Left ventricular contractility and contractile reserve in humans after cardiac transplantation

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ABSTRACT Limited data are available concerning left ventricular contractility and contractile reserve in the chronically denervated, transplanted human heart. This is primarily because of the inability of traditional tests of left ventricular performance to distinguish changes in contractility from alterations in ventricular loading conditions. In this study, load-independent end-systolic indexes of left ventricular contractility were measured by echocardiography and calibrated carotid pulse tracings in 10 patients who had undergone orthotopic cardiac transplant (age 48 ± 4 years; interval from operation to study 1.2 ± 0.8 years) and in 10 normal control subjects (age 25 ± 4 years) matched for donor heart age (25 ± 6 years). None of the transplant patients had evidence of rejection as determined by endomyocardial biopsy. Baseline left ventricular contractility was assessed over a wide range of afterload generated by infusion of methoxamine. Contractile reserve was measured as the response to an infusion of dobutamine plus methoxamine. Before afterload challenge, baseline left ventricular percent fractional shortening was higher for the transplant patients than for the control subjects (36.5 ± 5.7% vs 32.1 ± 2.1%; p < .05). These differences occurred at a time that end-systolic wall stress (a measure of afterload) was significantly lower for the transplant patients (38 ± 16 vs 50 ± 9 g/cm²; p < .05). When the left ventricular end-systolic pressure-dimension and stress-shortening relationships were determined for the transplant and control subjects, no differences in contractility or contractile reserve were noted. Thus the chronically denervated, transplanted, nonrejacting human left ventricle demonstrates normal contractile characteristics and reserve.


OVERALL PERFORMANCE of the denervated transplanted heart has been reported to be adequate under basal conditions in the absence of rejection.1–4 However, no study has determined whether the transplanted human left ventricle has normal contractility and contractile reserve. Previous investigations performed at rest or during exercise have used hemodynamic measurements at cardiac catheterization,1–6 ejection phase indexes of left ventricular performance determined by echocardiography,7,8 surgically implanted radiopaque myocardial markers,9–14 or radionuclide angiography15 in an attempt to address these issues. These traditional approaches for assessing left ventricular performance are limited by their inability to distinguish abnormalities in contractility from alterations in preload or afterload.16,17 This is particularly important since the ejection phase indexes are often used inappropriately as measures of contractility, whereas they truly reflect a complex interaction between contractile state and loading conditions.16,17

In recent years, several load-independent indexes of left ventricular contractility have been shown to be useful in the identification of preclinical ventricular dysfunction in humans.18–25 One index is the slope of the relationship between left ventricular end-systolic pressure and dimension, parameters that are related linearly over a wide range of values for a given contractile state.26,27 This slope is independent of preload, incorporates afterload, and is a sensitive measure of contractility.18–21 The relationship between left ventricular end-systolic wall stress (a measure of afterload) and percent fractional shortening also appears to be a reliable and clinically useful index of contractility in patients with normal intravascular volume.28,29 In this study, these two end-systolic indexes were used to assess left ventricular contractility in transplanted and normal hearts under baseline and augmented inotropic conditions.

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Methods

Patients. Ten male patients who underwent orthotopic cardiac transplant surgery at Harefield Hospital were studied. The patients were between 40 and 51 years of age (mean ± SD 47 ± 4) at the time of surgery. The age of the donor hearts ranged from 18 to 39 years (25 ± 6). The interval from operation to study ranged from 3 to 34 months (14 ± 9). No patient had evidence of rejection as determined by endomyocardial biopsy performed within 7 days of study. The patients had experienced an average of 1.6 ± 1.4 episodes of rejection before the study. Immunosuppressive medications included prednisone (nine patients), azathioprine (nine patients), and cyclosporin A (three patients).

The control group consisted of 10 healthy subjects (mean age 25 ± 4 years) matched for donor heart age. All control subjects had normal hearts upon examination and normal intracardiac anatomy by M mode and two-dimensional echocardiography. None of the control subjects were taking cardiovascular medications.

