Deficient Acceleration of Left Ventricular Relaxation During Exercise After Heart Transplantation

Walter J. Paulus, MD, PhD; Jean G.F. Bronzwaer, MD; Herbert Felice, MD; Narine Kishan, MD; and Francis Wellens, MD

**Background.** The exercise-induced rise in left ventricular filling pressures after cardiac transplantation is considered to be the result of a blunted heart rate response, of elevated venous return, and of unfavorable passive late-diastolic properties of the cardiac allograft. In contrast to passive late-diastolic left ventricular properties, the effect of left ventricular relaxation on the exercise-induced rise in left ventricular filling pressures of the cardiac allograft has not yet been studied. In the present study, the response of left ventricular relaxation to exercise was investigated in transplant recipients and compared with left ventricular relaxation observed in normal control subjects exercised to the same heart rate. Moreover, the response of left ventricular relaxation of the cardiac allograft to β-adrenergoreceptor stimulation, to reduced left ventricular afterload, and to increased myocardial activator calcium was investigated by infusion of dobutamine and of nitroprusside and by postextrasystolic potentiation.

**Methods and Results.** Twenty-seven transplant recipients were studied 1 year (n=17), 2 years (n=7), 3 years (n=2), and 4 years (n=1) after transplantation. All patients were free of rejection and of significant graft atherosclerosis at the time of study. Tip-micromanometer left ventricular pressure recordings and cardiac hemodynamics were obtained at rest, during supine bicycle exercise stress testing (n=27), during dobutamine infusion at a heart rate matching the heart rate at peak exercise (n=8), during nitroprusside infusion (n=9), and after postextrasystolic potentiation (n=10). Tip-micromanometer left ventricular pressure recordings were also obtained in a normal control group (n=9) at rest and during supine bicycle exercise stress testing to a heart rate, which matched the heart rate of the transplant recipient group at peak exercise. Left ventricular relaxation rate was measured by calculation of a time constant of left ventricular pressure decay (T) derived from an exponential curve fit to the digitized tip-micromanometer left ventricular pressure signal. In the transplant recipients, exercise abbreviated T from 43±6 to 40±8 msec (p<0.01) and caused a rise of left ventricular minimum diastolic pressure (LVMDP) from 5±2 to 9±6 mm Hg (p<0.001). In normal control subjects, exercise induced a 2.5 times larger abbreviation of T (from 42±7 to 34±6 msec; p<0.001) and a small drop in LVMDP from 5±2 to 4±3 mm Hg (p<0.05). In the transplant recipients, the change in T (ΔT) from rest to exercise was variable ranging from an abbreviation, as observed in normal controls, to a prolongation and was significantly correlated with the change in RR interval (ΔRR) and the change in left ventricular end-diastolic pressure (ALVEDP) (ΔT=0.068ΔRR+0.58ΔLVEDP−2.2; r=0.76; p<0.001). In a first subset of transplant recipients (n=8), dobutamine infusion resulted in a heart rate equal to the heart rate at peak exercise, a left ventricular end-diastolic pressure (8±7 mm Hg) lower than at peak exercise (22±6 mm Hg; p<0.05) and a T value (32±9 msec), which was shorter than both resting value (44±5 msec; p<0.005) and value observed at peak exercise (40±8 msec; p<0.01). In a second subset of transplant recipients (n=9), nitroprusside infusion and postextrasystolic potentiation resulted in a significant prolongation of T from 41±7 to 56±10 msec (p<0.05) and a characteristic negative dP/dt upstroke pattern with downward convexity as previously observed in left ventricular hypertrophy.

**Conclusions.** Exercise after cardiac transplantation resulted in a smaller acceleration of left ventricular relaxation than in a normal control group exercised to the same heart rate. These transplant recipients, who made the largest use of left ventricular preload reserve during exercise, showed least acceleration of left ventricular relaxation. This association between a rise of left ventricular end-diastolic pressure and slower left ventricular isovolumic relaxation was also evident in the individual transplant recipient from the slower isovolumic relaxation during exercise than during dobutamine infusion despite equal heart rates. After postextrasystolic potentiation during nitroprusside infusion, a slow left ventricular relaxation with downward convexity of the dP/dt signal was observed in the cardiac allograft. This finding suggests depressed function of the sarcoplasmic reticulum in left ventricular myocardium after transplantation, which could be related either to decreased adrenergic tone or to foregoing ischemic injury during organ retrieval or to hypertrophy caused by cyclosporine induced arterial hypertension. (*Circulation* 1992;86:1175–1185)

**KEY WORDS** • heart transplantation • hemodynamics • diastolic function • exercise
Exercise elevates left ventricular filling pressures in the cardiac allograft after orthotopic heart transplantation. This rise in left ventricular filling pressures, which decreases exercise tolerance after heart transplantation, has been related to an inadequate heart rate response and therefore an excessive dependence on preload reserve to raise cardiac output. The use of preload reserve induces a prompt rise in left ventricular filling pressures because of a diastolic left ventricular pressure-volume relation, which is steeper than normal and shifted to the left. This altered diastolic left ventricular pressure-volume relation of the allograft has been variably ascribed to a mismatch of donor-recipient heart size, to cyclosporine-induced arterial hypertension, to intervening episodes of allograft rejection, or to ischemic injury incurred during organ retrieval or caused by graft vascular disease. The exercise-induced rise in left ventricular filling pressures after cardiac transplantation is therefore considered to be the result of unfavorable passive late-diastolic left ventricular properties of the allograft and of a mismatch between venous return and heart rate.

