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Normalized Diastolic Properties After Left Ventricular Assist Result From Reverse Remodeling of Chamber Geometry

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Background—Normalization of diastolic properties after left ventricular (LV) assist may result from a change in myocardial material properties, chamber size, or both. This study tested the hypothesis that reported normalization of LV diastolic properties is primarily due to remodeling of chamber geometry.

Methods and Results—Hearts were obtained at transplantation from 8 patients with dilated cardiomyopathy (DCM), 6 patients with DCM plus 33 ± 5 days of LV assist, and 3 patients with no evidence of heart failure. LV assist normalized passive pressure-volume curves. Chamber dimensions decreased without a change in the ratio of radius to wall thickness. Midwall stress-stretch relations predicted from pressure-volume and dimension data were not different for DCM and LV assist hearts. Passive stress-stretch relations were measured in endocardial trabeculae and were not different for DCM and LV assist hearts. Myocyte size and collagen area fraction were unchanged at this brief duration of support.

Conclusions—These findings are all consistent with the hypothesis that early normalization of diastolic properties after LV assist device support results from remodeling of chamber geometry, not from changes in tissue stiffness. These data emphasize the importance of geometry to ventricular mechanics and demonstrate that reduction of heart size does not necessarily produce a reduction in wall stress. (*Circulation*. 2001;104[suppl I]:I-229-I-232.)

Key Words: diastole ■ elasticity ■ heart-assist device ■ heart failure ■ mechanics

Support with left ventricular assist devices (LVADs) normalizes diastolic chamber properties, as reflected by the diastolic pressure-volume relation.^{1,2} This normalization of diastolic properties may result from a change in myocardial material properties, chamber size, or both. Although it is obvious that increased myocardial stiffness will result in decreased chamber compliance, it may be less obvious that decreased chamber size alone will have the same effect.

The impact of chamber size on the diastolic pressure-volume relationship is best illustrated by considering a simple thin-walled sphere, for which the relationship between chamber pressure (P) and wall stress (T) is accurately described by the equation commonly called Laplace's law³:

$$(1) \quad T = \frac{Pr}{2h}$$

In this familiar equation, r is the chamber radius and h the wall thickness. According to this equation, for a given pressure increase, a smaller chamber will have a smaller increase in wall stress. If material properties relating wall stress to strain are the same, the change in pressure will induce smaller strains in the smaller chamber and therefore a

smaller volume increase. The result is that the smaller chamber will be less compliant than a larger chamber composed of the same material. This study therefore tested the hypothesis that reported normalization of LV diastolic properties is primarily due to remodeling of chamber geometry rather than to changes in passive myocardial stiffness.

Methods

Because the relationship between global and local diastolic properties is difficult to predict in hearts with various amounts of postinfarction scar tissue, this study was restricted to patients with dilated cardiomyopathy (DCM). Hearts were obtained at the time of transplantation from 8 patients with DCM and 6 patients with DCM plus 2 to 8 weeks of LV assist under a protocol approved by the Institutional Review Board of the Columbia-Presbyterian Medical Center. Tissue was obtained for comparison from 3 normal hearts judged unsuitable for transplantation.

Pressure-Volume Relationships

Hearts were perfused with cold hyperkalemic cardioplegia solution at explantation. The aortic root and LVAD inflow cannula were clamped, and a compliant water-filled latex balloon was placed within the LV chamber through the mitral annulus and secured; pressure was measured with a micromanometer (Millar Instruments Inc). To maintain tissue viability for subsequent biochemical studies,

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TABLE 1. Patient Information for LVAD, DCM, and Normal Groups

	DCM Plus LVAD				DCM Only			Normal		
	Patient Age, y	Sex	Days	HW, g	Patient Age, y	Sex	HW, g	Patient Age, y	Sex	HW, g
	21	M	52	312	62	F	486	49	F	478
	45	M	31	465	48	M	561	47	F	
	44	M	18	436	46	M	850	53	F	
	35	M	30	530	27	M	402			
	42	M	38	530	53	M	425			
	63	M	26	425	34	M	664			
					64	M	640			
					43	M	474			
Average	42		33	450	47		563	50		
SEM	6		5	33	5		53	2		

Days indicate days of LVAD support; HW, heart weight. In 2 normal hearts, heart weight was not determined because only limited tissue samples were available.

the protocol was designed to minimize total experiment time. A single inflation and deflation cycle to a pressure of ≈ 40 mm Hg was performed, with pressure and volume data acquired during deflation used for this analysis. Individual pressure-volume curves were fitted with cubic polynomials, and interpolated pressures from the fitted curves were used to generate average pressure-volume relationships for each group. The volume intercept, V_0 , of each pressure-volume relationship was calculated. Because the slope of the pressure-volume relationship varies with pressure, the slope of each relationship was assessed at a pressure of 10 mm Hg.