The protocol used to study the cardiac transplant patients met the criteria for human investigation previously established at Harefield Hospital. The protocol used for the normal control subjects was approved by the Committee on Human Protection from Research Risks of The University of Chicago Hospitals and Clinics. In all cases, informed consent was obtained.

Experimental protocol. The experimental protocol used in this study has been previously described in detail. Each transplant patient had simultaneous recordings of left ventricular M mode echocardiogram, phonocardiogram, electrocardiogram, indirect carotid pulse tracing, and blood pressure measurements performed under baseline conditions. An Irex System IIA ultrasound imaging device (Irex Corp., Ramsey, NJ) with physiologic transducers was used for both two-dimensional and M mode echocardiographic imaging. Peak systolic, diastolic, and mean blood pressure measurements were made with the Dinamap 845 Vital Signs Monitor (Critikon, Inc., Tampa, FL). This device has been shown to estimate central aortic pressures accurately over a wide range of systolic and diastolic pressures independent of the patient’s cardiac index, systemic vascular resistance, left ventricular ejection fraction, and body surface area. After completion of baseline recordings, all subjects received an intravenous infusion of the α1-adrenergic agonist methoxamine (infusion rate 1 mg/min). This agent has no direct effect on left ventricular inotropic state.

The left ventricular response to the pressor challenge was assessed with recordings obtained every 1 to 2 min until the peak systolic pressure had increased 30 to 60 mm Hg above baseline, at which time the methoxamine infusion was discontinued. The peak pressor effect lasted 2 to 5 min. When systolic arterial blood pressure had returned to within 5% of the initial value, an intravenous infusion of dobutamine hydrochloride (5 μg/kg/min) was begun. After 7 min new baseline recordings were performed. The methoxamine challenge was then repeated during the constant dobutamine infusion. In this manner, left ventricular contractility could be assessed over a wide range of pressures generated by afterload challenge alone or in conjunction with the β-adrenergic receptor agonist dobutamine. Serial two-dimensional echocardiographic images of the left ventricle were recorded in all subjects before and after dobutamine under baseline conditions as well as during the pressor challenge. In this manner, “on-line” assessment of left ventricular contraction pattern could be assessed.

Control subjects were studied with the same protocol. However, they were premedicated with atropine (0.010 to 0.015 mg/kg body weight, iv) to abolish reflex cardiac slowing induced by carotid baroreceptor stimulation secondary to the methoxamine infusion.

Left ventricular end-systolic dimension (Des) and wall thickness (hse) as well as end-diastolic dimension (Ded) and wall thickness (hde) were measured from M mode echocardiographic recordings as described previously. Measurements were determined as the mean value of five cardiac cycles. Left ventricular end-systolic and end-diastolic volumes were estimated from echocardiographic dimensions by the method of Teichholz et al. This assumes that the visualized portion of the left ventricle is representative of global left ventricular performance, an assumption shown previously to be valid in the absence of significant left ventricular asynergy. Left ventricular stroke volume, cardiac output, ejection fraction, and percent fractional shortening were calculated in the standard manner from these data. Total systemic vascular resistance was calculated as the mean aortic pressure (measured by the Dinamap Vital Signs Monitor) times the conversion factor 80 dynes/cm²/mm Hg divided by cardiac output. This assumes that the right atrial mean pressure is small and therefore has little effect on the calculation of systemic vascular resistance in normal subjects and in transplant patients without congestive heart failure. Left ventricular mass (LVM) was calculated from end-diastolic dimension and wall thickness by adapting the formula of Devereux et al:

$$LVM = 1.04\{(D_{es} + 2h_{es}) - (D_{ed})^3\} - 14 \text{ g}$$

Calibration of the carotid pulse tracings was performed with assignment of systolic blood pressure to the peak and diastolic pressure to the nadir of the tracing. Linear interpolation to the level of the incisura was then performed to estimate end-systolic pressure. Values obtained in this manner in adult subjects undergoing cardiac catheterization have been shown to differ by 3 ± 4 mm Hg (mean ± SD) from simultaneously recorded central aortic pressures with a correlation coefficient of .97.

