Central and Peripheral Limitations to Upright Exercise in Untrained Cardiac Transplant Recipients

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**Background** Functional capacity and quality of life are subjectively improved after cardiac transplantation. However, the objective improvement in exercise tolerance after transplantation has been disappointing. The extent to which allograft diastolic dysfunction contributes to this exercise intolerance has not been defined.

**Methods and Results** Thirty cardiac transplant recipients between 3 and 16 months after transplantation and 30 age-matched normal control subjects underwent maximal symptom-limited graded upright bicycle exercise testing with simultaneous radionuclide angiography, invasive hemodynamic monitoring, and breath-by-breath gas analysis. Mean blood pressure was higher in the transplant group at supine rest (112.1 versus 97.7 mm Hg), normalized with upright posture, and became lower than normal at peak exercise (121.1 versus 133.2 mm Hg). Systolic function as measured by ejection fraction was normal in both groups. However, the cardiac transplant recipients had significantly lower exercise tolerance, achieving a mean maximal work rate of 390 kilopond-meters per minute (kpm/min), compared with 825 kpm/min in the normal subjects. Peak oxygen consumption was 12.3 mL·min⁻¹·kg⁻¹ in the transplant group, 46% lower than the normal group’s value of 22.9 mL·min⁻¹·kg⁻¹. The transplant patients had a resting tachycardia (94 beats per minute) and a 79% reduction in exercise heart rate reserve compared with normal. Despite this chronotropic incompetence, stroke index response to exercise was consistently lower after transplantation, accounting for a 41% reduction in cardiac index at maximal exercise. The lower stroke index was accompanied by a 32% lower end-diastolic volume index at rest and a 14% lower end-diastolic volume index at peak exercise. Despite the smaller ventilatory volumes after transplantation, pulmonary capillary wedge pressure was 35% higher than normal at supine rest and 50% higher at maximal exercise. Right atrial and mean pulmonary arterial pressures were similarly elevated. The ratio of pulmonary capillary wedge pressure to end-diastolic volume index was significantly higher during the postural change and exercise, suggesting allograft diastolic dysfunction. Arteriovenous oxygen difference was similar between groups at rest and with submaximal exercise but was 24% lower at maximal exercise in the transplant group, suggesting an abnormality in peripheral oxygen uptake or utilization.

**Conclusions** Exercise tolerance is severely limited during the first 16 months after cardiac transplantation despite preservation of allograft left ventricular systolic function. This intolerance is due to inadequate cardiovascular index response from a combination of chronotropic incompetence and diastolic dysfunction limiting the appropriate compensatory use of the Starling mechanism. In addition, there is a peripheral abnormality in oxygen transport or utilization that may partially reflect the effects of deconditioning. (Circulation. 1994;89:2605-2615.)

**Key Words** exercise • transplantation • hemodynamics • diastole

Cardiac transplantation has become an accepted form of therapy for selected candidates with advanced congestive heart failure. The survival of transplant recipients approaches 68% at 5 years and 56% at 10 years,¹ comparing favorably to the expected 50% 1-year mortality in medically treated patients with New York Heart Association functional class IV heart failure.² Quality of life after transplantation is generally excellent, and many recipients are able to return to work.³ However, the exercise tolerance of these recipients is often limited,⁴ despite a preserved left ventricular ejection fraction.⁵ ⁶

Previous studies in patients during the first year after transplantation have documented severe chronotropic incompetence during exercise⁶ despite the expected compensatory increase in stroke volume.⁷ This has been accompanied by a rise in left ventricular filling pressures.⁸¹² Diastolic dysfunction in the cardiac allograft has been implicated as a contributor to these abnormal posttransplantation exercise hemodynamics.¹³ This has been supported by studies with invasive hemodynamics at rest.¹⁴ However, no exercise study is available that has measured the diastolic pressure/volume relation during upright exercise, and no age-matched normal control subjects have been included. It is therefore unclear to what extent left ventricular diastolic dysfunction, as opposed to limiting factors in the periphery, affects exercise tolerance in cardiac transplant recipients.