In contrast to passive late-diastolic left ventricular properties, the effect of left ventricular relaxation on the exercise-induced rise of left ventricular filling pressures after heart transplantation has not yet been investigated. After heart transplantation, denervation or a nonuniform and limited degree of reinnervation could lead to a blunted response of left ventricular relaxation to exercise, which could especially affect early diastolic left ventricular pressures. The important effect during exercise of left ventricular pressure decay on early diastolic left ventricular pressures is evident from previous observations in patients with coronary artery disease. When exercise induces ischemia in patients with coronary artery disease, left ventricular pressure decay is slower than normal and markedly elevates the early diastolic left ventricular pressure nadir.

In the present study, the response of left ventricular relaxation to exercise was investigated by obtaining high-fidelity tip-micromanometer left ventricular pressure recordings during supine bicycle exercise stress testing in transplant recipients and in a normal control group of patients, which was exercised to the same heart rate as the transplant recipients. To elucidate whether the abnormal response to exercise of left ventricular relaxation of the cardiac allograft could be attributed to a decreased responsiveness of left ventricular relaxation to \( \beta \)-adrenoreceptor stimulation, dobutamine was infused after the exercise stress test in a subset of transplant recipients to achieve a heart rate, which matched the heart rate at peak exercise. In another subset of transplant recipients, the effects on left ventricular relaxation of increased myocardial activator calcium and of left ventricular afterload were investigated by postextrasystolic potentiation and by administration of nitroprusside.

Methods

Patients

Control patients. The control study group comprised nine patients (four women, five men; ages, 36–66 years; mean age, 53 years) referred for evaluation of chest pain. There was no clinical or echocardiographic evidence of congenital, valvular, or cardiomyopathic heart disease. Left ventricular and coronary angiography revealed normal left ventricular volumes, normal ejection fraction, and absence of coronary artery disease. At the time of study, no patient was taking positive or negative inotropic drugs.

Transplant recipients. Twenty-seven patients (18 men, nine women; mean age, 50 years; age range, 24–66 years) were studied after orthotopic heart transplantation. Seventeen patients were studied 1 year after transplantation, seven patients 2 years after transplantation, two patients 3 years after transplantation, and one patient 4 years after transplantation. Patients were treated with cyclosporine, prednisone, and azathioprine immunosuppression. At the time of study, no patient had biopsy evidence of rejection requiring therapy. Eleven patients had experienced previous episodes (≤ two episodes) of moderate to severe allograft rejection, as assessed by serial endomyocardial biopsies and clinical course. Eighteen patients received treatment for arterial hypertension, which consisted of calcium channel blockers in 13 patients, of ACE inhibitors in two patients, and of prazosin in three patients. Routine annual postoperative left ventricular and coronary angiography revealed normal left ventricular function in all patients (ejection fraction, 72±10%; left ventricular end-diastolic volume index, 56±17 ml/m\(^2\)) and angiographically normal coronary arteries in the absence of accelerated graft atherosclerosis. Left ventricular end-diastolic volume index and ejection fraction were calculated from single-plane left ventricular cineangiograms performed in 30\(^\circ\) right anterior oblique projection using the area-length method and a regression equation. At the time of study, no patient received digitalis, \( \beta \)-blockers, or calcium channel blockers. The study protocol was approved by the local ethical committee. All patients gave informed consent, and there was no complication related to the procedure or study protocol.

Hemodynamic Studies

Catheterization protocol. Transplant recipients (\( n=27 \)) underwent left-right heart catheterization, left ventricular angiography, and coronary angiography as part of their routine annual postoperative clinical evaluation using right femoral artery and vein. Control patients (\( n=9 \)) underwent left heart catheterization, left ventricular angiography, and coronary angiography. All pressures were referenced to atmospheric pressure at the level of the midchest. Left ventricular pressure was measured with a high-fidelity tip-micromanometer catheter calibrated externally against a mercury reference and matched against luminal pressure. Pressure

From the Cardiovascular Center (W.J.P., H.F.), the Department of Cardiovascular Surgery (N.K., F.W.), O.L.V.Ziekenhuis, Aalst, Belgium; and the Department of Cardiology (J.G.F.B.), Free University Hospital, Amsterdam, The Netherlands.


H.F. was the recipient of an I.C.I. Belgium Research Fellowship Award.

Address for correspondence: Walter J. Paulus, MD, PhD, Cardiovascular Center, O.L.V.Ziekenhuis, Moorselbaan, B 9300 Aalst, Belgium.

Received September 30, 1991; revision accepted June 24, 1992.
Ventricular angiogram was obtained

text of transplant recipients

by administration of nitroprusside in a second subset of transplant recipients (n=10), who underwent bicycle exercise stress testing but no dobutamine infusion. The effects of postextrasystolic potentiation on left ventricular pressure decay were investigated by premature ventricular beats, which were induced at minimum coupling interval by a right ventricular pacing catheter (Table 5, postextrasystolic potentiation). Subsequently, in nine of the 10 patients, in