The left ventricular end-systolic meridional wall stress ($\sigma_{es}$) was calculated by an angiographically validated method as follows:

$$\sigma_{es} = \frac{(1.35)(P_{es})(D_{es})}{(4)(h_{es})}\left(1 + \frac{h_{es}}{D_{es}}\right)$$

where $\sigma_{es}$ is left ventricular wall stress (g/cm²) at end-systole, $P_{es}$ is the left ventricular pressure (mm Hg) at end-systole, $D_{es}$ and $h_{es}$ are the left ventricular end-systolic dimension and posterior wall thickness (cm), and 1.35 is a conversion factor (mm Hg to g/cm²).

Data analysis. The carotid pulse tracing as well as the left ventricular echocardiogram were analyzed with a Franklin Quantic 1200 (Bruce Franklin, Inc., Seattle). This instrument is equipped with a digitizing pad that has a sampling rate of 80/cm or approximately 400/sec. After data input, the device is programmed to correct the carotid pulse tracing for pulse delay by aligning the dicrotic notch with the first high-frequency component of the second heart sound, a commonly used marker of end-systole. This allows evaluation of dimension and pressure data in a temporally coordinated manner. Data were excluded when heart rate varied by more than 10 beats/min from the baseline rate for a given contractile state.

The relationship between left ventricular end-systolic pressure and dimension was assessed for the control and cardiac transplant subjects over a wide range of afterload (as defined by end-systolic wall stress) generated by methoxamine under basal and augmented contractility conditions. For each subject the slope of this relationship was calculated from a minimum of four $P_{es}$-$D_{es}$ data points by simple linear regression (least

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squares method) and used as a basis for comparison. Comparisons were also performed between groups with left ventricular percent fractional shortening (%ΔD) at equivalent levels of afterload (i.e., end-systolic wall stress of 50 g/cm²) obtained after linear regression analysis of the σ,-%ΔD data. This level of wall stress was chosen as the basis for comparison because it was the mean resting wall stress value for the control group.

An unpaired t test was used to compare baseline hemodynamic data as well as P, D, slopes and %ΔD values at σ₅₀ = 50 g/cm² for the control and transplant subjects before and during infusion of dobutamine. A p value < .05 was considered statistically significant.

Results

Baseline hemodynamics. The baseline hemodynamic data for the control and transplant groups are summarized in Table 1. Heart rate did not differ between the groups. The relatively rapid basal heart rate for the control subjects reflects pretreatment with atropine. Although the left ventricular end-systolic and end-diastolic dimensions and volumes were larger for the control subjects than for the transplant patients, there was no difference in stroke volume or cardiac output. In contrast, left ventricular peak and end-systolic pressures, aortic mean and diastolic pressures, total systemic vascular resistance, left ventricular end-systolic and end-diastolic wall thicknesses, and left ventricular wall mass were higher for the transplant patients. Interestingly, the increase in left ventricular mass was adequate to normalize peak systolic wall stress. The net effect was an elevated baseline left ventricular percent fractional shortening (36.5 ± 5.7% vs 32.1 ± 2.1%; p < .05) and ejection fraction (69 ± 10% vs 61 ± 4%; p < .05) for the transplant patients. These differences occurred at a time when afterload (as measured by end-systolic wall stress) was significantly lower for the transplant patients than for the control subjects (38 ± 16 vs 50 ± 9 g/cm²; p < .05). Thus, under basal conditions, the transplant patients' smaller end-systolic dimension (2.61 ± 0.34 vs 3.24 ± 0.14 cm; p < .05) and greater end-systolic wall thickness (1.80 ± 0.23 vs 1.38 ± 0.22 cm; p < .001) more than compensated for their higher end-systolic pressure (114 ± 8 vs 96 ± 8 mm Hg; p < .001).

