Right and Left Ventricular Function After Cardiac Transplantation
Changes During and After Rejection

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Background. Attempts to identify noninvasive markers of ventricular dysfunction accompanying acute rejection have been hampered by a lack of detailed simultaneous hemodynamic data. Therefore, we prospectively performed serial monitoring of detailed left and right heart hemodynamic parameters in cardiac transplant recipients at the time of routine endomyocardial biopsy to better define the physiology of the allograft heart during and after acute rejection.

Methods and Results. To better assess the pathophysiology of the rejection process, 18 cardiac transplant patients were prospectively studied by serial right heart micromanometer catheterization and digital image processing at the time of routine endomyocardial biopsy. Eleven patients had 18 episodes of rejection. Studies of baseline (negative biopsy preceding rejection), rejection (acute moderate rejection), and resolved (first negative biopsy after rejection) states were compared. Seven patients who did not experience an episode of rejection served as the control group. Right ventricular minimum and end-diastolic pressures increased from baseline values of 0.9±3.2 and 6.9±3.7 mm Hg, respectively, to 3.2±5.5 and 9.9±6.6 mm Hg, respectively, with rejection (both variables, p <0.05) and remained elevated despite histological resolution of rejection (4.3±5.5 and 10.0±7.1 mm Hg, respectively; p<0.05 for both variables compared with baseline values). Concurrently, right ventricular end-diastolic volumes (133±29, 119±27, and 114±30 ml; baseline, rejection, and resolved, respectively) and left ventricular end-diastolic volumes (133±24, 117±20, and 113±30 ml; baseline, rejection, and resolved, respectively) significantly decreased during rejection and remained decreased after resolution of rejection (rejection and resolved compared with baseline values, p<0.05). Right ventricular chamber stiffness (0.055±0.035, 0.085±0.057, and 0.092±0.076 mm Hg/ml; baseline, rejection, and resolution, respectively) significantly increased with rejection and remained elevated after resolution of rejection. Right ventricular peak filling rate also increased from a baseline value of 2.48±0.45 to 2.76±0.63 ml end-diastolic volumes per second with rejection (p<0.05). Elevation of right ventricular filling pressures, peak filling rate, and chamber stiffness with a concomitant decrease in end-diastolic volume is consistent with a restrictive/constrictive physiology. Mean arterial blood pressure and systemic vascular resistance were elevated after the resolution of rejection (compared with either rejection or baseline values, p<0.05) associated with a higher mean daily dose of prednisone (resolved compared with either baseline or rejection values, p<0.05). The control group experienced a time-dependent increase in mean and diastolic systemic arterial pressures (both comparisons, p<0.05) without detectable diastolic dysfunction.

Conclusions. Persistence of biventricular diastolic dysfunction may be due to an irreversible effect of rejection, although multifactorial changes in left ventricular afterload occur that may complicate serial assessment of ventricular function. (Circulation 1991;84:2409–2417)
logical rejection, are less marked with cyclosporin therapy, making noninvasive detection of rejection problematic.

Recently, multiple investigators have reported changes in left ventricular performance during rejection. Specifically, it has been observed that rejection can be associated with left ventricular diastolic restrictive/constrictive changes, whereas systolic function is relatively preserved. Indexes of diastolic function such as isovolumic relaxation times, diastolic filling period, and pressure half-times have been proposed as markers of acute rejection. Furthermore, left ventricular diastolic dysfunction and restrictive/constrictive physiology may be chronically present despite resolution of acute rejection by biopsy. There have been no studies detailing right ventricular function during rejection, although it has been proposed that the right ventricle may be more sensitive than the left ventricle to changes with rejection.

Attempts to identify noninvasive markers of ventricular dysfunction accompanying acute rejection have been hampered by a lack of detailed simultaneous hemodynamic data. Therefore, we prospectively performed serial monitoring of detailed left and right heart hemodynamic parameters in cardiac transplant recipients at the time of routine endomyocardial biopsy to better define the physiology of the allograft heart during and after acute rejection.