<table>
<thead>
<tr>
<th>Patient</th>
<th>Heart rate (bpm)</th>
<th>LVSPSP (mm Hg)</th>
<th>LV dP/dtmax (mm Hg/sec)</th>
<th>Cardiac output (l/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest Exercise</td>
<td>Rest Exercise</td>
<td>Rest Exercise</td>
<td>Rest Exercise</td>
</tr>
<tr>
<td>1</td>
<td>90 109</td>
<td>163 155</td>
<td>1,480 1,640</td>
<td>6.3 9.0</td>
</tr>
<tr>
<td>2</td>
<td>96 112</td>
<td>158 180</td>
<td>1,780 2,300</td>
<td>5.6 9.0</td>
</tr>
<tr>
<td>3</td>
<td>74 84</td>
<td>168 194</td>
<td>1,250 1,380</td>
<td>4.6 7.0</td>
</tr>
<tr>
<td>4</td>
<td>85 93</td>
<td>162 165</td>
<td>1,820 2,300</td>
<td>6.2 6.9</td>
</tr>
<tr>
<td>5</td>
<td>92 122</td>
<td>131 143</td>
<td>1,794 2,816</td>
<td>6.7 8.4</td>
</tr>
<tr>
<td>6</td>
<td>86 93</td>
<td>146 188</td>
<td>3,174 3,850</td>
<td>5.3 5.4</td>
</tr>
<tr>
<td>7</td>
<td>99 103</td>
<td>156 158</td>
<td>2,665 2,619</td>
<td>7.5 9.0</td>
</tr>
<tr>
<td>8</td>
<td>74 100</td>
<td>146 140</td>
<td>1,890 2,940</td>
<td>6.5 10.2</td>
</tr>
<tr>
<td>9</td>
<td>79 103</td>
<td>149 163</td>
<td>1,860 2,520</td>
<td>4.1 7.3</td>
</tr>
<tr>
<td>10</td>
<td>78 88</td>
<td>143 163</td>
<td>1,280 1,880</td>
<td>5.3 7.4</td>
</tr>
<tr>
<td>11</td>
<td>72 94</td>
<td>123 195</td>
<td>1,020 1,800</td>
<td>6.5 10.4</td>
</tr>
<tr>
<td>12</td>
<td>79 94</td>
<td>154 180</td>
<td>1,360 1,600</td>
<td>4.7 6.8</td>
</tr>
<tr>
<td>13</td>
<td>73 96</td>
<td>150 197</td>
<td>1,340 1,920</td>
<td>3.1 5.3</td>
</tr>
<tr>
<td>14</td>
<td>86 113</td>
<td>125 167</td>
<td>1,080 1,960</td>
<td>5.1 8.9</td>
</tr>
<tr>
<td>15</td>
<td>70 79</td>
<td>162 166</td>
<td>1,440 1,660</td>
<td>5.3 7.0</td>
</tr>
<tr>
<td>16</td>
<td>90 96</td>
<td>142 180</td>
<td>1,213 1,493</td>
<td>4.3 7.3</td>
</tr>
<tr>
<td>17</td>
<td>85 94</td>
<td>141 148</td>
<td>1,600 1,720</td>
<td>6.0 7.9</td>
</tr>
<tr>
<td>18</td>
<td>94 105</td>
<td>144 149</td>
<td>1,340 1,600</td>
<td>6.6 9.1</td>
</tr>
<tr>
<td>19</td>
<td>84 102</td>
<td>177 170</td>
<td>1,240 1,280</td>
<td>5.3 8.5</td>
</tr>
<tr>
<td>20</td>
<td>81 114</td>
<td>142 177</td>
<td>1,400 2,013</td>
<td>7.3 10.1</td>
</tr>
<tr>
<td>21</td>
<td>91 110</td>
<td>149 178</td>
<td>1,480 2,173</td>
<td>6.1 8.7</td>
</tr>
<tr>
<td>22</td>
<td>95 111</td>
<td>116 120</td>
<td>960 1,293</td>
<td>5.7 9.5</td>
</tr>
<tr>
<td>23</td>
<td>94 106</td>
<td>177 174</td>
<td>1,760 2,200</td>
<td>7.1 10.3</td>
</tr>
<tr>
<td>24</td>
<td>77 84</td>
<td>180 182</td>
<td>1,320 1,460</td>
<td>4.3 5.4</td>
</tr>
<tr>
<td>25</td>
<td>99 120</td>
<td>198 252</td>
<td>1,280 1,900</td>
<td>8.9 13.1</td>
</tr>
<tr>
<td>26</td>
<td>100 111</td>
<td>136 149</td>
<td>1,360 1,680</td>
<td>5.1 7.4</td>
</tr>
<tr>
<td>27</td>
<td>92 107</td>
<td>155 179</td>
<td>1,400 1,540</td>
<td>5.5 8.4</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>85 100*</td>
<td>152 171*</td>
<td>1,541 1,983*</td>
<td>5.7 8.3*</td>
</tr>
</tbody>
</table>

LVSPSP, left ventricular peak systolic pressure; LV dP/dtmax, left ventricular maximum rate of pressure development.

*p<0.001.

Signals and a bipolar standard lead of the electrocardiogram were recorded on a Gould ES 1000 multichannel recorder. Pressure signals were digitized on-line with a Hewlett Packard 9836 computer and averaged throughout a complete respiratory cycle.

**Bicycle exercise stress testing.** Left ventricular pressure and left ventricular dP/dt were recorded before and after the patient's feet were attached to the pedals of the bicycle and subsequently at one-minute intervals during supine bicycle exercise, which was performed at a constant submaximal workload for 6 minutes (Tables 1-3). In transplant recipients, cardiac output measurements (n=27) and right atrial pressure recordings (n=5) were obtained before exercise and during the last minute of exercise. The exercise factor was calculated as the ratio of the exercise-induced increment of cardiac output to the increment of oxygen consumption (normal value, 6.0). In six transplant recipients, a second left ventricular angiogram was obtained in the last minute of exercise.

