A Hemodynamic and Doppler Echocardiographic Study of Ventricular Function in Long-term Cardiac Allograft Recipients

Etiology and Prognosis of Restrictive-Constrictive Physiology

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Conventional hemodynamic measurements and Doppler echocardiography were used to assess ventricular physiology of the human cardiac allograft and to examine the influence of pertinent clinical factors on chronic myocardial performance. Sixty-four patients (18–55 years old; mean, 39 years) undergoing routine annual hemodynamic assessment were studied. Blood-flow velocity properties across the mitral, tricuspid, and aortic valves were analyzed from Doppler ultrasound recordings. Ten of these patients had elevated diastolic pressures associated with a sharp early diastolic dip followed by an exaggerated and abrupt rise in pressure, consistent with restrictive-constrictive ventricular physiology. Left ventricular dp/dt and stroke volume were lower in these patients compared with the other 54 patients. Doppler echocardiographic indexes of left ventricular filling and ejection in these 10 patients differed significantly. Isovolumic relaxation time and pressure half-time were shorter, peak early mitral and tricuspid flow velocities were higher, and mean aortic flow velocity and acceleration were lower. A higher rejection incidence was the only demonstrable clinical factor associated with impaired ventricular function. Doppler echocardiography may, therefore, noninvasively identify patients with hemodynamic evidence of restrictive-constrictive physiology. This abnormality occurs in approximately 15% of allograft recipients, is associated with impaired systolic performance, and may be related to rejection incidence. (Circulation 1989;79:66–75)

Cardiac transplantation is an established therapeutic option for patients with severe myocardial failure. In general, systolic function of the chronic allograft is well maintained. Nevertheless, the transplanted heart is affected by many factors that may alter left ventricular filling dynamics and thereby adversely affect diastolic function. Acute diastolic dysfunction, a recognized concomitant of acute rejection, has been demonstrated by conventional hemodynamic measurements and has been shown to be reversed by adequate rejection therapy. In contrast, chronic diastolic function of the nonrejecting allograft, and the factors influencing it, have not been fully elucidated.

The aims of the present study were 1) to assess left ventricular systolic and diastolic function of the nonrejecting cardiac allograft with conventional hemodynamic indexes and Doppler echocardiography; 2) to assess the frequency of restrictive-constrictive patterns of left ventricular filling in long-term cardiac allograft recipients; and 3) to examine the role of certain clinical factors in the development of restrictive-constrictive physiology in these patients.

Patients and Methods

Patients

All cardiac transplant recipients undergoing annual evaluation at Stanford University School of Medicine during a 9-month period were considered for...
the study; 64 of 95 patients had full hemodynamic and echocardiographic studies and were included. The remaining 31 were excluded because of either inadequate Doppler recordings (10 patients) or failure to obtain patient consent. All accepted patients gave informed consent to the protocol, which had been approved by the Committee for the Protection of Human Subjects at Stanford University Medical Center. The patient population consisted of 59 men and five women aged 18–55 years (mean, 39 years) who had undergone orthotopic cardiac transplantation 1–13 years (mean, 5 years) before the study. The indication for transplantation was myocardial failure due to dilated cardiomyopathy in 35 patients and coronary artery disease in 29 patients. Mean donor age was 21±4.6 years. Maintenance immunosuppression in nine patients consisted of azathioprine (0.5±0.08 mg/kg/day) and prednisone (0.2±0.07 mg/kg/day). The remaining 55 patients received cyclosporine (1.5–5.5 mg/kg/day; mean, 3.6±1.7 mg/kg/day) in addition to azathioprine (0.45±0.05 mg/kg/day) and prednisone (0.2±0.07 mg/kg/day).

All patients taking cyclosporine had documented systemic hypertension requiring medication: 30 were treated with prazosin (mean dose, 3 mg t.i.d.), 25 with hydralazine (mean dose, 50 mg t.i.d.), and 10 with atenolol (mean dose, 50 mg q.d.). None of the nine patients on the azathioprine and prednisone regimen had documented hypertension. New York Heart Association (NYHA) functional Class I in 54 patients, II in six patients, III in three patients, and IV in one patient.

