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Reversal of Chronic Ventricular Dilation in Patients With End-Stage Cardiomyopathy by Prolonged Mechanical Unloading

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Abstract

Background Ventricular dilation, indexed by marked shifts toward larger volumes of the end-diastolic pressure-volume relation (EDPVR), has been considered to represent an irreversible aspect of ventricular remodeling in end-stage heart failure. However, we hypothesized that such dilation could be reversed with sufficient hemodynamic unloading, such as can be provided by a left ventricular assist device (LVAD).

Methods and Results The EDPVRs of hearts from seven patients with end-stage idiopathic cardiomyopathy and comparable baseline hemodynamics were measured *ex vivo* at the time of cardiac transplantation; these were compared with EDPVRs from three normal human hearts that were technically unsuitable for transplantation. Four of the patients received optimal medical therapy; three of the patients, who deteriorated on optimal therapy, underwent LVAD support for (approximately) 4 months. Compared with the normal hearts, EDPVRs of hearts from medically treated patients were shifted toward markedly larger volumes. In contrast, EDPVRs of hearts from LVAD patients were similar to those of normal hearts.

Conclusions Chronic hemodynamic unloading of sufficient magnitude and duration can result in reversal of chamber enlargement and normalization of cardiac structure as indexed by the EDPVR, both important aspects of remodeling, even in the most advanced stages of heart failure. (Circulation. 1995;91:2717-2720.)

Biochemical composition of the ventricular wall, orientation of cardiac muscle fibers, and geometry of the ventricular chamber are all modified in states of chronic heart failure. Remodeling is the term commonly used to describe these facets of cardiac adaptation in disease. While some aspects of the remodeling process may be beneficial to overall heart function in disease, other aspects are likely to be maladaptive in the long run. One notable maladaptive aspect of remodeling is left ventricular dilation, which is characterized not only by an increase in ventricular end-diastolic volume but also by shifts of the end-diastolic pressure-volume relation (EDPVR) toward larger volumes [1]. Ventricular dilation increases wall stress and imparts mechanical disadvantage to the myofibrils; therefore, it is a critical event in the disease process.

Accordingly, there has been significant interest in understanding the mechanisms of ventricular dilation and in developing interventions to prevent and reverse this process. Both angiotensin-converting enzyme inhibitors and nitroglycerin have been shown to attenuate ventricular enlargement after myocardial infarction, suggesting, at least in part, that reduction of wall stress may be an important factor [2,3]. Preliminary studies also suggest that chronic beta-blocker therapy reduces ventricular mass and normalizes left ventricular shape in patients with heart failure [4]. Thus, while previous studies suggest that the remodeling process may be reversed to some degree by pharmacological interventions, the extent to which this could be achieved with adequate hemodynamic unloading is unclear. Accordingly, it is generally considered that ventricular dilation due to remodeling in advanced heart failure is an irreversible process.

Mechanical left ventricular assist devices (LVADs), which have been used in critically ill patients awaiting heart transplantation, can provide hemodynamic unloading of the left ventricle that is much greater than can be achieved by pharmacological agents. The goal of the present study was to test whether prolonged mechanical unloading of the ventricle by an LVAD in end-stage idiopathic dilated cardiomyopathy would lead to a reversal of the dilation process and normalization of the EDPVR.

Methods

Patient Population

Hearts explanted from seven patients with New York Heart Association class IV heart failure due to idiopathic dilated cardiomyopathy were studied at the time of cardiac transplantation. Four patients received optimal medical therapy with digitalis, diuretics, and a converting enzyme inhibitor, whereas three patients who continued to deteriorate despite optimal medical therapy underwent mechanical support with the Thermo Cardiosystems Heartmate 1000 IP LVAD [5] (Thermo Cardiosystems, Inc) for 127±20 (mean±SD) days as a bridge to cardiac transplantation. All patients had comparable baseline hemodynamic characteristics, as summarized in the Table. Three normal human hearts not suitable for transplantation for technical reasons were also available for study. Two hearts were from male donors and one was from a female donor, with ages ranging between 30 and 45 years. In all cases, the hearts were given cardioplegia and explanted, and their diastolic mechanical properties were studied as detailed below.

