects of LVAD Support

Hemodynamic data were collected from all but 4 patients under anesthesia at the time of heart transplantation; for the LVAD patients, the device was active in "auto" mode during acquisition of these hemodynamic data (Figure 1). Data from LVAD patients are subdivided into those who were supported for less than (n=10) or more than (n=20) 30 days because our prior study showed that this is the estimated minimum time required for hearts to complete the remodeling process.[3] Compared with medically supported patients, patients requiring LVAD support for ≥30 days had a significantly higher central venous pressure (11±6 versus 8±5, P=0.04), a lower pulmonary diastolic pressure (an index of LV filling pressure, 14±9 versus 21±9, P=0.01), and a trend toward lower pulmonary artery mean pressure (24±12 versus 30±14, P=0.01). Mean arterial pressure was similar in all groups, but cardiac output was significantly increased in LVAD patients (5.1±1.6 versus 3.8±1.0, $P<0.001$).

A representative transesophageal echocardiogram of a patient during LVAD support is shown in Figure 2. This typical result reveals that while the left ventricle is volume unloaded, the right ventricle remains volume loaded.

Left and Right Ventricular Size

Ventricular size, indexed by V_{30}, is summarized in Figure 3 for all groups of patients for both right and left ventricles. LVV_{30} of medically supported patients was ≈2.5 times that of normal hearts. After 30 or more days of LVAD support, LVV_{30} was significantly reduced, attaining a value less than half the difference between normal and medically supported transplant hearts (reverse structural remodeling). RVV_{30} of transplant recipients was almost twice that of normal hearts, and this did not change during the course of LVAD support. A separate analysis indicated comparable effects of LVAD support in hearts with ischemic and idiopathic dilated cardiomyopathy (DCM).

Myocyte Size

Myocyte diameters were measured in 4 normal hearts, 14 medically supported hearts, and 14 hearts supported with LVAD for >30 days (Figure 4A, 7 ICM and 7 DCM in each group). Myocytes of failing hearts were larger than those of normal hearts in both the right and left ventricles. LVAD support decreased LV myocyte diameter to a value comparable to that of normal hearts. However, RV myocyte diameter did not decrease significantly.

Interstitial Fibrosis

Interstitial fibrosis was measured in the same 4 normal hearts, 14 medically supported hearts, and 14 LVAD-supported hearts (Figure 4B; described above). Interstitial fibrosis increased with LVAD support in the LV and a similar trend

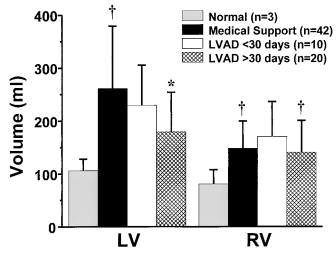

Figure 3. Ventricular volume required to achieve passive pressure of 30 mm Hg (V_{30}) from 3 normal hearts not suitable for transplantation, from medically supported patients undergoing transplantation not needing LVAD support, and in patients requiring LVAD for <30 days or >30 days. †$P<0.05$ vs normal values; *$P<0.01$ vs transplantation without LVAD; data are from unpaired *t* test with Bonferroni correction for multiple comparisons.

was present in the RV, but the latter was not statistically significant.

SERCA2a Protein Content

Myocardial SERCA2a protein content (with band intensities normalized to that of a common normal sample run on every gel) was measured by Western blot analysis in 14 medically supported and 14 LVAD-supported hearts (Figure 5, 7 ICM and 7 DCM in each group). As shown in the representative blot (A) and summary graph (B), LVAD support more than doubled LV SERCA2a protein content. For the RV, there was a trend for increased protein content, but this was of substantially smaller magnitude than in the LV and did not reach statistical significance.

Muscle Strip Force-Frequency Relation

To test for a functional significance of differential RV and LV SERCA2a content, myocardial force was measured as a function of stimulation frequency. The physical characteristics of the muscles were similar between groups, as summarized in Table 2. Peak isometric developed force at 1-Hz stimulation varied significantly within each group and was not statistically significantly different between medically supported and LVAD-supported hearts. In medically supported hearts, peak developed force decreased for both RV and LV strips with increasing pacing rate (typical example shown in Figure 6). In LVAD-supported hearts, increased pacing rate was associated with decreased force in the RV but increased force in the LV. A summary of results from all muscle strips, shown in Figure 7, reveals that the difference in behavior of LV trabeculae from LVAD-supported hearts compared with transplantation-alone hearts was statistically significant.

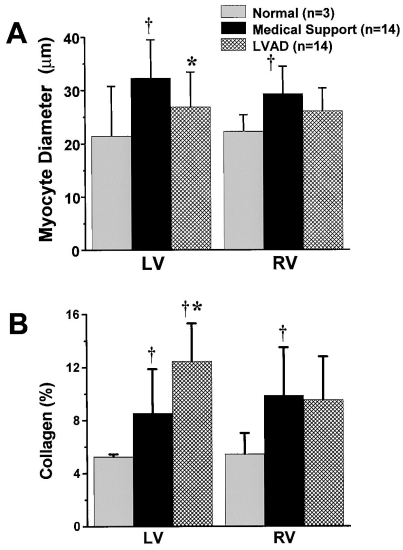

Figure 4. A, RV and LV myocyte diameters measured from normal hearts, patients undergoing transplantation without need for LVAD support, and patients having >30 days of LVAD support. B, Interstitial fibrosis expressed as percentage of visual field occupied by blue-staining collagen fibers. †$P<0.05$ vs normal values; *$P<0.05$ vs transplantation without LVAD.