The clinical characteristics of patients with restrictive-constrictive physiology by hemodynamic criteria as defined below were compared with those demonstrating a normal filling pattern. The factors examined were donor and recipient ages; graft ischemia time, defined as the time from cross-clamping the donor aorta to release of the recipient aorta; time from transplantation; NYHA classification; systemic arterial pressure; immunosuppressive regimen (ventricular function in the 10 patients whose immunosuppression did not include cyclosporine was compared with the remainder who were receiving cyclosporine); and total number of rejection episodes (for each patient, the absolute number of rejection episodes requiring augmentation of immunosuppressive agents, both early and late postoperatively, was tabulated).

**Cardiac Catheterization and Hemodynamic Measurements**

Left heart catheterization was performed from the femoral approach. Intracardial pressures and waveforms were recorded with a fluid-filled pigtail catheter attached to a micromanometer transducer. The system shows a flat frequency response to 18 Hz and less than 10% deviation to 24 Hz. Right heart pressures and contours were recorded with a balloon-tipped flow-directed thermodilution catheter. Cardiac output was calculated by the Fick method from triplicate measurements of oxygen consumption and normalized for body surface area (cardiac index). Stroke volume was computed from cardiac output and heart rate, and dP/dt and \( V_{\text{max}} \) were analyzed from left ventricular pressure recordings. Coronary arteriography was performed by the Judkins technique. Right ventricular endomyocardial biopsy specimens were obtained with a Caves-Schultz biop Tome from the internal jugular vein according to the previously described technique.

Hemodynamic classification as restrictive-constrictive or nonrestrictive ventricular physiology was made after review of all ventricular pressure tracings by three observers. Restrictive-constrictive physiology of either ventricle was diagnosed if all observers noted a characteristic sharp dip followed by an increased and abrupt rise in ventricular pressure in early diastole. It was required that the rise in diastolic pressure preceding the a wave exceed 4 mm Hg. Equalization of ventricular diastolic pressures was not a prerequisite for diagnosis.

**Endomyocardial Biopsy**

At least four biopsy specimens of right ventricular endomyocardial tissue were obtained from each patient and graded for rejection according to the Billingham criteria: normal, no rejection; mild rejection, cellular infiltrate without myocyte necrosis; moderate rejection, cellular infiltration and myocyte necrosis; and severe rejection, above abnormality plus hemorrhage.

Right ventricular biopsy specimens from a subset of 32 patients were graded independently for severity of fibrosis by an experienced cardiac pathologist without previous knowledge of the clinical features of each patient. Because of the patchy nature of myocardial fibrosis, two separate scores, each from 1 to 3, were assigned to each patient: one score was assigned to the most affected biopsy piece examined, and a second score was assigned to the least affected piece from each specimen. These scores were then averaged separately to give two mean scores for the group, one indicating the most severe and the other indicating the least severe fibrosis present on biopsy.

The above histologic features of endomyocardial biopsies from the patients demonstrating restrictive-constrictive hemodynamic properties were compared with those of the rest of the group.