Evaluation of left ventricular contractility and contractile reserve. There were no gross regional wall motion abnormalities noted on the two-dimensional echocardiograms under baseline conditions, at peak pressor effect, or during infusion of dobutamine for either the control subjects or transplant patients. Although three of the transplant patients did have flattened septal motion on the M mode echocardiogram, none had paradoxical septal motion. As seen in Figure 1, when %ΔD values were compared at the same level of afterload (i.e., σ₅₀ = 50 g/cm²), there were no differences in left ventricular shortening characteristics. When left ventricular contractility was assessed by the end-systolic pressure-volume relationship, comparable slopes

| TABLE 1 |
| Summary of baseline hemodynamics |
| Control | Transplant | p value<sup>a</sup> |
| Heart rate (bpm) | 88 ± 20 | 92 ± 6 | NS |
| Aortic peak systolic pressure (mm Hg) | 116 ± 6 | 135 ± 7 | < .001 |
| Aortic diastolic pressure (mm Hg) | 69 ± 8 | 90 ± 6 | < .001 |
| Aortic mean pressure (mm Hg) | 86 ± 7 | 112 ± 7 | < .001 |
| LV end-systolic pressure (mm Hg) | 96 ± 8 | 114 ± 8 | < .001 |
| LV end-diastolic pressure (mm Hg) | 4.77 ± 0.27 | 4.34 ± 0.53 | < .05 |
| LV end-diastolic dimension (mm Hg) | 3.24 ± 0.14 | 2.61 ± 0.34 | < .05 |
| LV percent fractional shortening | 32.1 ± 2.1 | 36.5 ± 5.7 | < .05 |
| LV end-diastolic volume (cm³) | 107 ± 13 | 85 ± 23 | < .05 |
| LV end-systolic volume (cm³) | 42 ± 4 | 26 ± 12 | < .05 |
| LV stroke volume (cm³/beat) | 65 ± 7 | 59 ± 10 | NS |
| Cardiac output (l/min) | 5.7 ± 0.6 | 5.4 ± 0.9 | NS |
| Total systemic resistance (dyne-sec-cm⁻⁵) | 1207 ± 127 | 1659 ± 249 | < .05 |
| LV ejection fraction (%) | 61 ± 4 | 69 ± 10 | < .05 |
| LV end-diastolic wall thickness (cm) | 0.92 ± 0.07 | 1.15 ± 0.09 | < .001 |
| LV end-systolic wall thickness (cm) | 1.38 ± 0.22 | 1.80 ± 0.23 | < .001 |
| LV mass (g) | 175 ± 28 | 205 ± 26 | < .05 |
| LV peak systolic wall stress (g/cm²) | 146 ± 17 | 137 ± 28 | NS |
| LV end-systolic wall stress (g/cm²) | 50 ± 9 | 38 ± 16 | < .05 |

<sup>a</sup>C vs T

LV = left ventricular.
were measured. Thus baseline left ventricular contractility is normal in the transplanted heart.

Dobutamine significantly increased both the extent of left ventricular shortening (i.e., %ΔD) at an end-systolic wall stress of 50 g/cm² and the $P_e$-$D_e$ slope for the transplant and control groups (table 2). The end-systolic indexes determined during infusion of dobutamine reflect left ventricular contractile reserve and were equally increased for both groups. This shows that despite chronic denervation, left ventricular contractile reserve in the transplanted heart is normal.

Heart rate response to a catecholamine challenge. As seen in table 2, dobutamine increased heart rate from $88 \pm 21$ to $97 \pm 20$ beats/min for the control subjects and from $92 \pm 6$ to $117 \pm 8$ beats/min for the transplant patients. Although this was a statistically significant change from baseline for both groups (p < .001), the transplant patients demonstrated a chronotropic response that far exceeded that experienced by the control subjects ($28 \pm 12\%$ vs $10 \pm 10\%$, respectively; p < .001).