The purpose of the present study was to characterize the central and peripheral hemodynamic responses to upright posture and exercise in patients during the first 16 months after orthotopic cardiac transplantation in
comparison with those of normal age-matched control subjects. A combined technique of right heart catheterization and radionuclide angiography was used to characterize the pressure and volume changes in the cardiac allograft.

Methods

Heart Transplant Recipients

Thirty orthotopic cardiac transplant recipients were included in this study. Selection for the study was based primarily on the patient’s willingness to perform an invasive exercise test for research purposes. In addition, patients with rejections necessitating augmentation of immunosuppressive treatment during the last scheduled biopsy were not eligible for the study. Finally, 2 patients were excluded from the study because of previous cerebral vascular accidents with significant residual hemiparesis limiting their mobility. All participants were otherwise unselected. All transplant recipients were asked to participate in the study without regard to their expected level of exercise tolerance.

Overall, 25 men and 5 women 49.6±9.0 years old participated in the study. Patients were studied between 3 and 16 months after transplantation to allow them sufficient time to recuperate from the surgery and to minimize the possibility of significant transplant coronary disease. The mean time after transplantation was 8.5±3.9 months.

Nineteen patients had ischemic cardiomyopathy before transplantation, compared with 9 with idiopathic cardiomyopathy and 1 each with valvular heart disease and postpartum cardiomyopathy. Twenty-five patients had functional class IV heart failure requiring intravenous and/or mechanical support at the time of transplantation, and the remaining 5 patients had advanced class III symptoms before transplantation. At pretransplantation catheterization studies, the average ejection fraction was 16.8±7.0%, mean pulmonary arterial pressure was 31.3±9.9 mm Hg, pulmonary capillary wedge pressure was 21.3±9.1 mm Hg, and pulmonary vascular resistance was 2.62±1.63 Wood units. Donor cardiectomy and allograft implantation were performed according to Shumway’s technique. Average donor age was 26.7±10.0 years, and average organ ischemic time was 134±39 minutes.

Although all subjects were ambulatory after transplantation, none had undergone formal physical rehabilitation. All patients were treated with prednisone (14±4 mg/d), azathioprine (1.67±0.45 mg·kg⁻¹·d⁻¹), and cyclosporine A (4.61±1.92 mg·kg⁻¹·d⁻¹) to achieve a trough serum level of 225 to 275 ng/mL. Routine surveillance right ventricular endomyocardial biopsies were performed at least monthly and more often if evidence of moderate or severe rejection was seen. Overall, only 13 of the 30 patients had rejections before the study, for a group average of 0.8±1.2 rejections. Ten patients had grade 2 rejection according to the Billingham classification, and the other 3 had grade 3A rejection. No patient had hemodynamic compromise associated with the rejection episodes. The average interval between the last rejection episode and the day of exercise testing was 7.0±4.5 months (the shortest being 5 weeks).

All patients had an ejection fraction of ≥55%, and no patient had mitral regurgitation demonstrated by echocardiography immediately before the exercise studies. Three patients had mild concentric left ventricular hypertrophy. Six patients had diabetes mellitus after transplantation. All patients were on antihypertensive medications, including 27 on calcium channel blockers (23 of them on diltiazem therapy), 12 on angiotensin-converting enzyme inhibitors, 4 on centrally acting α-agonists, and 2 on direct vasodilators. Six patients were treated with low-dose β-blockers for tachyarrhythmias associated with cyclosporine A therapy. Six other patients were on low-dose diuretic therapy (average furosemide dose of 40±22 mg/d). Renal function was only mildly impaired in the group (creatinine 1.7±0.6 mg/dL). The mean hemoglobin was 13.1±1.7 g/dL. Fifteen patients underwent coronary angiography between 4.5±0.2 months before and 12.3±6.8 months after the exercise study and had no evidence of flow-limiting coronary disease. All patients were free of cardiovascular symptoms at the time of exercise testing.

Normal Control Subjects

The control group consisted of 30 normal subjects selected to match the heart transplant cohort closely with respect to age (49.1±10.6 years), sex (25 men), and body size (mean body weight, 80 kg for both groups). All control subjects were sedentary and untrained. None had evidence of active or remote cardiopulmonary disease as determined by history, examination, and pulmonary function testing. No subject was under treatment with any medication.