**Effects of \(\beta_1\)-adrenoreceptor stimulation.** To investigate responsiveness of the cardiac allograft to \(\beta_1\)-adrenoreceptor stimulation in a subset of transplant recipients (n=8), the effect of dobutamine on left ventricular pressure decay was investigated after the exercise stress test after return of hemodynamics to baseline conditions (Table 4). Dobutamine infusion rate was adjusted to achieve a heart rate response equal to the maximal heart rate observed during exercise. Dobutamine was administered intravenously at an infusion rate of 2.5 \(\mu\)g/kg per minute in six patients, of 3.75 \(\mu\)g/kg per minute in one patient, and of 5 \(\mu\)g/kg per minute in one patient.

**Effects of postextrasystolic potentiation and arterial vasodilation.** The effects on left ventricular relaxation of increased myocardial activator calcium and reduced left ventricular afterload were investigated by postextrasystolic potentiation and by administration of nitroprusside in a subset of transplant recipients (n=10), who underwent bicycle exercise stress testing but no dobutamine infusion. The effects of postextrasystolic potentiation on left ventricular pressure decay were investigated by premature ventricular beats, which were induced at minimum coupling interval by a right ventricular pacing catheter (Table 5, postextrasystolic potentiation). Subsequently, in nine of the 10 patients, in
whom extrasystoles were administered, a nitroprusside infusion was started at an infusion rate of 0.5 μg/kg per minute and was increased by 0.5 μg/kg per minute every 3 minutes until mean aortic pressure had fallen by 20–30 mm Hg as compared with baseline measurements (Table 5, nitroprusside infusion), and premature ventricular beats at an identical coupling interval were again induced (Table 5, nitroprusside + postextrasystolic potentiation). The postextrasystolic data (Table 5) were the average of three postextrasystolic beats at an identical minimum coupling interval in each patient.

**Data Analysis**

The time constant of left ventricular pressure decay (T) was derived from the digitized pressure data points of isovolumic left ventricular relaxation using an exponential curve fit with zero asymptote pressure. Pressure data points were obtained at 3-msec intervals by digitizing the left ventricular pressure signal from the moment of left ventricular dP/dt min to a time at which left ventricular pressure equaled left ventricular end-diastolic pressure plus 5 mm Hg. When T values were compared with each other (Tables 2–5), the reported T values were derived for each patient from curve fits with identical starting point (the lowest pressure at which left ventricular dP/dt min occurred) and end point (the pressure that equaled the highest left ventricular end-diastolic pressure plus 5 mm Hg). This avoids erroneous changes in T induced by a shift of the starting or end point of the time constant analysis.\(^{13-15}\) The correlation coefficient for the exponential curve fits of the time constant analysis always exceeded 0.98.

Phase plane plots of the left ventricular pressure signal during isovolumic relaxation were constructed by matching corresponding left ventricular pressure and left ventricular dP/dt data points (Figures 4 and 6).\(^{14}\)

All data were reported as mean±SD. Statistical significance was set at p<0.05 and was obtained by Bonferroni method for a multiple comparison analysis and by Student's t test for paired data.

**Results**

**Exercise Hemodynamics of Cardiac Allograft**

The effects of supine bicycle exercise stress testing on systolic and diastolic left ventricular function of the
cardiac allograft are summarized in Tables 1 and 2 and compared with left ventricular function of a normal control group of patients exercised to the same heart rate in Table 3. In the normal control group of patients, exercise induced a rise in LVSP from 125±19 to 150±21 mm Hg (p<0.01), in left ventricular dP/dt max from 1,331±264 to 1,656±251 mm Hg/sec (p<0.05), and in left ventricular dP/dt min from 1,547±276 to 2,041±424 mm Hg/sec (p<0.001). Exercise induced a rise in heart rate from 72±9 to 99±10 beats per minute (p<0.001). Left ventricular minimum diastolic pressure fell from 5±2 to 4±3 mm Hg (p<0.05), whereas left ventricular end-diastolic pressure (LVEDP) remained unaltered (17±5 mm Hg). In the transplant recipients, exercise induced a significant rise in left ventricular peak systolic pressure (LVSP), left ventricular dP/dt max, and left ventricular dP/dt min (Tables 1 and 2). In contrast to the control group, left ventricular minimum diastolic pressure (LVMEDP) and LVEDP rose during exercise after transplantation (Table 2). In the transplant recipients, the exercise factor (exercise factor= ratio of the increase in cardiac output divided by the corresponding increase in oxygen consumption) equaled 6.7±2.3 (normal value=6.0). In these transplant recipients (n=5), in whom right atrial pressure was measured at rest and at peak exercise, right atrial pressure rose from 4±2 to 8±3 mm Hg (p<0.01). In these transplant recipients (n=6), in whom a second left ventricular angiogram was performed at peak exercise, left ventricular end-diastolic volume index rose from 60±8 to 75±10 ml/m² (p<0.01). Left ventricular ejection volume index (LVESVI) and left ventricular ejection fraction (LVEF) remained unaltered (LVESVI rest, 20±6 ml/m²; LVESVI exercise, 20±9 ml/m², p=NS; LVEF rest, 66±9%; LVEF exercise, 72±13%, p=NS). Diastolic left ventricular pressure-volume relations at rest and during exercise obtained in a single patient, representative of the transplant recipient group, are shown in Figure 1.

