Inflow Valve Regurgitation During Left Ventricular Assist Device Support May Interfere With Reverse Ventricular Remodeling

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Background. Left ventricular assist devices have been reported previously to reverse ventricular remodeling in patients with dilated cardiomyopathy. In patients with prolonged mechanical support, structural failure of the left ventricular assist device inflow valve can cause regurgitation into the left ventricle, which may affect adversely this process.

Methods. Left ventricular end-diastolic pressurevolume relation of hearts explanted from 8 patients with left ventricular assist device and 8 control subjects with idiopathic cardiomyopathy was determined ex vivo at the time of transplantation.

Results. Duration of mechanical support ranged from 210 to 276 days (mean \pm standard deviation = 283 \pm 76 days) in 3 patients with inflow valve regurgitation versus

L eft ventricular assist devices (LVAD) have been used to successfully "bridge" patients who have deteriorated hemodynamically while on the waiting list for heart transplant. Left ventricular assist device support improves the overall hemodynamics of the patients, leading to normalization of cardiac output, systemic blood pressure, and improved end-organ function [1]. In addition to short-term benefits, several reports have also suggested recovery of native ventricular function and reduction of left ventricular dimension after mechanical support [2–4].

Ventricular remodeling refers to the progressive increase in global left ventricular dimension observed in experimental and human heart failure. In general, it is thought that ventricular remodeling is a progressive and irreversible process that imparts a mechanical disadvantage to the myocytes and is believed to contribute to the deterioration of systolic left ventricular (LV) function. In a previous study, we have demonstrated that LVAD support resulted in an unprecedented degree of reverse ventricular remodeling [2]. In this setting, there is the potential for improved ventricular function, and LVAD explantation has been performed in several patients with 100 to 155 days (132 \pm 22 days) in 5 patients without (p = 0.005). The end-diastolic pressure-volume relation of all hearts supported mechanically was shifted to the left toward normal controls. This effect was markedly attenuated in patients with inflow valve regurgitation.

Conclusions. Mechanical assistance can cause reverse remodeling in patients with dilated cardiomyopathy as evidenced by the shift in the end-diastolic pressurevolume relation curve to the left. Inflow valve failure, associated with prolonged support, can attenuate changes in left ventricular structure and dimension. Ineffective pressure and volume unloading may explain these observations.

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nonviral forms of cardiomyopathy. As LVAD use becomes more common, there will be increasing interest in understanding the mechanisms that lead to reverse remodeling, improved LV function, and the factors that will predict the ability to successfully explant LVADs without transplantation. Accordingly, factors that may interfere with the reverse remodeling process should be better understood.

An infrequent observation in patients on long-term LVAD support has been the development of LVAD inflow valve regurgitation. The purpose of this retrospective study, was to determine whether inflow valve regurgitation, which may cause LV volume and pressure loading during LVAD systole, will interfere with the process of reverse remodeling.

Material and Methods

The hearts of 16 patients with New York Heart Association functional class IV idiopathic dilated cardiomyopathy were studied at the time of cardiac transplantation. All patients received maximal medical treatment with digoxin, diuretics, angiotensin-converting enzyme inhibitors, and, when needed, intravenous inotropic therapy. Routine pretransplantation evaluation for all patients included echocardiography and right heart catheterization. Data obtained from these studies were used to

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determine baseline ejection fraction, end-diastolic dimension, cardiac index, central venous pressure, and pulmonary capillary wedge pressure. Eight patients who remained "stable" on medical therapy received transplants during the study period as suitable donors became available. In the other 8 patients who deteriorated, the Thermo Cardiosystems (Woburn, MA) TCI 1000 IP LVAD was implanted according to previously published criteria [5]. Five of the LVAD patients had normal inflow valve function verified by intraoperative transesophageal echocardiography at the time of transplantation. In 3 of the LVAD patients with persistently elevated LVAD pump rates, echocardiography before transplantation showed moderate inflow valve regurgitation that was hemodynamically insignificant. All patients underwent uncomplicated heart transplantation. At the time of transplantation cardiac index, central venous pressure, and pulmonary capillary wedge pressure were determined with a Swan-Ganz catheter and the end-diastolic pressure-volume relation (EDPVR) was measured from the explanted hearts. In addition, three normal donor hearts, not suitable for transplantation because of preexisting coronary artery lesions, were also available for the study to serve as controls. Two of these hearts were from male donors and one from a female donor with ages ranging from 30 to 45 years.