Study Protocol

The exercise protocol was approved by the institutional review board at Duke University Medical Center, and all transplant and normal subjects signed a written informed consent to participate in this study. We followed a standard protocol for hemodynamic studies developed in our laboratory as described previously. To minimize the discomfort caused by invasive exercise testing with right heart catheterization, studies in the transplant group were performed on the same day as a scheduled endomyocardial biopsy. This allowed insertion of the pulmonary arterial catheter without further venipuncture. In normal subjects, right heart catheterization was performed via a right antecubital venous approach. A 7F balloon-tipped thermodilution Swan-Ganz catheter was directed into the right pulmonary artery under fluoroscopic guidance at the beginning of the study in both groups of subjects. An 18-gauge 2.5-inch plastic cannula was then placed into the brachial artery. After in vivo labeling of red blood cells with 30 mCi ⁹⁹ᵐTc, the study began with simultaneous hemodynamic, radionuclide, and expired-gas measurements in the supine and upright rest positions. Exercise was then performed in stages on a Fitron ergometer bicycle, beginning at 25 W (150 kilopond-meters per minute [kpm/min]). Workload was increased every 3 minutes by 25 W until one of two symptom-limiting end points was reached (severe dyspnea or leg fatigue). Hemodynamic measurements were made at rest and during the second minute of each exercise workload. Arterial and mixed venous blood samples were obtained simultaneously at rest and during the last minute of each stage of exercise. Breath-by-breath expired-gas measurements were obtained throughout the study with a commercially available system (Medical Graphics Corp or Sensormedics Corp) calibrated before each study. Oxygen consumption measurements were averaged over 45-second intervals at rest and at the end of each workload. Radionuclide angiograms were performed, and ejection fractions were calculated for each stage by a standard approach with a Siemens scintillation detector and a semiautomated edge detection algorithm. Particular care was taken to minimize upper-body movement of each subject during exercise to obtain optimal scintigraphic data. Subjects were asked not to grip the gamma camera during exercise.

Hemodynamic Monitoring

All hemodynamic measurements were referenced to the level of the right atrium. Pressure transducers were adjusted to this level with a radioactive marker detected by the scintillation camera. Systemic, right atrial, pulmonary arterial, and pulmonary capillary wedge pressures were obtained with a Hewlett-Packard pressure monitor and recorded continuously at a paper speed of 2.5 mm/s. Exercise measurements were taken at the midpoint of the respiratory cycle to average the effects of inspiration and expiration. Heart rate was measured from the arterial tracings.
Arterial and mixed venous blood samples (3 mL) taken during rest and exercise were chilled in ice immediately. They were analyzed within 30 minutes for oxygen saturation and content on an Instrument Laboratories oximeter, which had been calibrated with known concentrations of oxygen-saturated blood. The measured arteriovenous oxygen difference and oxygen consumption at each stage were used to calculate Fick cardiac output. Stroke volume was calculated by dividing Fick cardiac output by heart rate. End-diastolic volume was obtained by dividing the Fick stroke volume by ejection fraction, and end-systolic volume was taken as the difference between the end-diastolic volume and stroke volume. Systemic vascular resistance was calculated by dividing (mean systemic pressure minus right atrial pressure) by cardiac output. Similarly, pulmonary vascular resistance was calculated by dividing (mean pulmonary arterial pressure minus wedge pressure) by cardiac output. Each of these variables was indexed to the body surface area.

Statistical Analysis
All data are presented as mean±SD. The hemodynamic variables of the transplant and control subjects were compared by two-tailed Student's t tests. Differences were measured at supine rest, upright rest, and maximal exercise. The submaximal exercise was analyzed by repeated-measures ANOVA with the area-under-the-curve method in both groups. Statistical significance was set at P<.05. Linear regression analysis was used to compare hemodynamic variables with each other and with clinical variables of interest.

All measured hemodynamic variables for the transplant patients were correlated with the length of time after transplantation, and the correlation coefficients ranged from 0.02 to 0.4 (P=NS). Therefore, the transplant patients were considered as one group in comparison with the normal subjects.