Methods

Patient Demographics

Eighteen patients who underwent orthotopic cardiac transplantation were studied prospectively (1–13 months after transplant) at the time of routine endomyocardial biopsy. The patients received standard triple immunosuppressive therapy (cyclosporin, azathioprine, and prednisone with OKT3 monoclonal antibody induction given for 14 days after surgery). Rejection episodes were treated with pulsed steroid doses and tapered oral prednisone therapy. Cyclosporin levels were not adjusted because of the presence or absence of acute rejection. Fifteen patients (83%) were men, and three (17%) were women. Ages at time of transplantation were 27–59 years (mean, 45.9 years). Six patients (33%) underwent initial transplantation for idiopathic cardiomyopathy, 11 (61%) for ischemic heart disease, and one (6%) for postpartum cardiomyopathy. Four patients (22%) underwent repeat transplantation because of initial graft failure. One patient in the control group had a moderate pericardial effusion without evidence of tamponade that remained unchanged during the period of study. No patient had hemodynamically significant tricuspid or mitral regurgitation as shown by Doppler echocardiography. Informed consent was obtained from all patients, and the research protocol was approved by the Sharp Memorial Institutional Review Committee.

Hemodynamics

Systemic arterial pressure was measured by automated cuff (Dynamp). A balloon flotation micromanometer thermodilution catheter (75 Hz frequency response) (El Camino Labs, San Diego, Calif.) was introduced via the right internal jugular vein. All right heart pressures were measured relative to the level of the right atrium in the following manner: After external calibration, the tip of the micromanometer was advanced into the right atrium where the height of the external fluid-filled catheter transducer was adjusted until the mean fluid-filled catheter pressure equaled the micromanometer pressure, indicating that the exact height of the right atrium had been determined. After subsequent advancement of the catheter, the micromanometer pressure reading was offset to yield a mean pressure equal to that of the fluid-filled catheter. This procedure ensured that differences in pressure measured by the micromanometer were not because of varying hydrostatic anteroposterior positions within the body. Right ventricular, right atrial, pulmonary artery, and pulmonary capillary wedge pressures (mm Hg) were measured with the micromanometer, and pulmonary and systemic vascular resistances (PVR and SVR; dyne/sec/cm −5 ) were calculated. TriPLICATE determinations of cardiac output (CO; l/min), cardiac index (CI; l/min/m²), and stroke volume (SV; ml) were made by thermodilution.

Imaging Protocol

Intravenous ventriculography was performed in a General Electric MPX single-plane angiographic suite under fluoroscopy with constant amperage (mA) and voltage (kV[P]). Analog fluoroscopic images were displayed on a black-and-white Conrac 16-in. monitor and recorded on a ¼-in. Sony 5800 U-matic broadcast-quality VCR recorder. Digital image processing was performed as previously described with a Gould Deanza IP 8500 image processor linked to a Vax 11/780 processor. A Techstore high-speed disk served as a real-time storage device for the digitized and processed images.

Nonionic iodinated contrast medium (Isovue) was injected (15 ml/sec for 3 seconds) into the superior vena cava using a power injector (Medrad). The injection was timed in a 30° right anterior oblique projection under fluoroscopy at 30 frames/sec during held midinspiration, including several preinjection beats, until complete levophase left ventricular
opacification could be seen. Baseline ECG and right ventricular pressures were recorded after FM modulation on the VCR audio channels before ventriculography. Left and right ventricular opacification images, right ventricular pressure, and ECG signal recordings were digitized on the Vax 11/780 processor with the use of a 7.5-MHz analog/digital conversion board. The cycle chosen for analysis was the optimally opacified beat, and no attempt was made to control for recipient atrial timing. Digital subtraction and pixel-by-pixel analysis of 512×512 (8-bit 256 grey scale) images were performed on the IP8500 and the Techstore high-speed disk. Ejection fraction was determined for both ventricles by a method previously validated in our laboratory and elsewhere using a secondary background subtraction curve (Figure 1). Relative volume–time curves derived from logarithmic transformation and integration of video intensity over the ventricular silhouette were normalized to end-diastolic volume, smoothed with a four-harmonic algorithm, and interpolated to approximately 200 points (10 per frame) (Figure 2). The first derivative of this curve (Figure 2) was used to determine peak and time-to-peak ejection and filling rates (PER and PFR, end-diastolic volumes per second; TPER and TPFRR, msec). End-diastolic volumes for both ventricles were calculated as thermodilution stroke volume divided by ejection fraction. Right ventricular chamber stiffness was calculated as end-diastolic pressure divided by end-diastolic volume.

