MAINTENANCE OF ABNORMAL PASSIVE STRESS-STRETCH RELATIONSHIPS DURING LVAD-INDUCED REVERSE REMODELING

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INTRODUCTION

Left Ventricular Assist Devices (LVADs) were originally intended to provide temporary hemodynamic support to patients in critical end-stage heart failure while they awaited transplantation. However, studies of the physiologic effects of hemodynamic unloading with LVADs in patients who receive these devices have found dramatic reversal of structural, functional, and molecular features of heart failure. These findings have led to trials of LVAD support as a therapy, with the idea that LVAD-induced reverse remodeling would persist after the device has been turned off or explanted.

A critical question in considering these trials is whether LVAD support treats the underlying causes of heart failure. Are the many features of heart failure reversed by LVAD the etiologic factors or merely downstream consequences? Diastolic wall stress has been proposed as the driving signal for ventricular dilation, a prominent feature of end-stage heart failure. If this hypothesis is correct, then any successful long-term therapy would have to normalize diastolic wall stress to remove the signal for continued ventricular dilation. We therefore investigated whether LVAD-induced reverse remodeling normalizes the passive chamber and muscle stress-stretch relationships in a small subset of patients who underwent heart transplantation and a set of related studies at Columbia University.

METHODS

We studied hearts and endocardial trabeculae obtained at the time of transplantation from 8 patients with dilated cardiomyopathy (DCM) and 6 patients who received between 2 and 8 weeks of LVAD support. Control data were obtained from hearts donated for transplantation but deemed unsuitable at the time of harvest. All studies were conducted under a protocol approved by the Columbia-Presbyterian Medical Center Institutional Review Board.

Explanted arrested hearts were fitted with a compliant latex balloon connected to a volume infusion pump and a pressure transducer. A single passive inflation and deflation cycle was used to obtain pressure-volume curves. Pressure-volume relationships were averaged by fitting individual relationships with cubic polynomials and averaging interpolated pressures at a series of preselected volumes.

Left ventricular dimensions were measured at peak inflation and corrected to other volumes by modeling the left ventricle as an axisymmetric prolate ellipsoid with regionally uniform wall thickness. Circumferential stress was calculated using Mirsky's equation for a thick-walled axisymmetric ellipse composed of an isotropic linearly elastic material:

$$T = (Pb/h)\,[1-(b^2/2a^2)-(h/2b)+(h^2/8a^2)]$$

Midwall circumferential stress-stretch relationships were estimated from the calculated stresses and measured volumes. Midwall stretch calculations assumed zero tissue stretch at V_0, the volume at which the passive pressure-volume curve crossed zero pressure.

To validate the stress-stretch relationships calculated from the whole-heart studies, we compared them to diastolic stress-stretch data acquired during functional studies on endocardial trabeculae. Stretches were calculated with respect to L_0, the length at which diastolic force-length curves crossed zero force. Stress-stretch relationships were averaged by fitting individual relationships with cubic polynomials and averaging interpolated stresses at a series of preselected stretch values.

RESULTS

An average of 33±5 (mean±SEM) days of LVAD support shifted the passive pressure-volume relationship to smaller volumes and increased its slope, consistent with previous reports from our group that LVAD support for at least one month normalizes the passive pressure-volume relationship (Figure 1). [1,2] V_0 decreased from 194±18 to 107±13 ml (P=0.003) while slope at a pressure of 10 mmHg increased from 0.35±0.06 to 0.60±0.07 mmHg/ml (P=0.02). For comparison, V_0 for a single normal heart was 64 ml and the slope at 10 mmHg was 1.08 mmHg/ml.

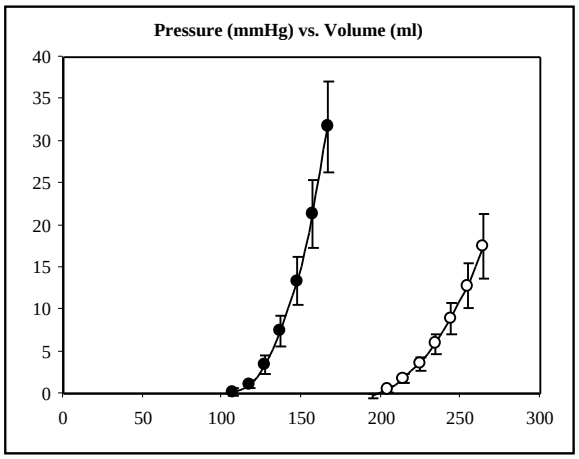

Figure 1: Average pressure-volume curves in isolated arrested hearts from patients with DCM alone (open circles) or DCM plus LVAD support (closed circles).