Results
Exercise Effort and Tolerance
Both groups of study subjects achieved a symptom-limited maximal exercise effort. This was supported by a gradual increase of the respiratory exchange ratio with exercise to a peak of 1.40±0.17 in the transplant recipients (all but three patients achieved a ratio of 1.18 or greater) and 1.45±0.19 in the normal subjects (Fig 1). Exercise capacity was significantly lower in the transplant recipients, with an average maximal work rate of 390±85 kpm/min compared with 825±192 kpm/min in the normal group. Weight-adjusted oxygen consumption increased with exercise in both groups (Fig 1), reaching a maximum of 22.9±3.45 mL·kg⁻¹·min⁻¹ for the normal cohort but only 12.29±3.98 mL·kg⁻¹·min⁻¹ in the transplant patients.

Supine Rest Hemodynamics
Table 1 displays the supine rest hemodynamics in both groups. Figs 2 through 6 display selected hemodynamic variables graphically. Left ventricular ejection fraction was similar in both groups (Fig 2). Mean systemic blood pressure was 15% higher in the transplant recipients than in the normal subjects, and systemic vascular resistance index was also higher in the transplant group (Fig 3). Resting heart rate was 32% higher in the transplant group than in the normal group (Fig 4). Despite their higher resting heart rate, cardiac index was 18% lower in the transplant group because of a 38% reduction in stroke index (Fig 4). This lower cardiac index accounted for the 16% lower weight-adjusted oxygen consumption (Fig 1), since arteriovenous oxygen difference was similar for both groups (Fig 4). The lower stroke index in the transplant group was accompanied by significantly lower end-diastolic and end-systolic volume indexes (Fig 5). The right atrial pressure tended to be higher in the transplant patients, but this difference did not reach statistical significance. In contrast, both mean pulmonary arterial pressure and pulmonary capillary wedge pressure (Fig 6) were significantly higher in the transplant group, reflected by their higher pulmonary vascular resistance index (Fig 6) compared with normal volunteers.

Linear regression analyses found no significant relation between supine wedge pressures and supine mean systemic pressures in either group (r=-.04 in transplant patients, r=.27 in normal subjects, P=NS). The 13 patients with rejection before exercise testing had filling pressures similar to those of patients without previous rejection (P>.10).
Postural Hemodynamic Responses

Table 1 demonstrates the postural hemodynamic responses within each group. Figs 2 through 6 graphically illustrate the postural changes in hemodynamic variables for the two groups. In the upright position, left ventricular ejection fraction was once again similar for the two groups (Fig 2). The mean systemic pressure remained higher in the transplant recipients, despite a fall in their pressure with upright posture along with a rise in pressure in the normal subjects (Fig 3). As in the supine position, heart rate was higher in the transplant group, since both groups increased their heart rate with upright posture to a similar extent (Fig 4). Cardiac index fell in both groups despite the postural rise in heart rate (Fig 4). This decrease in cardiac index was more marked in the normal subjects (21% versus 9%), which was accounted for by the greater increase in stroke index in normal subjects compared with transplant patients (31% versus 17%) (Fig 4). End-diastolic volume index decreased more in the normal group (Fig 5), reflecting the greater decrease in stroke index. However, the stroke index and left ventricular volume indexes remained significantly lower in the transplant recipients.

The right atrial and mean pulmonary arterial pressures (Fig 6) decreased by a similar extent with upright posture in both groups, so that mean pulmonary arterial pressure remained 44% higher in the transplant group. Since the pulmonary capillary wedge pressure decreased more significantly in the transplant patients, the wedge pressures were similar between groups at upright rest (Fig 6). The pulmonary vascular resistance index was only 46% higher in the transplant group with upright posture (compared with 81% in the supine position) because of a greater relative increase in this index in normal volunteers (Fig 6). Similarly, systemic vascular resistance index increased more significantly in the normal group, so that this index was similar between groups at upright rest (Fig 3). Both groups had a higher oxygen consumption but extracted more oxygen in the upright position (Table 1, Figs 1 and 4), reflecting the postural decrease in cardiac index.