Principles of LVAD Operation

The Heartmate 1000 IP LVAD is a pneumatic device of pusher-plate design [5] that sits over the abdominal cavity between the muscles and fatty layers of the abdominal wall. The inflow conduit connects with the LV chamber through a 1-in.-diameter hole created near the LV apex. The outflow conduit passes through the diaphragm, back into the thoracic cavity, and next to the heart to reach the ascending aorta with an end-to-side anastomosis. During normal operation, blood flows from the left ventricle into the LVAD chamber and out to the aorta. Since the ventricle generally empties into the compliant LVAD pumping chamber, LV volume and pressure are low. The degree of volume unloading was assessed by echocardiography performed during normal operation and during temporary (30- to 60-second) cessation of LVAD pumping. The degree of diastolic pressure unloading and hemodynamic support provided by the LVAD was assessed at 30 days after implantation by measurement of cardiac output, pulmonary capillary wedge pressure, and systemic blood pressure. Comparisons between hemodynamic measurements before and 30 days after LVAD implantation were performed with a Student's paired t test; $P < .05$ was considered significant.

Isolated Heart Experiment

The principal measure of LV size and structure examined in the present study was the EDPVR. The EDPVR was measured in all hearts in a state of cold cardioplegia (4 degrees C, hypocalcemic, hyperkalemic solution) by methods similar to those described previously [1]. Hearts from LVAD patients and transplant patients were studied within 1 hour of explantation; two of the normal hearts were studied after 2 hours and the third after 4 hours of explantation. Briefly, a compliant water-filled latex balloon was placed within the LV chamber and held in place by a metal adapter sutured to the mitral annulus; a clamp was placed around the remnants of the aortic root. The volume within the balloon was varied in steps from the volume that provided an intracavitary pressure of 0 mm Hg to the volume needed to obtain an end-diastolic pressure of at least 20 mm Hg. The resulting pressure at each volume was measured by a high-fidelity micromanometer placed in the intraventricular balloon. LV EDPVRs were then constructed by plotting the corresponding pressures and volumes.

Results

LVAD Provides Pressure and Volume Unloading

Volume unloading by the LVAD is demonstrated by the echocardiograms, obtained from a patient 7 days after implantation, shown in Fig 1, which is typical of those obtained from the other patients. Whereas end-diastolic dimension was >6 cm with the device temporarily turned off (top), it decreased to <3 cm during mechanical support (bottom). This pronounced degree of ventricular volume unloading was accompanied by a marked degree of pressure unloading, as evidenced by a reduction in the pulmonary capillary wedge pressure from a baseline of 29±4 mm Hg to 3±2 mm Hg ($P < .001$) measured 30 days after implantation. Despite ventricular pressure and volume unloading, there was an increase in cardiac output (from 2.2±0.4 to 5.1±0.3 L/min, $P < .001$) and an increase in mean systemic blood pressure (from 71±9 to 93±10 mm Hg, $P < .001$) also measured 30 days after implantation. All of these hemodynamic benefits have been shown previously to be realized immediately after LVAD implantation and to be maintained for the duration of LVAD support [6]. Another piece of indirect evidence suggesting systolic pressure unloading of the LV by the LVAD is obtained from echocardiography, which reveals that during normal LVAD operation, the aortic valve almost always remains closed; this implies that peak LV pressure generation is generally less than diastolic aortic pressure. Thus, the LVAD provides both pressure and volume unloading of the left ventricle while maintaining adequate systemic perfusion.

EDPVR Normalizes After Prolonged LVAD Support

The EDPVRs measured from all hearts studied are shown in Fig 2. Hearts from the medically treated patients (open circles) had EDPVRs that were shifted toward much larger volumes compared with those of the normal hearts (diamonds). Since the preoperative end-diastolic dimensions and hemodynamic profiles of the LVAD patients were similar to those of the medically treated patients (Table), it would be expected that the EDPVRs in

the LVAD group would have been similar to the medical treatment group before LVAD implantation. However, after LVAD support for 127±20 days, the EDPVRs of these hearts (filled circles) were shifted toward much lower volumes compared with those of the medically treated heart failure patients and were similar to those obtained from the normal hearts. Accompanying the leftward shift of the EDPVR was a trend for heart mass (combined LV and RV mass) to decrease: normal hearts weigh between 250 and 350 g; heart failure hearts weighed 393, 668, 487, and 905 g; and LVAD-supported heart failure hearts weighed only 270, 390, and 300 g.