Discussion

Our data demonstrate that the transplanted, chronically denervated left ventricle has normal contractility and contractile reserve. Unlike all previous studies of left ventricular performance in cardiac transplant patients, the experimental design used in this study permitted a load-independent comparison of the inotropic properties of the innervated and chronically denervated human left ventricle. In contrast to previous studies, which used patients with coronary artery disease and revascularization and even prior myocardial infarction as control subjects, the study used normal healthy individuals matched to donor heart age. This allowed more appropriate comparisons of indexes of cardiac performance.

Left ventricular wall mass and end-diastolic wall thickness were greater for the transplant patients than for the control subjects in the absence of significant differences in heart rate. Although it has been suggested that this may be an early sign of graft rejection, it is unlikely to be the case with our patients because none of them had evidence of rejection on endomyocardial biopsy. Rather, the increase in diastolic wall thickness and mass probably represent the left ventricle's normal physiologic response to increased systemic vascular resistance, peak systolic pressure, and peak systolic wall stress. In our study, "young" donor hearts (age 25 ± 6 years) were connected to older recipients' cardiovascular systems (age 47 ± 4 years). The donor heart is suddenly faced with a high impedance state due to the combined effects of peripheral vasoconstriction associated with end-stage heart disease, the side effects.
of immunosuppressive medications such as prednisone and cyclosporin A, and the normal increase in aortic impedance that occurs with aging. The donor left ventricle is initially “unprepared” for this increase in systemic load, which is present during the immediate postoperative period. Left ventricular wall stress rises and shortening characteristics fall. This may in part account for the depression in left ventricular performance seen in transplanted human hearts soon after surgery. Subsequently, the donor left ventricle (i.e., transplanted heart) becomes hypertrophic in an attempt to normalize peak systolic wall stress. This has multiple physiologic ramifications. The increased left ventricular wall thickness that is appropriate to normalize peak stress during early systole is excessive for the much lower left ventricular pressure present in the ventricle at end-systole. This results in relatively large left ventricular end-systolic wall thickness values and low end-systolic wall stress. Since there is an inverse relationship between end-systolic wall stress and the extent of fiber shortening, left ventricular shortening characteristics increase while chamber emptying is facilitated. This is demonstrated in our study by higher baseline \%ΔD for the transplant patients (36.5 ± 5.7% vs 32.1 ± 2.1%; p < .05) in association with lower end-systolic wall stress (38 ± 16 vs 50 ± 9 g/cm²; p < .05). As seen in table 2 and figure 1, when values for left ventricular shortening fraction are compared at the same level of afterload (i.e., \(\sigma_a = 50\) g/cm²), there is no difference in ventricular performance between the transplant and control groups (33.0 ± 2.1% vs 32.7 ± 1.5%).

In the innervated heart (i.e., control group), an afterload challenge with methoxamine raised systemic blood pressure, resulting in carotid baroreceptor stimulation, increased parasympathetic discharge, and subsequent bradycardia. Premedication of our control subjects with atropine blocked this reflex response. Transplant patients, who did not undergo pharmacologic blockade of their parasympathetic nervous system, failed to demonstrate a decrease in heart rate with the infusion of methoxamine. This suggests that cardiac reinnervation did not occur in our transplant patients over the long term after surgery and is in agreement with findings reported previously. However, the denervated left ventricle was capable of mounting a normal inotropic response to an adrenergic agonist, suggesting the presence of functionally intact adrenergic receptors. Interestingly, its heart rate response to the same challenge was greater than expected. This differential effect observed in transplant patients relative to control subjects may be due to differences in the density, number, or binding affinity of \(\beta\)-adrenergic receptors (“up-regulation”) associated with chronic cardiac denervation. A second explanation is that the inotropic and chronotropic responses of the transplanted heart are mediated by different receptors. In support of this theory are recent data suggesting that the inotropic actions of catecholamines occur through \(\beta_1\) receptors located in the ventricles, whereas the chronotropic effects are mediated through \(\beta_2\) receptors in the atria. This does not exclude the possibility that there are two subtypes of \(\beta_1\) receptors that independently mediate inotropic and chronotropic properties. Finally, it is possible that the \(\beta_1\)- and \(\beta_2\)-adrenergic receptors undergo different degrees of “up-regulation” and have different physiologic actions. The potential limitations of the methods used in this investigation have been discussed previously in detail. However, one issue specific to the present