Rejection Studies

Eighteen episodes of acute moderate rejection occurred in 11 patients. Nine of these represented the first clinical episode of acute moderate rejection. Hemodynamics were monitored for each patient as described during each biopsy. The first study was the last histologically negative biopsy that preceded an episode of moderate acute rejection. The second study was the episode associated with acute moderate rejection. The last study was the first subsequent biopsy free of any rejection (cellular infiltrates) following the moderate rejection. These studies were designated baseline, rejection, and resolved, respectively. The median time between baseline and rejection studies was 8 days, 33 days between rejection and resolved studies, and 58 days between baseline and resolved studies. One of the baseline studies demonstrated mild (infiltrative) rejection because of the lack of a preceding true-negative biopsy. Data for the resolved study were not obtained in one patient because of the patient’s death before resolution of rejection. In a second patient, data for the resolved study were not obtained because of the lack of a true-negative biopsy before a subsequent episode of acute moderate rejection.

Control Studies

Seven patients did not manifest an episode of acute moderate rejection during the study period and formed the control group. Two representative studies of serial hemodynamic monitoring were analyzed for each patient, selected so that the time interval between the studies was similar to that between the baseline and resolved studies in the rejection group. Median time between the two studies was 62 days.

Statistics

All hemodynamic data are expressed as mean±1 SD. Primary end point comparisons between baseline and rejection studies or the two control studies were performed using a paired Student’s t test. In addition, a two-way repeated measures analysis of variance (ANOVA) was used to determine differences among baseline, rejection, and resolved groups for each variable. Variables with groups demonstrating differences were tested with a Duncan multiple range test to determine individual group statistical significance (p<0.05).

Results

Rejection Studies

Hemodynamic data. Baseline right ventricular systolic (28.1±7.5 mm Hg), minimum (0.9±3.2 mm Hg), and end-diastolic (6.9±3.7 mm Hg) pressures rose significantly (p<0.05) with rejection (32.9±8.7, 3.2±5.5, and 9.9±6.6 mm Hg; systolic, minimum, and diastolic, respectively [Figure 3]) (see also Table 1). Although right ventricular systolic pressure returned to baseline (29.0±6.5 mm Hg) with resolution of rejection, minimum (4.3±5.5 mm Hg) and diastolic (10.0±7.1 mm Hg) pressures remained significantly elevated (compared with baseline values, p<0.05) with resolution of rejection. Morphological changes in right ventricular pressure and volume–time curves indicative of a restrictive/constrictive physiology were present in individual patients (Figure 4).

Pulmonary artery mean, systolic and diastolic, right atrial mean, and pulmonary capillary wedge pressures all rose slightly with rejection, but these changes did not achieve statistical significance. Heart rate, PVR, CO, and CI did not vary significantly with the onset or resolution of rejection. Arterial systolic, diastolic, and mean pressures at baseline (136±16, 85±12, and 99±15 mm Hg, respectively) did not change during rejection (137±19, 85±14, and 103±17 mm Hg, respectively). However, arterial systolic (143±21 mm Hg), diastolic (95±13), and mean (111±15) blood pressures were significantly elevated (compared with baseline values, p<0.05) with resolution of rejection. Systemic vascular resistance rose from baseline (1,238±407 dyne/sec/cm5) and rejection (1,276±352 dyne/sec/cm5) values with resolution of rejection (1,558±478 dyne/sec/cm2), resolved compared with either baseline or rejection values, p<0.05. Baseline mean daily prednisone dose (32±18, mg/day) was unchanged with rejection (30±22 mg/day) but increased (65±25 mg/day, compared with baseline and rejection values, p<0.05) at the time of resolution of rejection.
FIGURE 1. Top panel: Digital subtraction image after logarithmic transformation of right ventricle at end diastole with region of interest outlined. Bottom panel: Digital subtraction image of right ventricle at end systole with secondary background subtraction curve. Average intensity from the background subtraction region was used to mathematically correct for errors caused by scatter or misregistration.
Ventriculography. Ejection fraction did not significantly vary for either ventricle with the onset or resolution of rejection (see Table 2). Right ventricular peak filling rate rose from a baseline value of 2.48±0.45 to 2.76±0.63 end-diastolic volumes per second with rejection ($p<0.05$). Right ventricular peak filling rate returned to baseline levels with resolution of rejection (2.52±0.66 end-diastolic volumes per second). Peak ejection rates, left ventricular peak filling rate, and time-to-peak filling and ejection rates did not significantly vary with onset or resolution of rejection. Calculated end-diastolic volumes were significantly lower (rejection or resolved compared with baseline values, $p<0.05$) during and after the resolution of rejection for both the right (133±29, 119±27, and 114±30 ml; baseline, rejection, and resolved, respectively) and left ventricles (133±24, 117±20, and 113±30 ml; baseline, rejection, and resolved, respectively). Right ventricular chamber stiffness (0.055±0.035, 0.085±0.057, and 0.092±0.076 mm Hg/ml; baseline, rejection, and resolved, respectively). Right ventricular pressures increased significantly during rejection. Right ventricular peak filling rate was significantly higher during rejection, consistent with a restrictive/constrictive physiology, whereas left ventricular peak filling rate was relatively unchanged. Calculated end-diastolic volumes for both ventricles were significantly lower, and right ventricular chamber stiffness was significantly higher after rejection. Mean, systolic, and diastolic systemic arterial pressures and SVR all increased significantly in the period after rejection, associated with a significantly larger mean daily dose of prednisone increased to treat the preceding rejection episode. These hemodynamic changes were not seen in the control group, although a time-dependent increase in mean and diastolic systemic arterial pressures was noted.