**Doppler Echocardiographic Study**

Doppler echocardiography was performed within 24 hours of hemodynamic measurements. A control group of 16 normal volunteers of similar age (26–55 years; mean, 42 years) and gender distribution was studied for comparison of Doppler echocardiographic indexes of filling and ejection. Control subjects had normal physical examinations, no history of any cardiovascular disease, and a normal treadmill exercise test (those over the age of 45). Record-
FIGURE 1. Analysis of mitral and aortic flow velocity curves. Upper panel: Mitral flow velocity curve with pulsed wave Doppler ultrasound. Pressure half-time (PHT) is obtained by dividing the peak velocity (M₁) by 1.4 (\sqrt{2}) and measuring the time from peak velocity to the point at which this decrease in velocity is found. Isovolumic relaxation time (IVRT) is the interval between aortic valve closure (recorded as a high-intensity signal on the Doppler tracing and confirmed by phonocardiography) and the onset of mitral flow. Peak early mitral flow velocity (M₁) and the velocity following atrial systole (M₂) are measured from baseline to the maximum recorded velocity. Lower panel: Aortic velocity. Peak aortic velocity (cm/sec) is measured from baseline to maximum recorded velocity. Ejection time (msec) is measured from aortic valve opening (AVO) to aortic valve closure (AVC). Calibration marks on the upper panel are at 40 msec. Velocity calibration is 100 cm/sec vertically from baseline to the first set of twin dots.

ings in both patients and controls were made with the subject in the left lateral position after 15 minutes recumbent rest to achieve basal heart rate and blood pressure. Simultaneous echocardiograms, phonocardiograms, and Doppler ultrasound recordings were obtained with an Irex IIIB system with a combined imaging and Doppler transducer (2.5 or 3.5 MHz) positioned at the apex. Blood flow velocity and valve movements at the mitral and tricuspid valves were obtained with pulsed wave Doppler ultrasound, with the sample volume positioned at the leaflet tips. Blood flow velocity across the aortic valve was recorded with continuous wave Doppler ultrasound from a nonimaging transducer.

The parameters of left ventricular diastolic function measured are shown in Figure 1: isovolumic relaxation time (IVRT), peak early mitral valve flow velocity (M₁), rate of peak early mitral flow deceleration expressed as pressure half-time, and peak mitral flow velocity after left atrial systole (M₂). The ratio of peak early to late mitral flow velocity (M₁/M₂) was computed for each patient. Likewise, right ventricular filling characteristics during apnea were assessed in a subset of 22 patients by measurements of peak early flow velocity across the tricuspid valve (T₁), pressure half-time, and peak tricuspid flow velocity after right atrial systole (T₂). In each patient, the mean values obtained from five consecutive beats not influenced by recipient atrial contraction were obtained for the Doppler indexes.

The parameters of systolic function measured (Figure 1) were peak aortic flow velocity and time to peak velocity. The mean acceleration of the aortic velocity (ACC) was calculated as:

\[ \text{ACC} = \frac{\text{peak velocity}}{\text{time to peak}} \times 1,000 \text{ cm/sec}^2 \]

Ejection time was measured from discrete high-intensity signals of aortic valve opening and closure on Doppler ultrasound recordings. This measurement was corrected for heart rate and expressed as the ejection-time index. The hemodynamic criteria for restrictive-constrictive physiology as defined above were used as the gold standard by which to compare Doppler ultrasound indexes of ventricular filling.

Statistical Analysis

All hemodynamic and Doppler ultrasound measurements are expressed as mean ± SD. The differences between patients with restrictive-constrictive physiology and those with nonrestrictive patterns of filling were compared by analysis of variance with a Fisher’s protected least significant test for statisti-
RESTRICTIVE / CONSTRUCTIVE

NON-RESTRICTIVE

Fig. 2. Ventricular diastolic pressure recording from patients with restrictive-constrictive versus nonrestrictive physiology. Patients fulfilled the criteria for restrictive-constrictive physiology if they had increased diastolic pressure, an abrupt and rapid rise in pressure in early diastole, and rapid filling wave exceeding 4 mm Hg. Left ventricular diastolic pressure: rapid filling wave (↓). Restrictive, 5 mm Hg; nonrestrictive, 2 mm Hg.

cal significance between group means, p≤0.05 being accepted as evidence of statistical significance. Differences between restrictive-constrictive and nonrestrictive physiology were evaluated with respect to clinical factors by means of analysis of variance or Fisher’s exact test, as appropriate.