Discussion

Ventricular remodeling is the result of many factors, including the initial degree of myocardial impairment, the efficacy of endogenous repair mechanisms, and the balance of distending versus restorative mechanical forces [7]. In addition, the neurohormonal milieu in heart failure [8] (increased levels of angiotensin, norepinephrine, etc) substantially alters the phenotypic characteristics of myocytes and nonmyocytes (fibroblasts) that lead to hypertrophy and modifications in the extracellular matrix [9-11]. It is hypothesized that these physical stresses and alterations in biochemical composition set up an environment that fosters structural rearrangement and dilation of the failing heart. These intrinsic structural changes are reflected grossly as shifts of the EDPVR. This chronic change in structure differs from acute, reversible increases in ventricular end-diastolic dimension (as occurs, for example, during acute heart failure or exercise) that simply represent a stretching of muscles and interstitial components along a fixed EDPVR. In contrast, the changes in ventricular composition and structure in patients with end-stage cardiomyopathy have generally been considered to be irreversible.

Recently, there has been some evidence from both experimental and clinical heart failure that angiotensin-converting enzyme inhibitors can limit or reverse remodeling to a small degree [3,12-14]. However, such pharmacological therapies have been less effective than the mechanical assist device in normalizing ventricular size as reported in this study, perhaps because such agents produce only modest reductions in ventricular filling pressure and volume [13,15]. Although larger doses of vasodilator drugs may result in more pronounced ventricular unloading, the accompanying reduction in vital organ perfusion would limit the ultimate degree of unloading that could be achieved by these means. The results of the present study provide the first evidence that severe ventricular dilation due to idiopathic cardiomyopathy can be substantially reversed, even in the most advanced stages of heart failure.

Previous reports have suggested that restoration of other aspects of ventricular structure may also occur during long-term support with various types of ventricular assist devices. The most notable of these are normalization of fiber orientation [16] and regression of myocyte hypertrophy (ie, normalization of myocyte dimensions) [17]; the latter observation is consistent with the marked reduction of ventricular mass also observed in the present study. More recently, Frazier [18] observed a reduction in heart size, improved ejection fraction, and the ability of the native heart to support cardiac output and blood pressure after the LVAD was turned off in one patient who died of a thromboembolic event after 505 days of LVAD support.

The findings reported in this study are observational and do not elucidate the specific components or mechanisms involved in reverse remodeling. The marked hemodynamic unloading of the left ventricle by the LVAD may be the primary factor responsible for this dramatic change in heart structure. However, we must also consider that plasma concentration of several neurohormones that regulate myocardial growth (aldosterone, renin, norepinephrine) normalize during LVAD support, [6] and accordingly, these may contribute to the observed phenomenon. Independent of the mechanism, the findings are striking and raise several points that may contribute to future thinking about the nature of end-stage heart failure. First, the results challenge a long-held view regarding the irreversible nature of ventricular dilation in end-stage heart failure. In retrospect, this view was based on limitations of previously available therapies and not on an intrinsic inability of heart structure to be restored if the stimuli for dilation are withdrawn. In this regard, it will be important to examine separately changes in myocyte properties and changes in nonmyocyte properties in response to the unloading; the former may reveal important information pertaining to the processes involved in regression of hypertrophy, and the latter may reveal information pertaining to the regulation of extracellular matrix composition. Improved understanding of the hemodynamic, neurohormonal, and molecular events involved in reverse remodeling may lead to new strategies to attain the same goal by pharmacological means.

It is also important to recognize that normalization of ventricular structure does not mean normalization of ventricular function. While reduction of chamber size will lead to a stronger pump (via Laplace's law), [7] prolonged unloading of the heart is not expected to reverse intrinsic (perhaps genetically based) defects in muscle contractile properties. Thus, in thinking about future therapies for heart failure, restoration of heart size is only one, albeit an important, factor that needs to be addressed. One can imagine, as the era of cellular and gene therapy in cardiology approaches, that the circulation can be supported and the failing heart restored to normal size by temporary use of a mechanical support device while another therapy is applied to remedy the underlying molecular defect responsible for contractile dysfunction of the muscles.