### Acceleration of Left Ventricular Relaxation During Exercise

The control group of patients showed a consistent and significant abbreviation of the time constant of left ventricular pressure decay from 42±7 to 34±6 msec (p<0.001), when exercised to a heart rate, which matched the heart rate at peak exercise in the transplant recipient group. In the transplant recipients, the time constant of left ventricular pressure decay shortened slightly at peak exercise from 43±6 to 40±8 msec (p<0.01), but the response of left ventricular relaxation was highly variable (Table 2), ranging from an abbreviation (Figure 2) as observed in the normal control group to an unchanged value (Figure 3) or even a prolongation. Despite matching heart rates at peak exercise, the abbreviation of the time constant of left ventricular pressure decay was 2.5 times larger in the normal control group than in the transplant recipient group (Table 3). On multiple regression analysis for the pooled transplant recipient data (n=27), the change in the time constant of left ventricular relaxation from rest to exercise (ΔT) was significantly correlated with the change in RR interval (ΔRR) and with the change in LVEDP (ΔLVEDP) (ΔT=0.068 ΔRR+0.58 ΔLVEDP−2.2; r=0.76; p<0.001). The partial regressions for each independent variable were statistically significant (for ΔRR, p<0.001; for ΔLVEDP, p<0.001) and both ΔRR and ΔLVEDP were mutually independent as evident from the ab-

![Graph showing diastolic left ventricular pressure-volume relations at rest (◇) and at peak exercise (○) observed in a single patient, which is representative of the transplant recipient group.](http://circ.ahajournals.org/content/117916622/Fig1.jpg)
TABLE 5. Effects of Nitroprusside Infusion and Postextrasystolic Potentiation on Diastolic Function of Cardiac Allograft

<table>
<thead>
<tr>
<th></th>
<th>Rest (n=10)</th>
<th>PESP (n=10)</th>
<th>NIT (n=9)</th>
<th>NIT+PESP (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>88±9</td>
<td>...</td>
<td>89±12</td>
<td>...</td>
</tr>
<tr>
<td>LVPS (mm Hg)</td>
<td>158±27</td>
<td>158±37</td>
<td>113±16†</td>
<td>108±19‡</td>
</tr>
<tr>
<td>LVMdp (mm Hg)</td>
<td>6±5</td>
<td>5±4</td>
<td>2±2</td>
<td>2±3</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>16±7</td>
<td>15±4</td>
<td>10±3</td>
<td>10±3</td>
</tr>
<tr>
<td>LV dP/dtmax (mm Hg/sec)</td>
<td>1,888±595</td>
<td>2,328±586*</td>
<td>1,878±599</td>
<td>2,253±683‡</td>
</tr>
<tr>
<td>LV dP/dtmin (mm Hg/sec)</td>
<td>2,098±435</td>
<td>1,959±384</td>
<td>1,518±300†</td>
<td>1,068±343§§</td>
</tr>
<tr>
<td>T (msec)</td>
<td>41±7</td>
<td>44±6</td>
<td>46±7</td>
<td>56±102§§</td>
</tr>
</tbody>
</table>

PESP, postextrasystolic potentiation; NIT, nitroprusside infusion; LVPS, left ventricular peak systolic pressure; LVMdp, left ventricular minimum diastolic pressure; LVEDP, left ventricular end-diastolic pressure; LV dP/dtmax, left ventricular maximum rate of pressure development; LV dP/dtmin, left ventricular minimum rate of pressure development; T, time constant of left ventricular pressure decay.

*p<0.05 rest versus PESP; †p<0.05 rest versus NIT; ‡p<0.05 rest versus NIT+PESP; §p<0.05 PESP versus NIT+PESP; ||p<0.05 NIT versus NIT+PESP.

presence of correlation between DRR and ΔLVEDP. Therefore, during exercise after transplantation, the increase in heart rate accelerates left ventricular relaxation as evident from the correlation of ΔT with DRR and the use of left ventricular preload reserve slows left ventricular relaxation as evident from the correlation of ΔT with ΔLVEDP.

Comparative Effects of Exercise and Dobutamine on Left Ventricular Relaxation of Cardiac Allograft

In a subgroup of eight transplant recipients, left ventricular function was compared at peak exercise and during infusion of dobutamine at matching heart rates (Table 4, Figure 3). LVPS was not significantly different at peak exercise and during dobutamine infusion, but LVEDP was significantly higher during exercise than during dobutamine infusion. Despite use of left ventricular preload reserve, as evident from the rise in LVEDP, left ventricular dP/dtmax was comparable during exercise and during dobutamine infusion. Dobutamine infusion induced an abbreviation of the time constant of left ventricular relaxation (T), which was significant both with respect to resting value and value observed at peak exercise. Superimposed left ventricu-

FIGURE 2. Single-lead ECG, left ventricular (LV) dP/dt, and LV pressure recordings at rest and at peak exercise in a patient who showed adequate acceleration of LV relaxation during exercise and lower LV minimum diastolic pressure during exercise.