Results

Ten transplant recipients were found to have a pattern of left and right ventricular filling consistent with restrictive-constrictive physiology according to the hemodynamic criteria described, whereas the remaining 54 patients did not. Figures 2 and 3 illustrate the difference in left and right ventricular pressure contours in the two groups.

Hemodynamic measurements in the two groups (Table 1) differed significantly. Mean heart rate was significantly higher in patients with restrictive-constrictive physiology. All mean right and left heart filling pressures (right atrial pressure, right and left ventricular end-diastolic pressures, and pulmonary artery wedge pressure) were significantly higher in patients with restrictive-constrictive physiology. Indexes of afterload such as aortic systolic pressure, systemic vascular resistance, pulmonary artery systolic pressure, and pulmonary vascular resistance were not significantly different in the two groups. Indexes of left ventricular systolic performance (dP/dt and V max) were significantly lower in patients with restrictive-constrictive physiology compared with that of nonrestrictive transplant recipients. These abnormalities of systolic and diastolic function were associated with a significantly decreased stroke volume, without a measurable difference in cardiac index due to the correspondingly elevated heart rate.

Doppler Results

Doppler echocardiographic indexes of filling and ejection in patients fulfilling our defined hemodynamic criteria for restrictive-constrictive physiol-
ogy, nonrestrictive transplant recipients, and control subjects are summarized in Table 2.

Transplant recipients (restrictive-constrictive vs. nonrestrictive hemodynamics). Figure 4 compares the typical mitral flow velocity profile from restrictive-constrictive recipients with that of nonrestrictive transplant recipients. Patients with restrictive-constrictive physiology had shorter left ventricular IVRTs and pressure half-times and higher M1:M2 ratios. Right ventricular pressure half-time was shorter and T1 and T1:T2 were higher in patients with hemodynamic evidence of right ventricular restrictive-constrictive physiology.

Restrictive-constrictive transplant recipients versus control subjects. In patients with hemodynamic evidence of restrictive-constrictive physiology, left and right ventricular pressure half-times were shorter and M1:M2 and T1:T2 were higher compared with those of control subjects.

Nonrestrictive transplant recipients versus control subjects. Transplant recipients without hemodynamic evidence of restrictive-constrictive physiology differed from control subjects in that they had longer left ventricular IVRT, lower M1 and M2, shorter right ventricular pressure half-time, and lower T2.

Left ventricular systolic function. Patients with restrictive-constrictive physiology had a significantly lower peak aortic flow velocity and mean acceleration of aortic velocity compared with that of nonrestrictive transplant recipients. Peak aortic flow velocity and mean aortic acceleration were similar in nonrestrictive transplant recipients and control subjects.

Ejection time index was similar in all these groups.

Relation of Clinical and Histologic Characteristics to Ventricular Function

Table 3 shows the clinical and histologic features in patients with restrictive-constrictive compared with those of patients with nonrestrictive physiology. No statistically significant difference was demonstrable between the two groups with respect to donor and recipient age, graft ischemic time, duration after transplantation, and systemic blood pressure.

Symptoms of heart failure were significantly more frequent and severe in patients with restrictive-constrictive physiology. Eight of these 10 patients were NYHA Class II, III, or IV; only two of the remaining 54 patients were in one of these classes.

There was no significant difference in frequency of coronary artery disease in restrictive-constrictive recipients compared with nonrestrictive transplant recipients.

Severity of fibrosis varied widely among the pieces of myocardial biopsy tissue obtained from any individual patient. Although patients with restrictive physiology showed a trend toward a higher fibrosis

FIGURE 3. Ventricular diastolic pressure recording from patients with restrictive-constrictive versus nonrestrictive physiology. Patients fulfilled the criteria for restrictive-constrictive physiology if they had increased diastolic pressure, an abrupt and rapid rise in pressure in early diastole, and rapid filling wave exceeding 4 mm Hg. Right ventricular diastolic pressure: rapid filling wave (↓). Restrictive, 8 mm Hg; nonrestrictive, 3 mm Hg.
score in the least and most severely affected biopsy specimens, this difference was not significant.