Despite relatively normal heart function after cardiac transplantation, minor chronic hemodynamic dysfunctions are typically present in the transplant patient, possibly related to perioperative ischemia and reperfusion injury, hypertension, drug therapy, and/or rejection changes. Greenberg et al described several hemodynamic abnormalities in 18

**Control Studies (Table 3)**

Mean (104±13 to 113±7 mm Hg) and diastolic (87±14 to 97±6 mm Hg) systemic arterial pressures rose significantly between the two studies (both comparisons, $p<0.05$). All other hemodynamic and ventriculographic indexes did not vary significantly.

**Discussion**

To our knowledge, this is the first study to describe detailed hemodynamic changes in both right and left ventricular function during rejection as well as resolution of rejection. Right ventricular diastolic and minimum pressures rose significantly with rejection and remained elevated despite histological resolution of rejection by endomyocardial biopsy. Right ventricular systolic pressure also rose during rejection but returned to baseline after resolution of rejection. Right ventricular peak filling rate was significantly higher with rejection, consistent with a restrictive/constrictive physiology, whereas left ventricular peak filling rate was relatively unchanged. Calculated end-diastolic volumes for both ventricles were significantly lower, and right ventricular chamber stiffness was significantly higher during and after rejection. Mean, systolic, and diastolic systemic arterial pressures and SVR all increased significantly in the period after rejection, associated with a significantly larger mean daily dose of prednisone increased to treat the preceding rejection episode. These hemodynamic changes were not seen in the control group, although a time-dependent increase in mean and diastolic systemic arterial pressures was noted.

Despite relatively normal heart function after cardiac transplantation, minor chronic hemodynamic dysfunctions are typically present in the transplant patient, possibly related to perioperative ischemia and reperfusion injury, hypertension, drug therapy, and/or rejection changes. Greenberg et al described several hemodynamic abnormalities in 18

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**Figure 2.** Volume–time curve (top) normalized to end-diastolic volume. First derivative (bottom) of volume–time curve; peak ejection and filling rates given in end-diastolic vol/sec.

**Figure 3.** Graph showing right ventricular (RV) pressures before and during acute moderate rejection.
asymptomatic transplant patients undergoing annual evaluation; this included systemic hypertension (10 of 18), elevated left ventricular end-diastolic pressure (six of 18), low ejection fraction (six of 18), and depressed cardiac output (four of 18). Systemic hypertension is prevalent with cyclosporin therapy and routinely requires treatment. Fine interstitial fibrosis, associated with cyclosporin therapy and proliferative graft atherosclerosis, are also chronic consequences of orthotopic cardiac transplantation.

Orthotopic cardiac transplantation places significant functional burden on the right ventricle. Right ventricular dilatation and remodeling, associated with pulmonary hypertension, have been documented. Latent right ventricular restrictive/constrictive patterns that appear with rapid volume infusion also exist. These ventricular abnormalities may in part be related to myocardial fibrosis as well as to specific postoperative right ventricular enlargement because of preexisting heart failure–related increased pulmonary vascular resistance.