LVAD support significantly reduced both major and minor LV radii (Figure 2). Major radius was 43±1 mm in the DCM group and 38±2 mm in the LVAD group (P=0.02) at V_0; minor radius was 33±1 mm in DCM hearts and 26±1 mm in LVAD hearts (P=0.002). A small decrease in wall thickness was not statistically significant. Most important for stress estimates, the ratio of short axis radius to wall thickness did not change with LVAD-induced remodeling (2.35±0.25 DCM, 2.31±0.28 LVAD), remaining twice that of a normal comparison heart (Figure 2).

As a result of the persistent abnormal radius to wall thickness ratio, average calculated midwall stress-stretch relationships were identical for the DCM and LVAD groups (Figure 3). Actual passive stress-stretch curves measured in endocardial trabeculae reflected lower stresses than calculated but were also not different between the two groups (Figure 3).

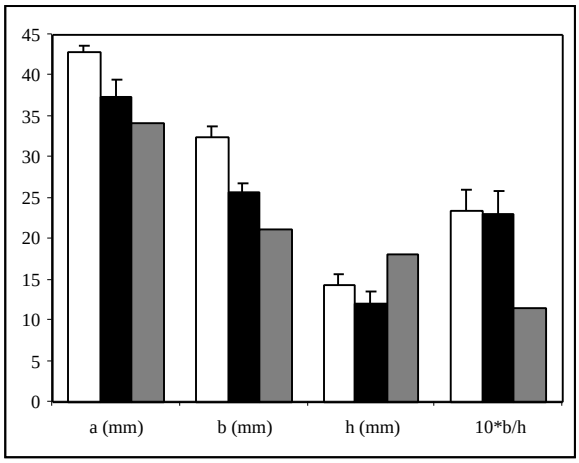

Figure 2: Geometric parameters at V_0 in DCM (open bars), DCM plus LVAD (black bars), and a single normal (gray bars) heart.

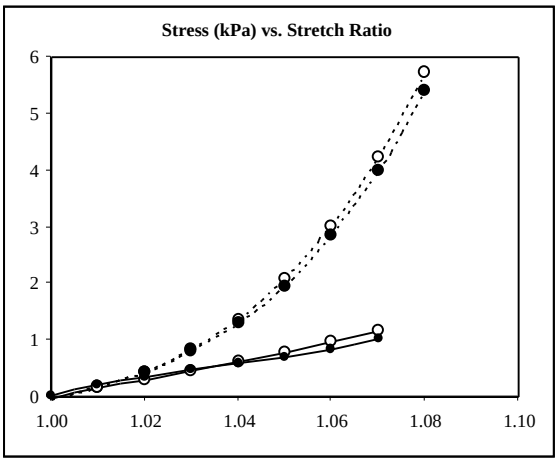

Figure 3: Calculated midwall (dotted lines) and actual trabecular (solid lines) stress-stretch relationships for DCM (open circles) or DCM plus LVAD (closed circles).

DISCUSSION

The findings of this study suggest that LVAD-induced reverse remodeling produces dramatic reductions in chamber size and unstressed volume but little change in underlying material properties or wall stresses. The 'normalization' of the diastolic pressure-volume relationship we reported previously derives primarily from changes in chamber geometry: a smaller chamber made of the same material is less compliant. The most interesting implication of our results is that patients would be expected to have roughly the same wall stresses after LVAD therapy is discontinued as when in critical failure. If wall stress is in fact the driving signal for left ventricular dilation and remodeling, we would expect rapid redilation and decompensation once LVAD therapy is discontinued.

This study has a number of significant limitations from a mechanics point of view. We used a very simple model for wall stress calculations, a single passive inflation of the left ventricle without preconditioning to obtain pressure-volume data, and uniaxial stress-stretch data from endocardial trabeculae. All of these limitations reflect our commitment to minimize interference with the many valuable functional and molecular analyses performed by multiple groups on these explanted hearts by minimizing both damage to the explanted hearts and the amount of tissue used for mechanical testing. We believe the finding that the left ventricle maintains an abnormal radius to wall thickness ratio despite dramatic reverse remodeling is an important one and implies that more sophisticated stress analyses will reach similar conclusions.

REFERENCES

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