For both groups of subjects, the higher the supine right atrial pressure, the higher the difference was between supine and upright atrial pressures (r=0.64 transplant group, r=0.82 normal group, P<.001 both groups). A similar relation held true for the supine and
Limitations to Upright Exercise

Exercise Hemodynamic Responses

The last exercise workload maintained for at least 2 minutes was considered the maximal exercise workload for the patient. An average maximal work rate was then calculated for each group and was referred to as the "mean of the maximum" work rate. A mean and SD was obtained for each variable at this maximal work rate.

Since all transplant patients finished the 300-kpm/min work rate but only 60% finished the 450-kpm/min work rate, 150 and 300 kpm/min were considered the submaximal work rates for both groups for the purpose of analysis. Figs 2 through 6 illustrate the response of selected hemodynamic variables to exercise. For the transplant group, variables during exercise were plotted at 150 and 300 kpm/min and also at the mean of the maximum work rate of 390 kpm/min. Since all normal control subjects finished the 600 kpm/min of exercise work rate, their variables were plotted at 150, 300, 450, and 600 kpm/min as well as the mean of the maximum work rate of 825 kpm/min. Table 2 tabulates the hemodynamics at maximal exercise in both groups, and within-group and between-group statistical analyses are listed.

Ejection fraction increased throughout exercise in both groups to a similar extent (Fig 2). The heart rate remained higher at submaximal exercise in the transplant group. However, the maximal heart rate response was 30% lower in the transplant recipients, producing a 79% lower heart rate reserve (Fig 4). Cardiac index increased with exercise in both groups but to a much greater extent in the normal subjects (Fig 4). At submaximal exercise, the cardiac index in the transplant group was only slightly lower, but at the maximal tolerated work rate, their cardiac index was 41% lower than that of the normal subjects. The lower cardiac index response at submaximal exercise was due to a lower stroke index (Fig 4) despite the higher heart rate. In contrast, the lower cardiac index at maximal exercise seen after transplantation was due mainly to chronotropic incompetence.

The arteriovenous oxygen difference increased similarly between groups during submaximal exercise but was 24% higher in the normal subjects at maximal exercise (Table 2 and Fig 4). There was no correlation between the exercise effort as represented by the respiratory exchange ratio and the arteriovenous oxygen difference (r = -0.09, P = NS). The three patients with the lowest arteriovenous oxygen differences (7.2, 8.0, and 8.1 vol%) had respiratory exchange ratios of 1.46, 1.38, and 1.42, respectively.

Mean blood pressure increased throughout exercise in both groups but to a greater extent in the normal subjects (Fig 3). The systemic vascular resistance index decreased in both groups with exercise, reaching a much lower level in the normal group at maximal exercise (Fig 3).

In contrast, the exercise right atrial and pulmonary capillary wedge pressures increased at a much steeper rate in the transplant recipients, with maximal right atrial pressure being 84% higher (Fig 6). Similarly, the net change in wedge pressure with exercise was 61% higher in the transplant group, leading to a 50% higher wedge pressure at maximal exercise (Fig 6). The mean pulmonary arterial pressure increased at a similar rate with exercise in both groups but remained higher in the transplant patients throughout exercise (Fig 6). The pulmonary vascular resistance index decreased at a similar rate throughout exercise in both groups, remaining 61% higher in the transplant group at the maximal tolerated work rate (Fig 6).

The end-diastolic volume index remained lower throughout exercise in the transplant group, despite a higher net increase with exercise (Fig 5). There was an insignificant increase in end-systolic volume index in the transplant group with exercise compared with an insignificant decrease in the normal group (Fig 5). The 14% smaller end-diastolic volume index in the transplant group at maximal exercise accounted for their accompanying 17% lower stroke index.

Linear regression analyses again found no correlation between maximal pulmonary capillary wedge pressures and mean systemic pressures in either group (r = -0.22 transplant group, r = -0.29 normal group, P = NS). Filling pressures were again similar between patients with or without rejection before exercise testing. Pulmonary
capillary wedge pressure tended to be higher in patients without previous rejection (14.4±5.7 versus 10.5±5.0 mm Hg), but this difference was not statistically significant (P=.09).