In summary, long-term LV unloading by mechanical circulatory support results in normalization of the EDPVR in patients with idiopathic dilated cardiomyopathy. Whether this reversal of the remodeling process truly represents restoration of detailed aspects of cardiac chamber ultrastructure with normalization of the

biochemical and cellular makeup of the chamber wall, as well as the permanence of the normalization, remains to be elucidated. Nevertheless, these findings are consistent with the concept that if sufficient ventricular unloading can be achieved, at least some aspects of cardiac remodeling, even when advanced, can be reversed.

Acknowledgments

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IMAGE GALLERY

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Table	Diagnosis	Sex	Age, y	CI, L · min ⁻¹ · m ⁻²	PCWP, mm Hg	EDD, cm	EF, %	Duration, days
1	DCM	F	61	1.7	24	6.2	28	100
2	DCM	M	57	2	30	7.5	20	151
3	DCM	F	52	1	32	6.9	20	131
4	DCM	M	56	0.8	26	7	14	...
5	DCM	M	49	2.1	18	7.4	20	...
6	DCM	M	31	2.4	36	8.4	16	...
7	DCM	M	58	2.2	36	9	15	...

Table 1

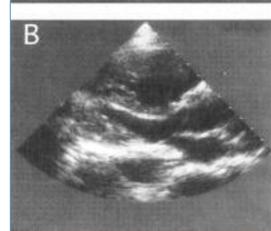
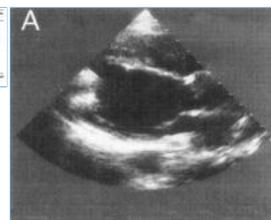


Figure 2

Figure 1

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Patient	Diagnosis	Sex	Age, y	CI, L · min ⁻¹ · m ⁻²	PCWP, mm Hg	EDD, cm	EF, %	Duration, days
LVAD patients								
1	DCM	F	61	1.7	24	6.2	28	100
2	DCM	M	57	2	30	7.5	20	151
3	DCM	F	52	1	32	6.9	20	131
Dilated cardiomyopathy patients								
4	DCM	M	56	0.8	26	7	14	...
5	DCM	M	49	2.1	18	7.4	20	...
6	DCM	M	31	2.4	36	8.4	16	...
7	DCM	M	58	2.2	36	9	15	...

LVAD indicates left ventricular assist device; CHF, congestive heart failure; CI, cardiac index; PCWP, pulmonary capillary wedge pressure; EDD, left ventricular end-diastolic diameter; EF, ejection fraction; and DCM, idiopathic dilated cardiomyopathy.

Table 1. Comparison of Clinical and Hemodynamic Characteristics of LVAD and End-Stage CHF Patients