Transplant recipients with restrictive-constrictive physiology had significantly more previous rejection episodes (6.7±2.5) compared with the nonrestrictive group (3.6±2.4). Nine of 10 restrictive-constrictive patients had six or more rejection episodes; the remaining patient had only one documented rejection episode. Eight of the 54 nonrestrictive patients had six or more rejection episodes.

**Acute Rejection Diagnosed at Time of Study**

Acute allograft rejection was diagnosed in six of 64 patients (moderate rejection in four and mild rejection in two patients). Five of these patients had restrictive-constrictive physiology and a history of recurrent rejection episodes. The remaining patient with moderate rejection and a nonrestrictive filling pattern had only two documented previous rejection episodes. Of the 10 patients with restrictive-constrictive physiology, three had moderate rejection and two had mild rejection. Five patients with restrictive physiology had no biopsy evidence of rejection.

**Clinical Course of Patients**

Eight of the 10 patients with restrictive-constrictive physiology had symptoms of heart failure: four were functional Class II, three were Class III, and one was Class IV. The remaining two patients were asymptomatic. The patient with the most severe symptoms (Class IV) died 3 months later of end-stage ventricular failure. Autopsy of the allograft revealed a nondilated hypertrophied heart with extensive myocardial fibrosis and pericardial thickening.

One of the functional Class III patients had hemodynamic evidence of left ventricular systolic dysfunction as well as restrictive physiology. He was evaluated for pericardial constriction, and although M-mode echocardiography suggested a thickened pericardium, a computed tomographic scan failed to confirm this. Retransplantation was planned but avoided because of intraoperative finding of an extensively thickened pericardium. Total pericardial resection was therefore performed. This was followed by symptomatic improvement to functional Class II, decreased diastolic pressures, and improvement in his Doppler ultrasound indexes of left and right ventricular filling. However, his left ventricular pressure half-time remains short at 40 msec, and abnormal systolic function persists at 12 months after pericardectomy.

Another Class III patient had angiographic evidence of coronary artery disease and died suddenly 3 months later. The third patient died of intractable heart failure 20 months after transplantation.

The four patients in functional Class II have remained stable for up to 12 months after this study. The two asymptomatic patients with restrictive-constrictive physiology were found to have extensive coronary artery disease on angiography performed 12 months later, and both have successfully undergone retransplantation. Two of the 54 nonrestrictive patients were in functional Class II and have remained stable during the ensuing 12 months.

**Discussion**

Using conventional hemodynamic methods and Doppler echocardiography to evaluate ventricular

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**TABLE 1. Hemodynamic Results (mm Hg)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Transplant recipients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Restrictive-constrictive</td>
</tr>
<tr>
<td>Patients (n)</td>
<td>10</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>102±14</td>
</tr>
<tr>
<td>RA (mean) (mm Hg)</td>
<td>12.7±2.7</td>
</tr>
<tr>
<td>RVEDP (mm Hg)</td>
<td>10.9±6.1</td>
</tr>
<tr>
<td>RF (right ventricle)* (mm Hg)</td>
<td>6.4±3.7</td>
</tr>
<tr>
<td>PAW (mm Hg)</td>
<td>16.6±11.1</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>16.0±7.3</td>
</tr>
<tr>
<td>RF (left ventricle)* (mm Hg)</td>
<td>8.2±4.7</td>
</tr>
<tr>
<td>PA (systolic) (mm Hg)</td>
<td>24±4.8</td>
</tr>
<tr>
<td>AO (mean) (mm Hg)</td>
<td>108±27</td>
</tr>
<tr>
<td>SVR (res. units)</td>
<td>19.6±7.0</td>
</tr>
<tr>
<td>PVR (res. units)</td>
<td>1.8±1.2</td>
</tr>
<tr>
<td>dP/dt (left ventricle) (mm Hg/sec)</td>
<td>1,562±391</td>
</tr>
<tr>
<td>SV (ml/beat)</td>
<td>47±21</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>2.5±0.7</td>
</tr>
</tbody>
</table>

HR, heart rate; RA, right atrial pressure; RVEDP, right ventricular end-diastolic pressure; RF, rapid filling wave; PAW, pulmonary artery wedge pressure; LVEDP, left ventricular end-diastolic pressure; PA, pulmonary artery pressure; AO, aortic pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; SV, stroke volume; CI, cardiac index.