Predicted Myocardial Stiffness

Major and minor axes of the LV were measured in the isolated hearts and combined with pressure-volume data to predict wall stress-stretch relationships for midwall myocardium. Wall thickness was calculated from external dimensions and the known cavity volume. Wall stress was calculated with a formula derived by Mirsky³:

$$(2) \quad T = \left(\frac{Pb}{h} \right) \left(1 - \frac{b^2}{2a^2} - \frac{h}{2b} + \frac{h^2}{8a^2} \right).$$

This formula assumes that the heart can be represented as a thick-walled axisymmetric ellipse composed of an isotropic linearly elastic material. These assumptions are clearly oversimplifications for the heart but must be balanced against the technical difficulty of obtaining realistic 3D geometry and material properties in human hearts. Stretch ratio calculations used V_0 as a reference state and assumed that major and minor axes change proportionally during passive inflation and deflation.

Measured Myocardial Stiffness

Passive force-length data were acquired as part of a protocol to examine muscle function of beating, isolated endocardial trabeculae from DCM and LVAD hearts. Minimum force at each muscle length was normalized by cross-sectional area to calculate stress. Lengths were normalized in each muscle by L_0 , the length at which the diastolic force-length curve crossed zero. The resulting stress-stretch ratio curves were fitted by use of cubic polynomials, averaged as described for pressure-volume curves, and used to assess uniaxial myocardial stiffness.

Histology

Tissue samples obtained from the LV free wall were fixed in 10% buffered formalin, embedded in paraffin, sectioned, and mounted on glass slides. Samples were sectioned perpendicular to the local fiber direction at a thickness of 10 μ m and stained with Masson's trichrome. Myocyte size was assessed in images acquired at $\times 200$

total magnification by blinded measurement of 2 orthogonal diameters per myocyte in 50 myocytes per patient. Collagen area fraction was assessed in images acquired at $\times 40$ total magnification by blinded digital color separation and thresholding to calculate the ratio of green (collagen) to nonwhite (total tissue) pixels in 5 fields per patient.

Statistics

All values are reported as mean \pm SEM. Differences between the DCM and LVAD groups were assessed by Student's *t* test, with a value of $P < 0.05$ indicating statistical significance.

Results

Isolated pressure-volume and dimension data were obtained in 8 hearts from patients with DCM (Table); isolated trabeculae were successfully studied in 5 hearts, and histological data were obtained in 5 hearts. Pressure-volume and dimension data were obtained in 6 patients after 33 ± 5 days of LVAD support (Table); isolated trabeculae were successfully studied in 4 of these hearts, and histological data were obtained in 5. Pressure-volume data were acquired in a single normal heart from which trabeculae were also studied (Table). In 2 additional hearts, trabeculae were obtained from portions of the LV, but the remainder of the ventricle was unavailable; in 1 of these hearts, histology was also performed.

Pressure-Volume Relationships

In 6 DCM patients, 33 ± 5 days of LVAD support normalized the passive pressure-volume relationship (Figure 1), consistent with previous reports.^{1,2} V_0 was reduced from 194 ± 18 to 107 ± 13 mL ($P = 0.003$), and the slope at a pressure of 10 mm Hg increased significantly, from 0.35 ± 0.06 to 0.60 ± 0.07 mm Hg/mL ($P = 0.02$). Comparison of chamber dimensions at V_0 revealed a significant reduction in both major (LVAD 37.5 ± 2.0 mm versus DCM 42.9 ± 0.8 mm, $P = 0.02$) and minor (LVAD 25.7 ± 1.1 mm versus DCM 32.6 ± 1.1 mm, $P = 0.002$) radii (Figure 2). Neither wall thickness ($P = 0.45$) nor the ratio of minor radius to wall thickness ($P = 0.56$) changed significantly with LVAD-induced remodeling.