Previous studies have documented left ventricular diastolic hemodynamic changes during rejection in the transplanted heart. Griep et al were the first investigators to describe diastolic dysfunction associated with acute rejection after cardiac transplantation; however, hemodynamic parameters were not reported. Dawkins et al and Valantine et al observed a shortened isovolumic relaxation time and pressure half-time by echocardiography in the left ventricle during rejection. Paulsen et al noted prolonged duration of rapid diastolic filling with rejection, also indicative of abnormal diastolic function. Although Dawkins et al reported that isovolumic relaxation time returned to baseline after the resolution of acute rejection, a subsequent study by Valantine et al showed that diastolic dysfunction, associated with increased frequency of myocardial rejection episodes, may be cumulative and not completely reversible.

In models of rejection, myocyte dysfunction due solely to leukocyte cytokines, such as tumor necrosis factor and interleukin-1 released during acute moderate rejection, would be expected to be reversible. Nevertheless, failure of right ventricular minimum and end-diastolic pressures to return to baseline values after resolution of rejection supports Valantine et al’s hypothesis that rejection causes possible cumulative and irreversible damage to the myocardium. Our observations that end-diastolic volumes for both ventricles decrease and right ventricular chamber stiffness increases during rejection (and remain abnormal even after resolution of rejection by biopsy) indicate that elevated filling pressures are probably caused by the loss of mechanical ventricular distensibility instead of by volume loading or other glucocorticoid effects, which would be expected to be accompanied by an increase in end-diastolic ventricular volume and unchanged right ventricular chamber stiffness. Hypertrophy of surviving myocytes might play a role in the preservation of systolic function after acute moderate rejection, but irreversible changes in diastolic function are also present.

### Table 1. Hemodynamic Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline (n=18)</th>
<th>Rejection (n=18)</th>
<th>Resolved (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>83±9</td>
<td>85±9</td>
<td>90±12</td>
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<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>136±16</td>
<td>137±19</td>
<td>143±21†</td>
</tr>
<tr>
<td>Diastolic</td>
<td>85±13</td>
<td>85±14</td>
<td>95±13*</td>
</tr>
<tr>
<td>Mean</td>
<td>99±15</td>
<td>103±17</td>
<td>111±15*</td>
</tr>
<tr>
<td>Mean right atrial pressure (mm Hg)</td>
<td>6.6±3.4</td>
<td>8.6±6.6</td>
<td>7.9±6.4</td>
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<tr>
<td>Right ventricular pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>28.1±7.5</td>
<td>32.9±8.7*</td>
<td>29.0±6.5</td>
</tr>
<tr>
<td>Minimum</td>
<td>0.9±3.2</td>
<td>3.2±5.5*</td>
<td>4.3±5.5*</td>
</tr>
<tr>
<td>Diastolic</td>
<td>6.9±3.7</td>
<td>9.9±6.6*</td>
<td>10.0±7.1*</td>
</tr>
<tr>
<td>Pulmonary artery pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>19.6±4.9</td>
<td>22.1±6.1</td>
<td>20.2±5.6</td>
</tr>
<tr>
<td>Systolic</td>
<td>29.5±6.5</td>
<td>31.7±8.6</td>
<td>27.5±7.2</td>
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<tr>
<td>Diastolic</td>
<td>14.2±3.5</td>
<td>16.5±5.4</td>
<td>15.9±5.3</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (mm Hg)</td>
<td>12.4±5.0</td>
<td>14.5±7.4</td>
<td>13.8±6.4</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>6.3±1.4</td>
<td>6.1±1.3</td>
<td>5.6±1.5</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>3.4±0.6</td>
<td>3.2±0.6</td>
<td>2.9±0.7</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>76±18</td>
<td>72±17</td>
<td>65±22</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyne/cm²)</td>
<td>1,238±407</td>
<td>1,276±352</td>
<td>1,558±478†</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (dyne/cm²)</td>
<td>97±55</td>
<td>104±49</td>
<td>112±73</td>
</tr>
</tbody>
</table>

Values are mean±SD.  
* p<0.05 compared with baseline.  
† p<0.05 compared with rejection.
Figure 4. Line graphs showing right ventricular pressure and right and left ventricular volume-time curves in an individual patient showing morphological changes indicative of a restrictive/constrictive physiology.