FIGURE 3. Single-lead ECG, left ventricular (LV) dP/dt, and LV pressure recordings at rest, at peak exercise, and during dobutamine infusion in a patient who used LV preload reserve during exercise, as evident from the elevated LV end-diastolic pressure during exercise. In this patient, isovolumic LV relaxation rate failed to improve during exercise with a concomitant increase of LV minimum diastolic pressure. During dobutamine infusion, heart rate response equaled heart rate response at peak exercise. Despite equal heart rate response and comparable LV peak systolic pressure, isovolumic LV relaxation rate was faster during dobutamine infusion than at peak exercise.
lar pressure recordings and corresponding phase-plane plots (left ventricular pressure versus left ventricular dP/dt) of isovolumic left ventricular relaxation were constructed at rest, at peak exercise, and during dobutamine infusion (Figure 4).

**Effects of Nitroprusside Infusion and Postextrasystolic Potentiation on Left Ventricular Relaxation of the Cardiac Allograft**

To investigate the effect of left ventricular afterload, left ventricular relaxation rate was measured in a subset of transplant recipients after nitroprusside infusion, which lowered left ventricular peak systolic pressure from $158\pm27$ to $113\pm16$ mm Hg (Table 5). Lowering of left ventricular peak systolic pressure prolonged the time constant of isovolumic left ventricular relaxation from $41\pm7$ to $46\pm6$ msec. This prolongation failed to reach statistical significance on the multicomparison analysis of Table 5 but reached statistical significance ($p=0.045$) on single comparison analysis between resting and nitroprusside values. The effect of increased myocardial activator calcium on isovolumic left ventricular relaxation rate was investigated in the cardiac allograft in potentiated beats preceded by a single ventricular extrasystole at minimum coupling interval. At rest, postextrasystolic potentiation did not alter isovolumic left ventricular relaxation rate, but during nitroprusside infusion, the same intervention resulted in a significantly slower left ventricular relaxation rate, as evident from the prolongation of the time constant of left ventricular relaxation (T) from $46\pm7$ to $56\pm10$ msec. In eight of the nine patients subjected to this protocol, this prolongation was accompanied by a negative dP/dt upstroke pattern with downward convexity, as evident from the recordings shown in Figure 5. Superimposed left ventricular pressure recordings and corresponding phase-plane plots (left ventricular pressure versus left ventricular dP/dt) of isovolumic left ventricular relaxation were constructed at rest, after postextrasystolic potentiation, during infusion of nitroprusside, and after postextrasystolic potentiation during infusion of nitroprusside (Figure 6).

**Discussion**

An increase in left ventricular filling pressures with exercise has been repeatedly observed in cardiac transplant recipients and contributes to the lower than normal exercise tolerance after orthotopic heart transplantation. This increase in left ventricular filling pressures has mainly been attributed to the use of preload reserve during exercise because of the blunted heart rate response and a steeper than normal diastolic left ventricular pressure-volume relation. Elevated left ventricular filling pressures during exercise could result not only from abnormal passive diastolic left ventricular properties but also from altered left ventricular relaxation kinetics. Left ventricular relaxation kinetics of the cardiac allograft have so far only been investigated at rest and not during exercise.

**Effect of Exercise on Left Ventricular Relaxation**

In the normal control group, submaximal supine bicycle exercise induced an acceleration of left ventricular isovolumic relaxation, which significantly exceeded the acceleration of left ventricular relaxation in the transplant recipients despite matching heart rates at peak exercise. Similar improvements in left ventricular relaxation rate during exercise were reported in normal subjects by other investigators. This faster isovolumic left ventricular relaxation of the normal left ventricle during exercise probably contributed to the significant fall in left ventricular minimum diastolic pressure.
observed in the present and previous studies. In patients with coronary disease and exercise-induced ischemia, the exercise-related acceleration of left ventricular relaxation was smaller than in normal subjects and was accompanied by a significant rise of left ventricular minimum diastolic pressure, as observed in the present study in the transplant recipient group. A depressed acceleration of left ventricular relaxation during exercise was observed also in patients with hypertrophic cardiomyopathy and could have contributed to the exercise-induced elevation of left ventricular filling pressures observed in these patients.

**Deficient Acceleration of Left Ventricular Relaxation During Exercise After Heart Transplantation**

In the present study, the acceleration of left ventricular relaxation during exercise was investigated in transplant recipients. For the entire study group, exercise induced a small (<10%) acceleration of left ventricular relaxation. Individual patient response was variable, which ranged from an almost normal response to paradoxical slowing of isovolumic relaxation. On multiple regression analysis, the acceleration of left ventricular relaxation during exercise was correlated with the increase in heart rate and the increase in left ventricular filling pressure. As evident from the correlation of ΔT with ΔLVEDP, the use of left ventricular preload reserve was associated with slower left ventricular isovolumic relaxation. As evident from the correlation of ΔT with ΔARR, the increase in heart rate was associated with accelerated left ventricular isovolumic relaxation. This acceleration could be the result of a direct heart rate dependent effect (Bowditch phenomenon) or adrenergic stimulation. In conscious dogs, pacing tachycardia from 100 to 200 beats per minute resulted in no change of the time constant of left ventricular pressure decay. When heart rate was held constant at 200 beats per minute, exercise produced a fall in the time constant of left ventricular pressure decay to a value, which equaled the value observed during unpaced exercise at the same heart rate. From these observations, it appears that the acceleration of left ventricular relaxation is mediated through adrenergic stimulation and not through a direct heart rate dependent effect.