### Left Ventricular Compliance

Since none of the patients had any clinically significant mitral valve or pulmonary disease, their measured pulmonary capillary wedge pressures should closely approximate their left ventricular end-diastolic pressures at each stage. To represent left ventricular compliance in both groups, we plotted the slope of the pulmonary capillary wedge pressure/end-diastolic volume index relation against work rate (Fig 7). As shown in this figure, there was a significantly elevated pressure/volume relation in the transplant patients at supine rest, which decreased to near normal with upright rest. This ratio increased dramatically with exercise and was significantly higher both at submaximal and maximal exercise in the transplant group. By linear regression analysis, the slope of the pressure/volume relation during upright exercise was significantly higher in the transplant group (P<.001), indicating markedly decreased left ventricular compliance after transplantation independent of exercise testing.

### Discussion

The purpose of the present study was to explore the mechanism of exercise intolerance after cardiac transplantation by studying the central and peripheral responses to posture and upright exercise. The study design included the use of an unselected and untrained transplant recipient group, an age-matched sedentary normal control population, maximal upright exercise with invasive monitoring of central and peripheral factors, and characterization of the diastolic pressure/volume relation during exercise. These unique features allowed us to significantly enhance our understanding of exercise physiology in the posttransplant patient.

The major new finding of this study was the discovery of both central hemodynamic and peripheral limitations to maximal exercise after transplantation. We demonstrated a significantly reduced exercise capacity in the 30 patients studied between 3 and 16 months after transplantation, achieving a 53% lower maximal workload and a 43% lower peak weight-adjusted oxygen consumption compared with 30 well-matched normal control subjects. Despite a 30% higher basal heart rate, the transplant group achieved a 30% lower maximal exercise heart rate compared with their normal counterparts, providing a 79% lower heart rate reserve. Despite their severe chronotropic incompetence, the transplant cohort made less use of the Starling mechanism than the normal group. The lower stroke index seen throughout exercise was associated with a consistently smaller end-diastolic volume index with similar end-systolic volume index and higher pulmonary capillary wedge pressure compared with the normal group, suggesting that the inability to rely on the Starling mechanism to increase stroke index was due to diastolic...
maximal exercise effort as reflected by their symptoms and high peak respiratory exchange ratios. Since none of the transplant recipients were anemic, their lower arteriovenous oxygen differences resulted from less oxygen extraction at submaximal and at peak exercise compared with their normal counterparts. This implies either a vascular insufficiency with inadequate peripheral oxygen delivery or an intrinsic muscular metabolic defect of oxygen utilization.

### Other Studies

Many studies of posttransplantation exercise capacity have been performed, using bicycle or treadmill stress testing. These studies demonstrated reduced peak oxygen consumption up to 18 months after transplantation, ranging from 14 to 21.7 mL·min⁻¹·kg⁻¹.⁴⁻⁵,¹⁷⁻²³ The maximal oxygen consumption in the present study was lower than has been described in the literature. Our patient cohort was unselected and untrained. It is possible that other studies involved more motivated or trained patient groups. The presence of indwelling Swan-Ganz and arterial catheters is unlikely to have selectively affected the exercise performance of our transplant patients.

Although we believe ours to be the most comprehensive and carefully controlled study of posttransplantation exercise response to date, hemodynamic data from other studies are available for comparison. The exercise intolerance observed after transplantation has been accompanied by a well-described resting tachycardia and chronotropic incompetence,⁶⁻¹⁰,¹²,¹³,¹⁹⁻²²,²⁴,²⁵ as seen in the present study. Also consistent with our findings, transplant patients have demonstrated preserved left ventricular systolic function as measured by ejection fraction.⁶⁻⁷,²⁶⁻²⁸

Several studies have measured serial supine rest hemodynamics up to 1 year after transplantation,²⁹⁻³² showing markedly elevated filling pressures 1 day to 2 weeks after transplantation, which gradually decreased with time. Our filling pressures agreed well with those described between 6 and 10 months after transplantation.²⁹,³⁰ Supine bicycle exercises have been performed 3 to 24 months after transplantation¹¹,¹² and have demonstrated elevated filling pressures at rest and with exercise, similar to our findings. Unlike previous studies, we were able to confirm these abnormally high filling pressures by studying well-matched normal control subjects.