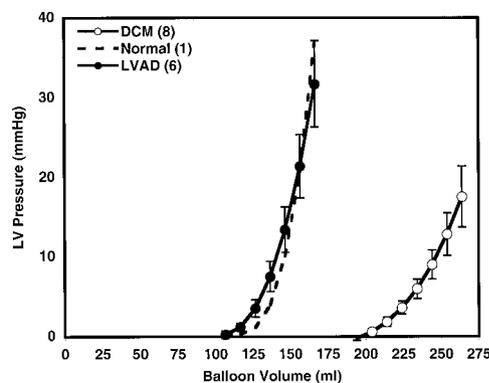


Figure 1. Average pressure-volume curves for isolated hearts from 8 DCM and 6 LVAD patients; 1 normal heart is shown for comparison. Normalization of passive pressure-volume curve after LVAD included a significant drop in unstressed volume V_0 ($P=0.003$) and a significant increase in slope at a pressure of 10 mm Hg ($P=0.02$).

Predicted Myocardial Stiffness

Predicted stress-stretch curves calculated as described in Methods were similar for DCM and LVAD hearts (Figure 3). Because these curves were nonlinear, the predicted stress at a stretch ratio of 1.07 (the maximum stretch for which prediction was possible for all hearts) was taken as an index of stiffness and was not significantly different for DCM and LVAD hearts (LVAD 4.0 ± 1.6 kPa versus DCM 4.2 ± 1.1 kPa, $P=0.90$).

Measured Myocardial Stiffness

Measured force-length curves from isolated trabeculae were normalized as described in Methods and confirmed the prediction that myocardial stress-stretch curves are not different in DCM and LVAD hearts (Figure 4). Measured stress at a stretch ratio of 1.07 was 1.0 ± 0.2 kPa in trabeculae from LVAD hearts versus 1.2 ± 0.2 kPa in trabeculae from DCM hearts ($P=0.66$). Although a number of simplifying assumptions were made in predicting stress-stretch relationships from pressure-volume data, measured stresses were not sig-

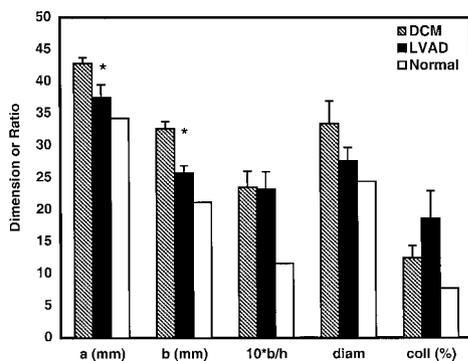


Figure 2. Geometric remodeling after LVAD decreased cavity dimensions without a significant change in ratio of radius to wall thickness. Changes in myocyte diameter and collagen area fraction were not significant after 35 ± 5 days of LVAD support. a indicates major radius at V_0 ; b, minor radius at V_0 ; b/h, ratio of minor radius to wall thickness at V_0 (multiplied by 10 for presentation); diam, average myocyte diameter (μm); and coll, collagen area fraction. $*P < 0.05$, LVAD vs DCM.

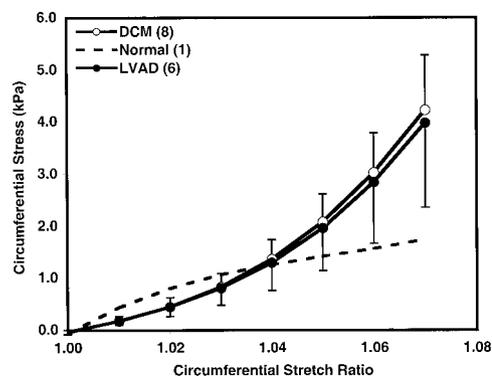


Figure 3. Predicted average midwall myocardial stiffness was the same for DCM and LVAD patients; predictions for 1 normal heart are shown for comparison.

nificantly different from predicted stresses (DCM $P=0.10$, LVAD $P=0.38$ at a stretch ratio of 1.07) in the hearts from which trabeculae were studied.

Histology

Trends toward a decrease in myocyte diameter (LVAD 27.6 ± 2.1 μm versus DCM 33.4 ± 3.5 μm , $P=0.20$) and an increase in collagen area fraction (LVAD $18.6 \pm 4.3\%$ versus DCM $12.4 \pm 1.9\%$, $P=0.23$) were not significant after 35 ± 5 days of LV assist in the hearts for which histology data were available (Figure 2). A new analysis of the DCM patients from a previous study² found that the decrease in myocyte diameter was significant (LVAD 24.8 ± 3.0 μm versus DCM 34.2 ± 2.5 μm , $P=0.03$), whereas the increase in collagen area fraction was not (LVAD $15.6 \pm 2.5\%$ versus DCM $11.3 \pm 2.8\%$, $P=0.27$), after a longer period of support, 89 ± 9 days.