The effects of use of left ventricular preload reserve on isovolumic left ventricular relaxation rate are complex. Animal studies showed slowing of left ventricular relaxation at higher left ventricular end-diastolic volumes, but if left ventricular systolic pressure was kept constant after diastolic left ventricular volume infusion, the time constant of isovolumic left ventricular relaxation remained unaltered. Similar conclusions were reached when left ventricular preload was reduced, as reported in normal control subjects early after inferior vena cava occlusion. In contrast to these studies, the relation between use of left ventricular preload reserve and isovolumic left ventricular relaxation was observed in the present study during exercise. Increased responsiveness of contractile proteins to calcium because of increased muscle preload could possibly counteract decreased responsiveness of contractile proteins by β-receptor stimulation and explain the relation between use of left ventricular preload reserve and slower isovolumic left ventricular relaxation observed in the present study during exercise after transplantation.

In the present study, left ventricular isovolumic relaxation rate during exercise was significantly slower than during dobutamine infusion at rest despite similar β-adrenoceptor stimulation, as evident from the equal heart rate responses during both interventions. Because of significantly higher left ventricular end-diastolic pressure during exercise than during dobutamine infusion, slower left ventricular isovolumic relaxation rate during exercise confirmed in the individual transplant recipient the association between use of left ventricular preload reserve and impairment of left ventricular isovolumic relaxation during exercise. This association was already evident from the multiple regression analysis on the pooled transplant group data, which revealed during exercise a similar inverse correlation between the acceleration of left ventricular relaxation and the rise of left ventricular end-diastolic pressure. Slower isovolumic left ventricular relaxation during exercise than during dobutamine infusion despite equal heart rate response could result from different actions of humorally administered and neurally released β-mimetics. Because of its humoral administration route, dobutamine infusion causes uniform stimulation of the left ventricle. Exercise after transplantation results not only in elevation of circulating catecholamines but also probably in some neural release of catecholamines because of recently demonstrated partial reinnervation. As previously observed during intracoronary isoproterenol infusion, a spatially heterogeneous release of catecholamines, as occurs during partial reinnervation, could contribute to slower left ventricular relaxation kinetics during exercise than during dobutamine infusion.

During dobutamine infusion, the time constant of left ventricular pressure decay of the cardiac allograft was significantly smaller than at rest (32 msec versus 44 msec). This finding is consistent with preserved respon-
siveness of left ventricular relaxation of the cardiac allograft to β-adrenoreceptor stimulation. This response of left ventricular relaxation in transplant recipients even exceeds the response in normal subjects as evident from a recent study,26 which observed during dobutamine infusion (5 μg/kg per minute) an 8-msec decrease in the time constant of left ventricular pressure decay, which was, however, accompanied by a larger increase (95%) in left ventricular dP/dt max than the currently observed increase (30%) in the cardiac allograft. Similar discrepancies between contraction and relaxation phase responses to β-adrenoreceptor stimulation were also observed in the failing human left ventricle and could be consistent with differentially mediated effects of β-adrenoreceptor stimulation on voltage dependent calcium channel and on sarcoplasmic reticular calcium reuptake.26,27

Elevated Left Ventricular Filling Pressures During Exercise After Heart Transplantation

In the transplant recipients, exercise induced a significant rise in left ventricular minimum and end-diastolic pressures, whereas in the normal control group, exercise to a similar heart rate induced a small but significant drop in left ventricular minimum diastolic pressure and no change in left ventricular end-diastolic pressure. This elevation of left ventricular filling pressures in the cardiac allograft during exercise could be the result of slower early diastolic left ventricular pressure decay, of altered elastic left ventricular recoil, of altered late diastolic properties, or of ventricular interaction related to elevated right atrial pressures.

After mitral valve opening, the decay of contractile activity has been estimated from an extrapolation of isovolumic left ventricular pressure decay.28,29 Such an extrapolation revealed a substantial contribution of residual contractile activity to early diastolic left ventricular pressures. Slower isovolumic left ventricular pressure decay during exercise in the transplant recipients than in the control group could, therefore, explain the higher left ventricular minimum diastolic pressure during exercise after transplantation. The precise interaction between decay of contractile activity, early diastolic left ventricular pressures, and left ventricular filling was investigated in anesthetized dogs30 and in isolated papillary muscles.31 In the canine left ventricle, an earlier onset of left ventricular filling blunts the rate of left ventricular pressure decay,30 and in the isolated papillary muscle, isometric force in the postextention phase is larger when reextension occurs earlier. During exercise after transplantation, there is an important rise in left ventricular filling pressures and, therefore, also in mitral valve opening pressure with a concomitant earlier onset of mitral inflow, which, in turn, could lead to further slowing of left ventricular pressure decay after mitral valve opening and to further elevation of early diastolic left ventricular pressures.

In conscious dogs,20 left ventricular end-systolic volume during exercise was unaltered. In human control subjects,17 left ventricular end-systolic volume index fell slightly at peak exercise. In the present study, left ventricular angiograms obtained at peak exercise revealed an unchanged left ventricular end-systolic volume in the transplant recipients. An unchanged left ventricular end-systolic volume at peak exercise would leave early diastolic left ventricular elastic recoil unchanged and could contribute to higher early diastolic left ventricular filling pressures in transplant recipients during exercise.