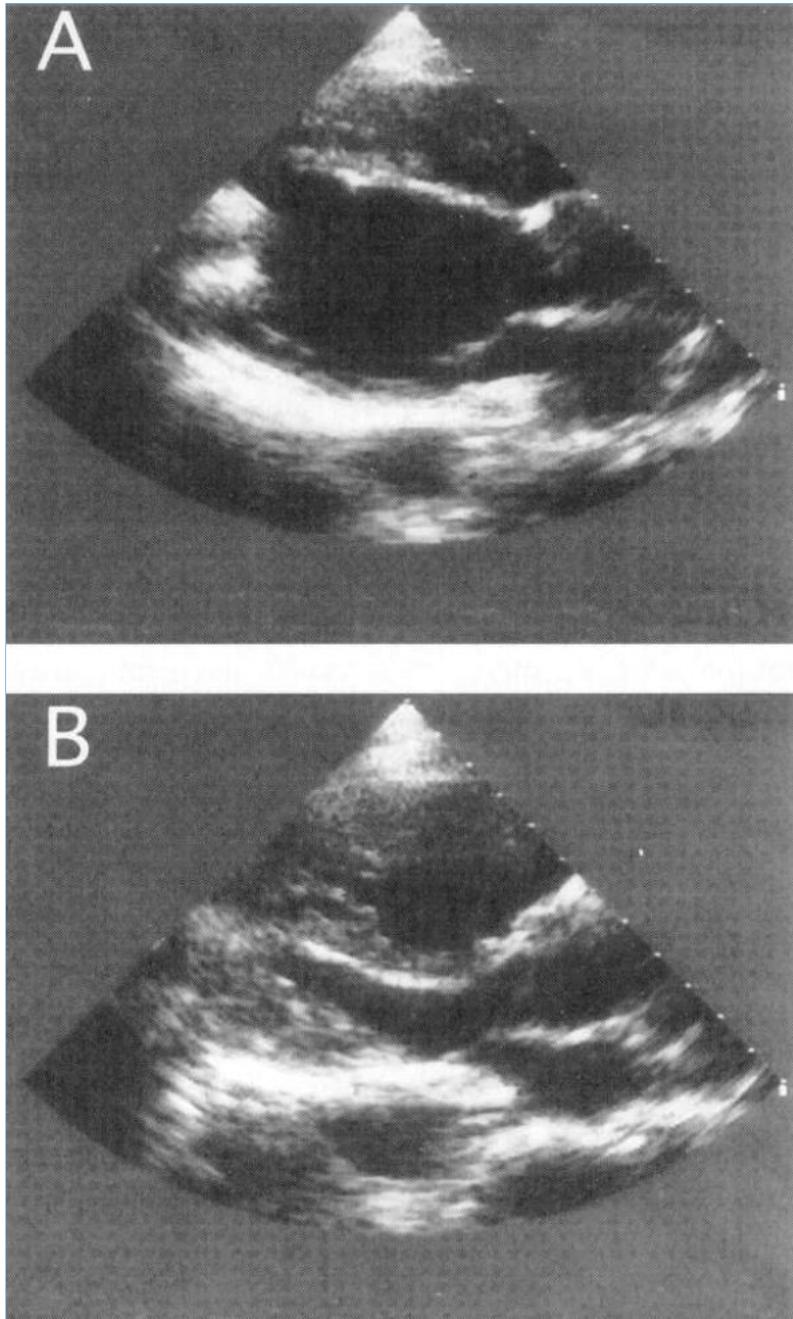


Figure 1. Echocardiograms of a patient 1 week after left ventricular assist device (LVAD) surgery taken at end diastole. A, LVAD operation was temporarily suspended (for approximately 45 seconds) during a routine venting procedure. End-diastolic dimension is >6 cm, indicating a dilated ventricular cavity. B, This image showing internal dimension of (approximately) 3 cm with thickened LV wall was taken within 1 minute after LVAD operation was restored. The LVAD provides substantial volume unloading of the heart

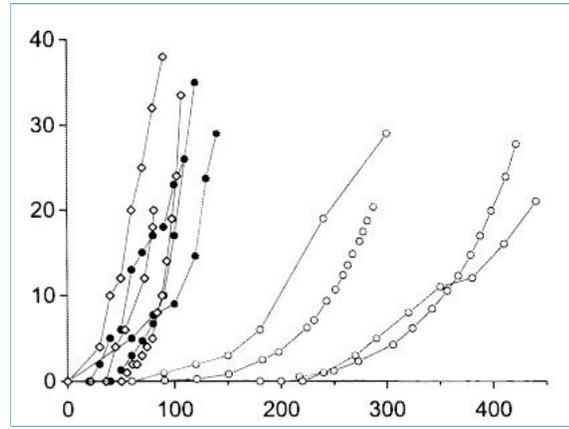


Figure 2. Graph showing end-diastolic pressure-volume relation (EDPVR) of hearts from four medically treated patients with end-stage idiopathic cardiomyopathy ((open bullet)), three heart failure patients after prolonged left ventricular assist device (LVAD) support ((bullet)), and three normal subjects ((open diamond)). Whereas EDPVRs of hearts from medically treated patients were shifted far to the right of the normal hearts, EDPVRs from the LVAD groups were close to normal. x axis shows volume in milliliters; y axis, pressure in mm Hg

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