Only a few studies have measured posttransplantation left ventricular end-diastolic and end-systolic volumes during exercise after transplantation, using radionuclide angiography to estimate these volumes.⁷,²⁸ The findings described in these studies have been generally consistent with ours, with small differences being explained by technical variability. Since we measured Fick outputs and no patient had significant pulmonary disease or mitral regurgitation, our calculated volumes should closely approximate true left ventricular volumes.

Paulus et al¹⁴ directly measured left ventricular pressures and estimated volumes using single-plane contrast ventriculography during submaximal supine bicycle exercise in 27 patients 1 to 4 years after transplantation. End-diastolic pressures and volumes, both at rest and during exercise, closely approximated those measured in the present study. In addition, there was a consistent and significant abbreviation in the time constant of left
ventricular pressure decay in the control group. At the same peak heart rate, the transplant patients had only a mild reduction in this time constant, suggesting abnormal diastolic relaxation. Even though the present study did not measure diastolic relaxation directly, the abnormal pressure/volume relation with exercise measured early after transplantation also suggested abnormal diastolic relaxation.

No previous investigators have described the inadequate peripheral oxygen extraction with exercise after transplantation uncovered in the present study. Greenberg et al found no difference in resting arteriovenous oxygen difference between 18 patients 13 months after transplantation compared with a significantly older control population with atypical chest pain syndromes, agreeing with our findings. Clark et al reported seven patients 1 year after transplantation undergoing submaximal supine bicycle exercise. By estimation from their reported data, the arteriovenous oxygen difference increased from 5 vol% at rest up to 8.5 to 9 vol% at the end of exercise. The arteriovenous oxygen differences were reported to be higher than expected at each level of oxygen consumption compared with the normal range established by Donald et al in 1955, which was contrary to our findings. However, the number of patients included in this study was small, and comparison was made with non-age-matched normal subjects studied 18 years earlier. In addition, the values for most of Clark's patients were actually within the normal range established by Donald.

Potential Mechanisms

The present study described significant central and peripheral hemodynamic abnormalities with upright posture and with exercise after transplantation but did not reveal the underlying mechanisms responsible for the abnormalities. The chronotropic incompetence described is no doubt a result of the effects of denervation. Transplant recipients rely on elevated plasma catecholamine levels for their exercise heart rate response. In the present study, the effects of denervation were clear. In addition, diltiazem was used frequently in our study population and might have contributed to the severe chronotropic incompetence in our transplant recipients.

The pathogenesis of the severe diastolic dysfunction seen after transplantation is not clear. Cold preservation may cause diffuse left ventricular ischemia and consequent left ventricular chamber stiffness and dysfunction. The ischemic time in our patients was not particularly long; two hours of cold ischemia would be unlikely to lead to lasting effects up to 16 months after transplantation. In addition, if ischemia were important in the function of the cardiac allograft, its systolic function should be affected to some degree. This, of course, was not the case in the present study or in the literature.

Another possible cause of diastolic dysfunction seen after transplantation is rejection. Our transplant patients were relatively free of rejection, averaging less than one episode per patient. Severe rejection could
obviously be associated with hemodynamic compromise. None of our patients had hemodynamic compromise associated with their rejections. There was also no difference in hemodynamics in patients with and without rejection.

Although systemic hypertension induced by cyclosporine A therapy could also be contributory to diastolic dysfunction, our transplant patients would not be expected to develop end-organ damage from hypertension during the first year after transplantation.

Occult ischemia caused by transplant coronary disease could play a role in the abnormal pressure/volume relation described in the present study. Although this issue was not specifically addressed in our study, 15 of our patients who had coronary angiograms either before or after their exercise study showed no flow-limiting coronary lesions. However, we cannot rule out the possibility of microvascular coronary disease contributing to subendocardial ischemia and abnormal diastolic relaxation.