TABLE 2

Left ventricular response to dobutamine challenge

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Transplant</th>
<th>Control vs transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fractional shortening at</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>end-systolic stress = 50</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>g/cm²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>32.7 ± 1.5</td>
<td>p &lt; .001</td>
<td>NS</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>39.3 ± 1.6</td>
<td>38.0 ± 1.7</td>
<td>p &lt; .001 NS</td>
</tr>
<tr>
<td>% Difference</td>
<td>20 ± 7</td>
<td>15 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>End-systolic pressure-dimension slope</td>
<td>104 ± 13</td>
<td>p &lt; .001</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate</td>
<td>88 ± 21</td>
<td>p &lt; .001</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline</td>
<td>97 ± 20</td>
<td>117 ± 8</td>
<td>p &lt; .001 NS</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>10 ± 10</td>
<td>28 ± 12</td>
<td>p &lt; .001 NS</td>
</tr>
</tbody>
</table>

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study should be addressed. Although none of our cardiac transplant patients had paradoxical sepal motion on the M mode echocardiogram, three did have flattened sepal motion. The septum demonstrated normal systolic thickening in these patients, making it unlikely that intrinsic abnormality of the septum was present. This conclusion is further reinforced by the lack of regional wall motion abnormalities on two-dimensional echocardiographic studies. When the M mode and two-dimensional echocardiographic recordings were assessed simultaneously, it became evident that the sepal motion abnormality was caused by extrinsic rather than intrinsic factors. In these cases there was exaggerated anterior motion of the entire left ventricle during systole relative to the chest wall. Since the M mode echocardiographic recording represents “net” motion of an intracardiac structure, it is not surprising that in some patients the posterior wall endocardium and epicardium demonstrated an “increased” net excursion whereas the septum demonstrated a “decreased” net excursion. The left ventricular posterior wall endocardium and epicardium moved concurrently and had a normal relationship to the left septal surface. Thus measurements of left ventricular wall thicknesses and dimensions throughout the cardiac cycle were not affected by the M mode echocardiographic appearance of flattened sepal motion.

In summary, baseline left ventricular shortening characteristics are higher for the transplant patients than for age-matched control subjects because of differences in afterload conditions rather than a hypercontractile state. The transplanted, chronically denervated, nonrejecting left ventricle demonstrates normal contractility and contractile reserve as well as an exaggerated chronotropic response to a catecholamine challenge.

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Errata

An error appeared in a recently published article by Lee et al. (Circulation 71: 579, 1985). The first sentence of the first paragraph beginning on page 583 should have read: “At energy levels of 40 to 80 W over 1 sec, five of 15 laser discharges (33%) produced wall motion abnormalities, a significant difference compared with the 100% incidence of wall motion abnormalities after electrical shock (p < .05).”

In a recently published article by Hashimoto et al. (Circulation 71: 363, 1985), Dr. Hashimoto’s first name was misspelled. It should have read Hidekazu Hashimoto, M.D. Dr. Hashimoto’s current address is: Clinical and Research Teaching Staff, Second Department of Medicine, Nagoya University School of Medicine, Nagoya 466, Japan.
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