Previous studies explained the abnormal rise in left ventricular filling pressures during exercise after transplantation by use of left ventricular preload reserve and by a steeper than normal diastolic left ventricular pressure-volume relation. This steeper diastolic left ventricular pressure-volume relation, which was recently confirmed by calculation of diastolic left ventricular stiffness moduli at rest,16 could be the consequence of a mismatch between donor and recipient heart size,9 of ischemic injury incurred at the time of graft retrieval,16,32 of repetitive episodes of rejection,33–35 or of cardiac hypertrophy triggered by cyclosporine-induced arterial hypertension.36 The present study confirmed the use of left ventricular preload reserve during exercise after transplantation as obvious from the rise in left ventricular end-diastolic pressure and in left ventricular end-diastolic volume. During exercise after transplantation, the initial portion of the diastolic left ventricular pressure-volume relation was shifted upward and the mid to terminal portion of the diastolic left ventricular pressure-volume relation coincided with the rest curve (Figure 1). In conscious dogs20,37 and in human control subjects,17 exercise induced a downward shift of the diastolic left ventricular pressure-volume relation, especially in its initial portion. An upward shift of the initial portion of the diastolic left ventricular pressure-volume relation, as observed during exercise after transplantation, was also reported in conscious dogs during exercise after β-blockade20 and related to inappropriate sympathetic stimulation, which affects early diastolic contractile tension decay.

During exercise after transplantation, a significant rise in right atrial pressures was observed in the present study. Because of pericardial constraints or ventricular interaction, a rise in right atrial or diastolic right ventricular pressures could shift the diastolic left ventricular pressure-volume relation upward. Such an upward shift would, however, not be limited to the initial portion of the diastolic left ventricular pressure-volume relation, as observed in the present study but would affect the entire diastolic left ventricular pressure-volume relation.

Left Ventricular Relaxation of Cardiac Allograft: Effects of Afterload and Activator Calcium

The effects of reduced left ventricular afterload and of increased myocardial activator calcium on left ventricular relaxation were investigated in transplant recipients by administration of nitroprusside and by postextrasystolic potentiation. As evident from the superimposed left ventricular pressure recordings of Figure 6, administration of sodium nitroprusside was accompanied by an earlier onset of left ventricular isovolumic relaxation. This earlier onset of left ventricular isovolumic relaxation resulted not only from arteriolar vasodilation but also probably from myocardial deactivation because of a nitroprusside-induced elevation of myocardial cyclic guanosine monophosphate level.38 In contrast to the normal left ventricle,39 lowering of left ventricular peak systolic pressure by nitroprusside infusion induced prolongation of the time constant of left ventricular pressure decay from 41 to 46 msec.
prolongation failed to reach statistical significance on multicomparison analysis but reached statistical significance (p=0.045) on single comparison analysis between resting and nitroprusside values. This trend in the cardiac allograft for slower left ventricular relaxation at lower arterial load argues against the rise of left ventricular peak systolic pressure during exercise as the cause of the deficient acceleration of left ventricular relaxation.

After postextrasystolic potentiation, there was no change in the time constant of left ventricular pressure decay at rest, as previously reported in normal subjects. 40 During nitroprusside infusion, however, postextrasystolic potentiation resulted in a marked prolongation of the time constant of left ventricular pressure decay to 56 msec. This prolongation was accompanied by a negative dP/dt upstroke pattern with a downward convexity (Figure 5). This negative dP/dt upstroke pattern has previously been reported in acute coronary occlusion 41 and in the hypertrophied left ventricle of aortic stenosis after drastic left ventricular unloading by combined aortic valvuloplasty-nitroprusside infusion. 14 The induction of this slow left ventricular relaxation pattern in the cardiac allograft by unloading and postextrasystolic potentiation could suggest delayed myoplasmic calcium removal in left ventricular myocardium after transplantation similar to the delayed myoplasmic calcium removal previously observed in hypertrophied myocardium. This could be the result of a depressed function of the sarcoplasmic reticulum either because of decreased adrenergic tone caused by denervation or limited reinnervation or because of ischemic injury at the time of organ retrieval or because of hypertrophy related to cyclosporine-induced arterial hypertension.

Conclusion

Exercise after orthotopic heart transplantation resulted in an acceleration of left ventricular relaxation, which was 2.5 times smaller than in a normal control group exercised to the same heart rate. The individual response of left ventricular relaxation to exercise was variable, which ranged from normal acceleration of isovolumic relaxation to paradoxical slowing of isovolumic relaxation. Those patients, who had the largest elevation of left ventricular end-diastolic pressure during exercise, showed least acceleration of isovolumic relaxation rate. This association between a rise of left ventricular end-diastolic pressure and slower left ventricular isovolumic relaxation was also evident in the individual transplant recipient from the slower isovolumic left ventricular relaxation during exercise than during dobutamine infusion at equal heart rates. After postextrasystolic potentiation during nitroprusside infusion, a slow relaxation with downward convexity of the dP/dt signal was observed in the cardiac allograft. This finding suggests depressed function of the sarcoplasmic reticulum in left ventricular myocardium after transplantation, which could be related either to decreased adrenergic tone or to foregoing ischemic injury during organ removal or to hypertrophy caused by cyclosporine induced arterial hypertension.

References


15. Paulus WJ, Nellens P, Heyndrickx GR, Andries E: Can time constants of left ventricular pressure decay be correctly compared, when asymptote pressures are unequal? (abstract) Eur Heart J 1989;9(suppl 1):305


Deficient acceleration of left ventricular relaxation during exercise after heart transplantation.
W J Paulus, J G Bronzwaer, H Felice, N Kishan and F Wellens

_Circulation_. 1992;86:1175-1185
doi: 10.1161/01.CIR.86.4.1175

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1992 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/86/4/1175

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/