*Criteria for group separation prospectively.
function, this study examines the diagnosis, etiology, and prognosis of restrictive-constrictive physiology in cardiac transplant recipients. Abnormal ventricular function was observed in 15% of the patients studied beyond 1 year after transplantation. The hemodynamic abnormality defined was a dip followed by an abrupt and exaggerated rise in early diastolic ventricular pressure, consistent with restrictive-constrictive physiology. This diastolic abnormality was associated with impaired systolic performance. Abnormal systolic function was never documented in the absence of the defined diastolic dysfunction. The criteria for diagnosis of restrictive-constrictive physiology were broader than what is conventionally used and thus was subject to criticism. This choice was based on observations that many patients had abnormal ventricular pressure contours despite normal pressure measurements; thus, raised diastolic pressure was not an absolute criterion for diagnosis. Likewise, equalization of pressures was not uniformly present in patients with hemodynamically significant restrictive-constrictive physiology.

The instantaneous pressure drop at the atrioventricular valve is related to the pressure half-time, both of which can be accurately measured from the Doppler ultrasonic mitral velocity signal. Before the present study, to our knowledge Doppler echocardiography has not been used to assess diastolic abnormalities in long-term transplant recipients. Results of the present study indicate that abnormalities of the characteristic waveform across the mitral and tricuspid valves reflect abnormalities in ventricular filling dynamics. Thus, Doppler echocardiography provides a sensitive noninvasive method for assessing ventricular diastolic function in the chronic allograft. Mitral and tricuspid flow velocity profiles revealed characteristic abnormalities mirroring the hemodynamic findings: abrupt and rapid deceleration of mitral and tricuspid blood flow velocities (reflected in shortened pressure half-times) were consistent with abrupt and rapid rise in early diastolic pressure or rapid filling waves. Increased left atrial pressure may result in relatively earlier opening of the mitral valve and so account for the shortened IVRT compared with that in nonrestrictive conditions. In this way, mitral valve opening during especially rapid ventricular pressure decline may explain the high peak early mitral flow velocities characteristically seen in these patients. High peak early tricuspid flow velocity may be similarly explained.

Mitrail valve pressure half-time in patients without hemodynamic evidence of restrictive physiology was similar to that of control subjects, suggesting a normal left ventricular pressure response to filling in early diastole. Despite normal hemodynamic findings, these patients differed significantly from control subjects in some Doppler ultrasound indexes of left ventricular function, suggesting possible subtle diastolic abnormalities of the long-term human allograft. For example, left ventricular IVRT was longer in nonrestrictive transplant recipients compared with that of control sub-