Discussion

This study focused on remodeling of diastolic properties during LV assist. LVAD-induced remodeling was associated with a shift of the passive pressure-volume relationship toward smaller volumes and a significant increase in slope, concentric remodeling of the cavity that maintained a constant ratio of radius to wall thickness, no predicted changes in myocardial stress-stretch relationships, and no measurable

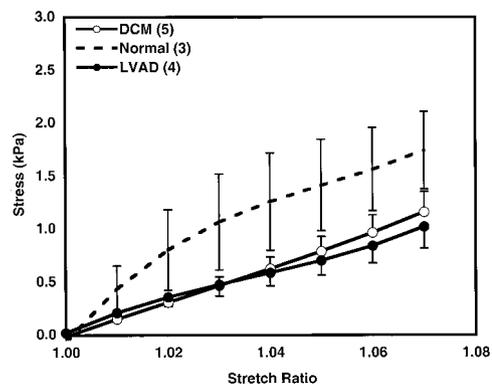


Figure 4. Measured uniaxial stiffness of isolated trabeculae was the same for 5 DCM and 4 LVAD patients, confirming calculations. Data from 3 normal hearts are shown for comparison.

changes in uniaxial myocardial stiffness. These findings are all consistent with the hypothesis that early normalization of diastolic properties after LVAD support results from remodeling of chamber geometry, not from changes in tissue stiffness. These data emphasize the importance of geometry to ventricular mechanics and suggest some additional comments regarding hypertrophy and LVAD-induced reverse remodeling.

First, the calculated stress-stretch relationships demonstrate that reduction of heart size does not necessarily produce a reduction in wall stress. Because the heart can remodel wall thickness as well as chamber size, the net effect of remodeling on wall stress is difficult to predict. This study focused on diastolic properties and stresses; the impact of remodeling on systolic wall stress will depend not only on geometry but also on loading conditions, heart rate, and other factors. Predicting the overall impact on pump function will be complex⁴ and will require good in vivo patient studies.

Second, the fact that the reverse remodeling observed in this study maintained a constant ratio of radius to wall thickness and constant predicted wall stress may support the theory that some aspects of myocyte growth are regulated by stress. In 1975, Grossman and colleagues⁵ noted that calculated wall stress was the same in patients with chronic pressure overload and patients with no evidence of heart disease. They interpreted this finding as evidence that myocytes add sarcomeres in parallel to normalize systolic wall stress by increasing myocyte cross-sectional area. Ventricles unloaded by LVAD are exposed to diastolic levels of pressure during support and may therefore remodel to normalize diastolic wall stress. If this were true, it might be possible to direct remodeling during LVAD support by regulating cavity pressure.

Because we have already reported that the time constants for structural and biochemical remodeling during LVAD support range from 15 to 39 days,² the absence of significant changes in myocyte diameter and collagen area fraction in this study was not surprising, given the relatively short period of LVAD support. After longer periods of support, both increases^{6,7} and decreases^{2,8,9} in myocyte size have been reported, generally with an increase in fibrosis or collagen content.^{2,6,7} These changes may significantly affect myocardial stiffness in patients supported longer than those in the present study.

Limitations and Sources of Error

This study was limited to patients with dilated idiopathic cardiomyopathy or DCM plus a relatively short period of LVAD support (average 33 days, range 18 to 52 days). It is

probably inappropriate to extend the conclusions to patients with ischemic cardiomyopathy. Ischemic cardiomyopathy patients will continue to present a challenge in understanding the basis for global ventricular properties because of the need to account for the impact of regional variations in material properties in scar, border-zone, and nonischemic tissue. As an example, this is the second study¹ from our group to find complete normalization of the diastolic pressure-volume relationship in DCM patients, whereas a study using the same methods in the same laboratory in patients with mixed pathogenesis found only incomplete normalization.²

The equation used to calculate wall stress assumes the heart to be an axisymmetric thick-walled ellipse composed of material that is isotropic (stiffness the same in the fiber and cross-fiber directions) and linearly elastic (linear stress-strain relationship).¹⁰ All of these assumptions are known to be incorrect for the heart, but with present methods, it is impractical in most experimental and all clinical situations to obtain enough information to use a more sophisticated model. More realistic geometry can now be obtained with MRI or 3D echocardiography, and this will probably become important for patient-specific analysis and prediction. Material properties of the myocardium are very difficult to measure, however, and will most likely be the limiting factor in developing more accurate stress calculations in the heart.

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