Cyclosporine A has been found to cause perimyocytic fibrosis not seen in the nontransplanted heart.38,39 This fibrosis is not thought to be progressive38 but could potentially contribute to the development of a noncompliant ventricle. Interestingly, hemodynamic studies performed before the introduction of cyclosporine A therapy also demonstrated abnormal rise in filling pressures and limited stroke index response to exercise,40,41 so cyclosporine A alone does not provide the entire explanation for the diastolic dysfunction seen.

The limited peripheral oxygen extraction during exercise after transplantation seen in the present study implied a peripheral abnormality in oxygen delivery and/or oxygen utilization. It is well known that patients with varying severity of congestive heart failure have a similar level of oxygen extraction at peak exercise42 and that differences in the maximal oxygen consumption reflect cardiac output reserve.

It is also well known that short-term improvement in cardiac output may not translate into increased exercise endurance or peak oxygen consumption.43,44 Peak arteriovenous oxygen difference has been seen to decrease with acute dobutamine43,45 or vasodilator treatment,46,47 suggesting that improved cardiac output uncovered a preexisting abnormality in peripheral oxygen delivery or uptake. The specific mechanisms responsible for this are unknown, but potential contributors include an increase in systemic vascular resistance50,51 and abnor-
malities in skeletal muscle metabolism independent of blood flow. These skeletal muscle changes have been found to closely mimic those accompanying deconditioning and appear to at least partially reverse with exercise training.

The findings in our study patients were analogous to the dobutamine and vasodilator studies described above. By improving cardiac output reserve, cardiac transplantation in our group of heart failure patients appeared to have uncovered preexisting peripheral defects of oxygen delivery or utilization. Since limb blood flow was not measured in the present study, we could not assess the precise mechanism responsible for the decreased peripheral oxygen utilization during exercise.

**Limitations of the Study**

One of the limitations of this study, inherent to any study of the transplant population, was the lack of an appropriate comparison group with whom to compare the cardiac responses to exercise. For this purpose, it might be more appropriate for the comparison cohort to be matched to the age of the allograft rather than the age of the recipient. We chose to age-match the recipients, since the primary objective of the study was to investigate the mechanisms underlying their reduced exercise tolerance. In any case, diastolic abnormalities shown in our study would probably have been even more pronounced in comparison with a younger control group.

Another limitation of this study was our inability to comment on any potential change in allograft function over time. We were surprised to find no correlation of any hemodynamic variable with the time after transplantation over a range of 3 to 16 months after the operation. However, if we had performed serial studies, we might have demonstrated an improvement or deterioration of allograft function with time.

Finally, we did not make direct left ventricular pressure measurements, and we derived left ventricular volumes from Fick stroke volumes and radionuclide ejection fractions. However, since none of our patients had significant pulmonary or mitral valve disease, the Fick-derived volumes and pulmonary capillary wedge pressures should closely approximate true left ventricular end-diastolic volumes and pressures. Our study also agreed with the findings of recent studies involving direct measurements of left ventricular dynamics after transplantation. Direct left ventricular studies necessitate supine exercise testing, which is less functionally applicable than our upright bicycle exercise.

**Clinical Implications**

Our study confirms that cardiac transplant recipients have diminished exercise capacity during the first 16 months after transplantation. The present study uncovered three potentially reversible factors that account for exercise intolerance: chronotropic incompetence, diastolic dysfunction, and peripheral abnormalities of oxygen extraction. Chronotropic incompetence seems to improve with time, and specific treatment may not be warranted. However, the potential benefits of antihypertensive medications such as β-blockers or nondihydropyridine calcium channel blockers will have to be carefully weighed against their potential worsening of chronotropic incompetence. The diastolic dysfunction described in the present study was a major limiting factor to exercise capacity. Potential therapies such as calcium channel blockers or angiotensin-converting enzyme inhibitors as well as aggressive control of hypertension, rejection, and silent ischemia may improve the left ventricular diastolic function. Finally, transplant patients also have vascular and/or skeletal muscular abnormalities contributing to exercise intolerance. The exact nature of these abnormalities is unclear, but a contribution from peripheral deconditioning appears likely. Rehabilitation may reverse some or all of these peripheral abnormalities and may play a vital role in maximizing the functional improvements after cardiac transplantation.

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