### Table 2. Doppler Ultrasound Indexes of Left and Right Ventricular Function in Transplant Recipients and Control Subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Transplant recipients</th>
<th>Nonrestrictive</th>
<th>Control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricle</td>
<td>(n = 10)</td>
<td>(n = 54)</td>
<td>(n = 16)</td>
</tr>
<tr>
<td>IVRT (msec)</td>
<td>65 ± 16*</td>
<td>84 ± 13†</td>
<td>70 ± 14</td>
</tr>
<tr>
<td>M1 (cm/sec)</td>
<td>82 ± 22</td>
<td>73 ± 16†</td>
<td>89 ± 17</td>
</tr>
<tr>
<td>PHT (msec)</td>
<td>34 ± 7*</td>
<td>50 ± 12</td>
<td>52 ± 8‡</td>
</tr>
<tr>
<td>M2 (cm/sec)</td>
<td>42 ± 12</td>
<td>44 ± 12‡</td>
<td>61 ± 18‡</td>
</tr>
<tr>
<td>M1/M2</td>
<td>2.1 ± 0.8*</td>
<td>1.6 ± 0.3</td>
<td>1.6 ± 0.5‡</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>(n = 9)</td>
<td>(n = 14)</td>
<td>(n = 16)</td>
</tr>
<tr>
<td>T1 (cm/sec)</td>
<td>61 ± 14*</td>
<td>47 ± 15</td>
<td>56 ± 9</td>
</tr>
<tr>
<td>PHT (msec)</td>
<td>38 ± 13*</td>
<td>48 ± 11†</td>
<td>63 ± 9‡</td>
</tr>
<tr>
<td>T2 (cm/sec)</td>
<td>32 ± 14</td>
<td>29 ± 13†</td>
<td>38 ± 6</td>
</tr>
<tr>
<td>T1:T2</td>
<td>2.1 ± 0.9*</td>
<td>1.5 ± 0.2</td>
<td>1.5 ± 0.3‡</td>
</tr>
<tr>
<td>Systolic function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak aortic velocity (cm/sec)</td>
<td>83.0 ± 13.0*</td>
<td>95.0 ± 19.0</td>
<td>97.0 ± 22.0</td>
</tr>
<tr>
<td>Mean acceleration (cm/sec²)</td>
<td>11.0 ± 4.0*</td>
<td>14.0 ± 2.0</td>
<td>13.0 ± 4.0</td>
</tr>
<tr>
<td>Ejection time index (msec)</td>
<td>389.0 ± 25.0</td>
<td>389.0 ± 53.0</td>
<td>397.0 ± 16.0</td>
</tr>
</tbody>
</table>

IVRT, isovolumic relaxation time; M1, peak early mitral valve flow velocity; PHT, pressure half-time; M2, peak mitral flow velocity after left atrial systole; T1, peak early tricuspid valve flow velocity; T2, peak tricuspid flow velocity after right atrial systole.

* p < 0.05, restrictive-constrictive transplant recipients vs. nonrestrictive transplant recipients.
† p < 0.05, nonrestrictive transplant recipients vs. control subjects.
‡ p < 0.05, restrictive/constrictive transplant recipients vs. control subjects.
FIGURE 4. Mitral flow velocity curve from patients with a nonrestrictive pattern of ventricular filling (upper panel) versus that from patients with a restrictive-constrictive physiology (lower panel). Note the short isovolumic relaxation time and pressure half-time and increased $M_1$ in restrictive-constrictive patients. IVRT, isovolumic relaxation time; $M_1$, peak early mitral flow velocity; $M_2$, peak mitral flow velocity at atrial systole; PHT, pressure half-time. Calibration marks on both panels are at 40 msec. Velocity calibration is 100 cm/sec vertically from baseline to the first set of twin dots.

jects. This abnormality, previously documented in other patient populations, may be related to the presence of systemic hypertension and relatively early aortic valve closure. Alternatively, delayed mitral valve opening, as a consequence of slow left ventricular relaxation, could explain the prolonged IVRT and lower peak early mitral flow velocity. Left ventricular filling would thus commence at a lower ventricular pressure and during less rapid decline of left ventricular pressure. Impaired relaxation has been described in other conditions of left ventricular hypertrophy and in cardiac transplant recipients. Although left ventricular mass was not measured in the present study, left ventricular hypertrophy is a recognized sequela of cardiac transplantation.