Determination of End-Diastolic Pressure–Volume Relation

At the time of explantation, all hearts were arrested with cold crystalloid cardioplegia. Within 30 minutes, EDPVR measurements were carried out at 4°C. The mitral valve chordae were severed and a metal adapter was secured to the mitral annulus. A balloon connected to noncompliant tubing was placed in the left ventricle and the tubing was secured to the metal adapter (Fig 1). A metal clamp was applied to the remnants of the aortic root. Saline solution was slowly infused at 25-mL increments and intraventricular pressure was measured by a high fidelity micromanometer (Millar Instruments, Houston, TX). All data were digitized at 200 Hz using a 12-bit analog-to-digital board (AD Instruments, Milford, MA) and recorded with the MacLab system for analysis. Left ventricular EDPVRs were constructed by plotting corresponding pressures at each volume increment.

Results

Table 1 demonstrates baseline hemodynamic characteristics of all patients determined during their transplant evaluation. For the LVAD patients these values reflect hemodynamic status before deterioration prompting LVAD implantation. There was no significant difference in mean values for cardiac index, pulmonary capillary wedge pressure, end-diastolic dimension, or ejection fraction among patients who received medical therapy and those who underwent mechanical assistance, regardless of whether inflow valve regurgitation developed or not.

In the LVAD group, hemodynamics measured at the



Fig 1. Experimental setup for determination of end-diastolic pressure–volume relation. A balloon placed inside the left ventricle is inflated at 25-mL increments and pressure is recorded simultaneously. The remnants of the aortic root are cross-clamped. This setup offers an accurate means of controlling preload and afterload in an ex vivo system.

time of transplantation showed marked improvements regardless of whether inflow valve regurgitation developed or not (Table 2). Cardiac index had increased to more than 3 L \cdot min⁻¹ \cdot m⁻², PCWP had decreased to less than 10 mm Hg, and central venous pressure decreased to less than 5 mm Hg. Development of inflow valve regurgitation was significantly associated with longer duration of mechanical support (mean ± standard deviation = 283 ± 76 days versus 132 ± 22 days; *p* < 0.005).

Figure 2 demonstrates the static mean (±standard deviation) EDPVR in all patients and the three normal hearts. The 8 patients with dilated cardiomyopathy exhibited large LV volumes as indicated by the shift in the EDPVR curve to the far right. In 5 patients with normal LVAD function, the EDPVR was characterized by smaller LV volumes as demonstrated by the leftward shift of this curve toward normal control hearts. Finally, in 3 patients with LVAD inflow valve regurgitation, the EDPVR curve was shifted toward smaller volumes compared with patients without mechanical assistance, but this leftward shift was markedly attenuated when compared with other patients with normal LVAD valve function.

At time of explantation, all patients with inflow valve regurgitation demonstrated rupture of the porcine valve leaflets, primarily at the commissures. There was no evidence of vegetations on the leaflets and routine postoperative cultures from all valves were negative.

Comment

The beneficial hemodynamic effects of LV dilation seen with acute hemodynamic stress can eventually become maladaptive when the ventricle exhibits substantial remodeling. These changes in LV geometry can be demonstrated by shifts of the EDPVR toward larger volumes

Hemodynamics	$(L \cdot min^{-1} \cdot m^{-2})$	PCWP (mm Hg)	EDD (cm)	EF
LVAD (–)IR	1.6 ± 0.4	28 ± 6	7 ± 0.5	0.21 ± 0.05
LVAD (+)IR	1.7 ± 0.5	26 ± 5	7 ± 0.6	0.16 ± 0.02
DCM	1.7 ± 0.5	27 ± 7	7.2 ± 0.8	$\textbf{0.18} \pm \textbf{0.04}$

Table 1. Baseline Hemodynamics in All Patients Before Cardiac Transplantation^a

^a There is no significant difference among any of the groups with regard to cardiac index (CI), pulmonary capillary wedge pressure (PCWP), end-diastolic dimension (EDD), or ejection fraction (EF). All values are reported as mean \pm standard deviation.

DCM = dilated cardiomyopathy; IR = inflow regurgitation; LVAD = left ventricular assist device.

[6]. Changes in both myocyte and nonmyocyte compartments probably contribute to ventricular dilation. At the cellular level, changes in function, morphology, and distribution of cardiac myocytes occur [7, 8], as well as changes in the type, structure, orientation, and amount of tissue collagen [9, 10]. Pharmacologic interventions have a limited effect in altering these processes. Angiotensinconverting enzyme inhibitors are among the most widely studied drugs that have been shown in both experimental and clinical trials to attenuate the progression of ventricular dilation and possibly cause mild reversal [11, 12]. A similar modest effect has been suggested for nitroglycerin, β -blockers, and calcium-channel blockers [13–15].