Table 2. Ventriculography Data

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n=18)</th>
<th>Rejection (n=18)</th>
<th>Resolved (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Right ventricle</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>58±9</td>
<td>61±9</td>
<td>57±11</td>
</tr>
<tr>
<td>Peak filling rate (end-diastolic vol/sec)</td>
<td>2.48±0.45</td>
<td>2.76±0.63*</td>
<td>2.52±0.66</td>
</tr>
<tr>
<td>Peak ejection rate (end-diastolic vol/sec)</td>
<td>-3.12±0.70</td>
<td>-3.31±0.59</td>
<td>-2.78±0.57</td>
</tr>
<tr>
<td>Time-to-peak filling rate</td>
<td>131±19</td>
<td>139±23</td>
<td>140±27</td>
</tr>
<tr>
<td>Time-to-peak ejection rate</td>
<td>122±29</td>
<td>131±27</td>
<td>126±3</td>
</tr>
<tr>
<td>End-diastolic volume (ml)</td>
<td>133±29</td>
<td>119±27*</td>
<td>114±30*</td>
</tr>
<tr>
<td>Chamber stiffness (mm Hg/ml)</td>
<td>0.055±0.035</td>
<td>0.085±0.057*</td>
<td>0.092±0.076*</td>
</tr>
<tr>
<td><strong>Left ventricle</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>60±12</td>
<td>62±8</td>
<td>58±11</td>
</tr>
<tr>
<td>Peak filling rate (end-diastolic vol/sec)</td>
<td>2.84±0.87</td>
<td>2.95±0.84</td>
<td>2.38±0.64</td>
</tr>
<tr>
<td>Peak ejection rate (end-diastolic vol/sec)</td>
<td>-3.31±1.28</td>
<td>-3.35±0.81</td>
<td>-3.11±1.18</td>
</tr>
<tr>
<td>Time-to-peak filling rate</td>
<td>142±26</td>
<td>144±19</td>
<td>154±35</td>
</tr>
<tr>
<td>Time-to-peak ejection rate</td>
<td>136±33</td>
<td>147±34</td>
<td>149±37</td>
</tr>
<tr>
<td>End-diastolic volume (ml)</td>
<td>133±24</td>
<td>117±20*</td>
<td>113±30*</td>
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</tbody>
</table>

Values are mean±SD.
*p<0.05 compared with baseline.
of rejection. Prednisone therapy is associated with a Cushingoid state including an increased incidence of hypertension without overt sodium or fluid retention.27-29 Although the mechanism of its action is not clear, it appears that increased prednisone therapy during the period after rejection increases systemic arterial pressures and systemic vascular resistance. Methods for noninvasive detection of resolution of rejection will be hampered by possible cumulative effects of rejection, altered physiological states caused by changing drug treatments, and time-dependent effects such as increased hypertension seen in the control group.

One limitation of our study is the relatively less-detailed data available from the left ventricle. Left ventricular pressures were not measured directly; therefore, only limited comparisons between left ventricular and right ventricular physiology during and after rejection can be made. Also, data derived from levophase digital imaging may be inherently less precise than dextrophase right ventricular imaging data because of noise caused by residual contrast in the right heart and pulmonary vasculature. Echocardiographic studies were performed as clinically indicated and were not available for all study dates. Although variable degrees of tricuspid regurgitation may have affected the relative changes in calculated right ventricular end-diastolic volume, changes were seen of similar direction and magnitude as those of calculated left ventricular end-diastolic volume. Furthermore, no consistent change in tricuspid regurgitation occurs during acute rejection.30 Finally, doses of medications were not specifically maintained constant during the period of study. Indeed, increases in prednisone dosage clinically indicated for the treatment of rejection may have contributed to hemodynamic changes after the resolution of rejection.

Serial functional ventricular studies, particularly of the right ventricle, should be of value in detecting the diastolic dysfunction that accompanies rejection. However, they will be less useful in predicting histological resolution of rejection. Because of the number of factors involved, it is unlikely that monitoring of any functional parameter will replace biopsy as a means of rejection surveillance but instead aid in its timing. The present study demonstrates that diastolic dysfunction persists beyond the presence of cellular infiltrates, which is not surprising since myocyte necrosis is an irreversible cellular process that elicits a healing response. Further investigation to determine the acute and persisting effects of rejection is justified to help in the recognition, prediction, and prevention of acute moderate rejection characterized by myocyte necrosis after heart transplantation. Whether chronic graft dysfunction represents a culmination of partially but not totally reversible insults to the myocardium is unclear. If so, more aggressive clinical surveillance or immunosuppressive regimens to limit the amount of myocyte necrosis may be justified to improve long-term graft viability.

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References

Key Words: diastolic dysfunction • ventricular interaction • hypertension • immunosuppression
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