Deceleration of blood flow across the mitral valve (indicated from the pressure half-time) was similar in nonrestrictive transplant recipients and control subjects, suggesting similar normal ventricular pressure response to left ventricular filling in early diastole. Despite this, mitral flow velocity after atrial systole ($M_2$) was lower in nonrestrictive transplant recipients compared with control subjects. This may be related to abnormal atrial function in transplant recipients. The human allograft has enlarged atria composed of two portions: a recipient atrial remnant that may vary in size and function and a donor atrium that is incomplete. Although it is well recognized that both atria may contribute to ventricular filling, the dissociation of recipient and donor atrial contraction and relaxation may result in varying atrial pressure and varying contributions to left ventricular filling. Hence, the lower $M_2$ in nonrestrictive transplant recipients could be explained by increased overall atrial compliance as well as the influence of dissociated donor and recipient atrial function.

The shortened right ventricular pressure half-time in nonrestrictive transplant recipients compared with control subjects, despite normal diastolic pressures, suggests right ventricular restriction in these patients. These subtle abnormalities in right ventricular function may be related to incomplete recovery from early postoperative pulmonary hypertension and may be effectively borne out by the
respiratory response of T1 and by the central venous pressure recordings.12

The implications of acute and chronic diastolic dysfunction of the human allograft are uncertain. Hemodynamic evidence of acute diastolic dysfunction associated with human allograft rejection during the early postoperative period was reported by Griep et al.19 Stinson et al.20 documented an exaggerated rise in ventricular diastolic pressure on exercise in patients studied 1 year after cardiac transplantation. More recently, other investigators have documented restrictive ventricular physiology after saline infusion in otherwise normally functioning cardiac transplant recipients.12,21 In the present study, Doppler echocardiography identified hemodynamically significant diastolic dysfunction in 15% of transplant recipients.

Because some patients with restrictive-constrictive physiology appear to develop clinically significant ventricular dysfunction, it is important that the etiology of diastolic abnormalities be explored. The present study documents an association between impaired ventricular function of the human allograft and rejection incidence. This suggestion of cumulative immune-mediated ventricular dysfunction, not previously reported, could have important implications for the prevention and management of acute and chronic rejection. Since the introduction of cyclosporine, clinical and histologic features of acute rejection have become less florid22; consequently, there has been a tendency to treat less aggressively. For example, many centers, including our own, do not augment immunosuppression unless there is evidence of myocyte necrosis on biopsy specimens. Because 50% of mild rejection episodes progress to myocyte necrosis (M.E. Billingham, personal communication), recognition of associated ventricular dysfunction may influence management of these patients.

Autopsy examination of the transplanted heart supports the hypothesis that ventricular diastolic function may be due to coronary disease of the graft.23 This obliterative proliferation of the coronary artery endothelium may be a manifestation of chronic rejection, which may in turn be linked to acute rejection incidence.24 In the present study, however, there was no demonstrable relation between angiographically defined coronary artery disease and ventricular dysfunction. This is consistent with some reports but contrasts with others that document an association between rejection incidence and coronary artery disease. The discrepancy may be due to the poor sensitivity of conventional arteriography as a means of diagnosing allograft coronary artery disease. Hence, occult coronary artery disease may have contributed to the abnormal ventricular physiology noted in two patients who were subsequently found to have severe coronary artery disease within 12 months.

Fibrosis is a recognized consequence of several possible insults to the heart, of which recurrent inflammation is one. Thus, the trend toward a higher fibrosis score in patients with restrictive physiology may reasonably be attributed to higher rejection incidence in these patients. An early report of myocardial fibrosis occurring in association with cyclosporine treatment25 prompted speculation that cyclosporine may contribute to diastolic abnormalities of the allograft. More recently, Greenberg1 failed to confirm an association between myocardial fibrosis and use of cyclosporine. Our results are consistent with the absence of a direct relation between impaired ventricular function and cyclosporine use.

Finally, in a small proportion of patients, restrictive-constrictive physiology appears to develop despite an unremarkable rejection history or angiographically defined coronary artery disease, as in one patient in the present study. These relations are clearly complex and will require further study to define the link between abnormal diastolic function and immune-mediated damage of the allograft.

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