Recent reports on patients on LV mechanical assistance have suggested that chronic LVAD support can lead to substantial reversal of LV chamber dilation and in some cases improved cardiac function [2–4]. The factors influencing these processes are not known, although hemodynamic unloading has been postulated as one possible mechanism. In this respect, LVADs provide the unique advantage over pharmacologic treatment in that myocardial pressure and volume unloading can be accomplished without an accompanying decrease in systemic blood pressure. The LVAD inflow valve regurgitation during long-term support can possibly counteract these hemodynamic benefits.

In this study, measurements of EDPVR were used as a means of determining the degree of restoration of ventricular geometry toward normal. Cold cardioplegia arrest of all hearts and prompt determination of EDPVR curves minimized false errors in ventricular compliance.

 Table 2. Hemodynamic Improvement After Left Ventricular

 Assist Device Support^a

Hemodynamics	Mean Baseline	Mean LVAD (–)IR	Mean LVAD (+)IR
CI	1.6	3	3.2
PCWP	28	8	9
CVP	15	4	3
Duration (days)		132 (100-155)	283 (210–363) ^b

^a Both left ventricular assist device groups regardless of presence of inflow valve regurgitation show similar hemodynamic improvements. Duration of left ventricular assist device support was significantly longer in patients in whom regurgitation developed. ^b p < 0.005.

CI = cardiac index; CVP = central venous pressure; IR = inflow regurgitation; LVAD = left ventricular assist device; PCWP = pulmonary capillary wedge pressure. This technique is also more accurate than twodimensional echocardiographic or plain radiographic methods because loading conditions are controlled [6]. We have demonstrated previously that chronic LVAD support allows for EDPVR curves to shift toward smaller volumes characteristic of normal hearts [2]. Although EDPVR was only measured at the time of transplantation in each patient because of obvious limitations, all patients in this study were similar at baseline in terms of ventricular function and dimension. Therefore, the EDPVRs of LVAD patients most likely were originally similar to those of the medically treated group and the smaller volumes at LVAD explantation suggest an active reverse remodeling process. In the 3 patients with incompetent outflow valves, the pressure and volume load imposed by the regurgitation resulted in attenuation of the reverse remodeling process.

Previous histologic studies of hearts after a period of mechanical assistance have shown a reduction in wavy fibers and contraction band necrosis, an increase in interstitial fibrosis, and normalization of fiber orientation [16–19]. The mechanism leading to these structural alterations are not known. Animal models of renovascular hypertension [20] have shown increased levels of angiotensin and aldosterone to be associated with increased myocardial fibrosis. Treatment with angiotensinconverting enzyme inhibitors or spironolactone reduces remodeling suggesting a role for these effector hormones. Physiologic and functional recovery of patients on



Fig 2. End-diastolic pressure–volume relationship determined at time of cardiac transplantation. Values are reported as mean \pm standard deviation. (DCM = dilated cardiomyopathy; IR = inflow regurgitation; LVAD = left ventricular assist device; NL = normal.)

LVADs are paralleled with decreased levels of plasma renin activity, angiotensin II, aldosterone, and other hormones known to be elevated in heart failure patients [21, 22]. Thus, restoration of normal hemodynamics may turn off the effector mechanisms responsible for progression of heart failure [23]. Similarly, the patients in this study all had hemodynamic recovery to the same extent. Although hormone levels were not directly measured, it is doubtful that the level of neuroendocrine activation attenuated the degree of ventricular remodeling in the 3 patients with valvular insufficiency. A more plausible explanation would encompass the fact that additional volume, and possibly pressure, loading imparted by the regurgitation, may have acted locally to attenuate reversal of LV chamber geometry.

Whatever the molecular mechanism for these changes, the findings reported in this study suggest that the heart exhibits structural plasticity. With LVAD support, the myocyte and nonmyocyte components of the heart undergo changes that lead to restoration of normal LV geometry. This process is attenuated by volume and pressure loading. Whether normalization of ventricular geometry by itself improves systolic function has not been determined. On theoretical grounds and based on modeling studies, a smaller LV chamber is associated with a stronger pump, even if contractility is held constant [24, 25]. It is conceivable that in the future, subgroups of patients can be identified in whom reversal of dilated ventricle with mechanical assistance combined with pharmacotherapy to treat underlying cardiac disease will obviate the need for heart transplantation. Use of LVADs as a "bridge to recovery" necessitates understanding the molecular mechanism involved in promoting reverse remodeling and adverse factors that impact on this process. This report highlights one potential problem that can interfere with this process, inflow valve regurgitation. Valvular insufficiency was observed only in patients with prolonged support time. The accelerated nature for failure of porcine xenografts used in the LVAD suggests several possible mechanisms such as excessive handling of the valves intraoperatively, effect of device migration overtime, or existence of a large pressure gradient across the valve precipitated by chamber design or kinking of LVAD outflow graft. Design of devices for prolonged or permanent use should take these factors into consideration to assure valve competency.

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