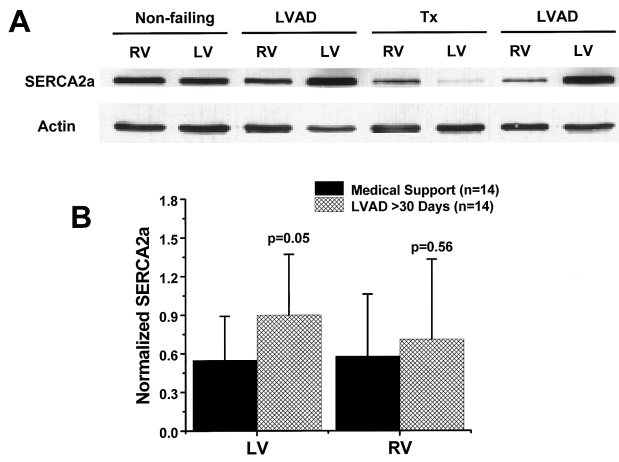

Figure 5. A, Typical Western blot probed for sarcoplasmic reticular calcium ATPase (SERCA2a) content of RV and LV samples from normal (nonfailing) hearts, medically supported transplant hearts not requiring LVAD (transplantation), and from hearts supported by LVAD for >30 days. B, Summary data from 14 heart failure and 14 LVAD-supported hearts showing SERCA2a protein content expressed as fraction of normal. Relative constancy of actin band confirms uniform protein loading.

Discussion

LVAD support provides pressure and volume unloading of the LV with improved systemic hemodynamics. This has been associated with LV reverse remodeling, including reduced myocyte and chamber size,[2,18,19] more normal molecular expression of a multitude of genes (at the RNA level),[7,20] improved expression of SERCA2a with increased sarcoplasmic reticular calcium sequestration[7] and improved contractile response during increased pacing rate,[6,7] improved myocardial β-adrenergic responsiveness,[6,9] and normalization of ryanodine receptor phosphorylation.[9] All indications are that the list of characteristics known to be abnormal in heart failure and improved during LVAD support will increase.

Just as many factors contribute to ventricular remodeling in heart failure, a multitude of mechanisms likely contribute to reverse remodeling during LVAD support. Although poorly understood, increased mechanical stress on myocytes modifies gene expression, typically switching globally to a fetal gene program.[21,22] There is a net increase in protein synthesis leading to the cellular hypertrophy with all of its abnormal phenotypic characteristics. There is also evidence that me-

TABLE 2. Physical Characteristics of Right and Left Ventricular Trabeculae

	Medical Support		LVAD Support	
	RV	LV	RV	LV
n	8	8	6	8
Length, mm	3.93±1.12	6.20±4.8	4.41±1.16	4.61±2.08
Diameter, mm	0.55±0.22	0.48±0.25	0.46±0.32	0.36±0.24
Mass, mg	2.11±0.83	2.64±1.86	2.00±1.56	1.59±1.15
Isometric stress at 1 Hz	20.7±16.9	22.8±18.9	25.6±14.4	12.7±8.5

Values are mean±SD unless otherwise indicated.

chanical stretch may cause myocardial cells to secrete substances that may act in an autocrine/paracrine fashion to influence local myocardial properties. Hemodynamic unloading by LVADs reduces myocyte mechanical stress. Reverse remodeling could be mediated by the same pathways responsible for hypertrophy, the kinetics of which are now being modulated by a low mechanical stress state created by LVAD support. Our observation of differential left and right ventricular reverse remodeling on several of the characteristics we studied suggest a primary role of mechanical stress as an underlying factor. This hypothesis is further supported by our prior observation that reverse remodeling is prevented when the LVAD inflow valve fails (a rare occurrence), and, despite maintenance of normal systemic blood pressure and flow, the left ventricle is hemodynamically reloaded.[23]

The spectrum of phenomena examined in the present study is not exhaustive. It is expected that other aspects of myocardial physiology could be primarily influenced by neurohormonal status rather than by hemodynamic load. For example, it might be expected that myocardial β-adrenergic responsiveness and phosphorylation of intracellular proteins (such as has been demonstrated for the ryanodine receptor[9]) could be primarily modulated by neurohormonal factors.

Prior studies have shown that ACE-I can prevent or reverse structural remodeling after myocardial infarction and in the setting of heart failure.[24] ACE-I have direct hemodynamic effects to reduce ventricular preload and afterload as well as effects on the neurohormonal system. It has been hypothesized that both hemodynamic and neurohormonal factors contribute to the beneficial effects of ACE-I on remodeling. However, in the settings studied thus far, it has not been possible to separate these factors as has been done in the present study. A clear understanding of the relative importance of mechanical load and biochemical milieu as well as a deeper understanding of the molecular transduction mechanisms could lead to more effective, less invasive means of reversing the structural and contractile derangements in heart failure.

Limitations

Abnormally elevated neurohormone levels, including catecholamines, angiotensin, aldosterone, naturetic peptides, and cytokines (eg, tumor necrosis factor-α), have been shown to contribute to hypertrophy, interstitial fibrosis, ongoing cell death (apoptosis), and myocyte dysfunction in heart failure. LVADs have been shown in the past to normalize neurohormone levels[4,6] and local tumor necrosis factor-α tissue content.[8] We did not measure these factors in our group of patients, which may be considered a limitation of the present study. However, in prior studies, the degree of normalization of these factors has been profound and uniform. If such factors were the primary mediators of reverse remodeling, we would have observed more

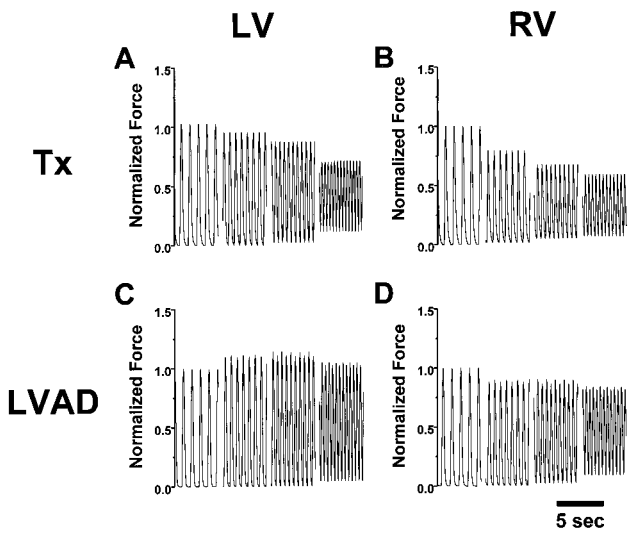

Figure 6. Typical force tracings at different stimulation frequencies (1.0, 1.5, 2.0, and 2.5 Hz) obtained from RV and LV endocardial trabeculae from explanted hearts obtained from medically supported patient undergoing transplantation (Tx) without LVAD support and patient who had 40 days of LVAD support before transplantation. In transplantation, force declines for both RV and LV muscle at increasing stimulation rates. After LVAD support, RV remains negative but LV force increases with increased stimulation frequency.

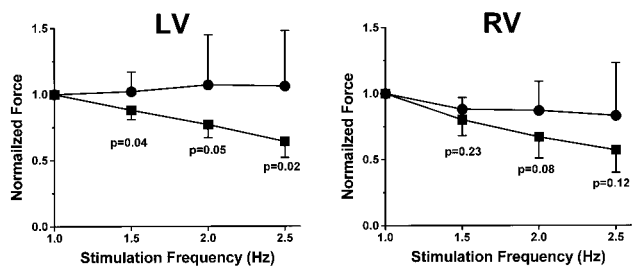

Figure 7. Summary of effect of stimulation frequency on force development (normalized to force at 1 Hz) in LV and RV trabeculae. As in Figure 6, force declines for both RV and LV muscle at increasing stimulation rates in medically supported explanted hearts (■). After LVAD support, force increases in LV but not in RV (●). Probability values are from unpaired *t* tests applied to data at each stimulation frequency. See Table 2 for further details about muscle characteristics.

similar reverse remodeling in right and left ventricular chambers and cells. Furthermore, interstitial fibrosis, believed to be influenced significantly by aldosterone and angiotensin,[25] would have been expected to be reduced, not increased, during LVAD support. We observed and reported previously on increased relative interstitial fibrosis,[3] which we hypothesize may reflect regression of myocyte hypertrophy with little change in total tissue collagen content.

Another limitation is that we assumed that the properties of the medically supported patients reflect those of the LVAD patients before LVAD insertion. However, patients requiring LVAD support have more severe disease. Thus, while this assumption may not be valid, the structural, functional, and molecular derangements encountered in the medically supported hearts may underestimate those actually existing in the LVAD patients at the time of LVAD insertion.

Conclusions

Comparison of characteristics of the right and left ventricles of LVAD-supported hearts suggests that reduction of mechanical load is a primary factor underlying reverse remodeling of several important features of this process, including ventricular structure, SERCA2a expression, and the force-frequency relation. These findings do not preclude the possibility that neurohormonal factors could be the primary factor underlying other facets of reverse remodeling during LVAD support. This information is important not only for understanding reverse remodeling during LVAD support but more broadly in helping to define the mechanisms underlying ventricular remodeling in heart failure.

Acknowledgments

This work was supported by research funds of the Cardiac Physiology Laboratory, Divisions of Circulatory Physiology and Cardiology, Columbia University. Dr Oz received research support from Thoratec.

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