Abnormal Exercise Hemodynamics in Cardiac Allograft Recipients 1 Year After Cardiac Transplantation

Relation to Preload Reserve

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The well-established elevation in left ventricular filling pressures during exercise in patients after transplantation may contribute to decreased exercise tolerance. A proposed mechanism for this increase in filling pressures is an abnormal pressure-volume homeostasis of the transplanted heart. Twenty-three patients undergoing routine 1-year evaluations performed supine bicycle exercise during right heart catheterization. Within 24 hours, these patients underwent supine bicycle exercise to the identical work load during radionuclide ventriculography. For the group, resting hemodynamics and resting left and right ventricular ejection fractions were normal. With exercise, right atrial and pulmonary wedge pressures rose markedly (from 6±2 to 14±7 mm Hg, p<0.0001, and from 10±3 to 20±6 mm Hg, p<0.0001, respectively). Left ventricular ejection fraction increased appropriately with exercise (from 0.58±0.08 to 0.63±0.07, p=0.004). End-diastolic volume also increased mildly (from 100±31 to 117±39 ml, p=0.001), but change in end-diastolic volume was highly variable. Patients with little or no change in end-diastolic volume with exercise had the greatest resting and exercise left ventricular filling pressures resulting in significant negative correlations between filling pressures and change in end-diastolic volume (r=−0.64, p=0.002 and r=−0.50, p=0.025, respectively). Negative linear relations between exercise left ventricular filling pressures or resting heart rates and donor to recipient body weight ratio (r=−0.35, p=0.10, and r=−0.37, p=0.06, respectively) suggested that initial donor heart size influenced subsequent cardiac function. However, unlike hemodynamics 3 months after transplantation, the effect of donor to recipient body weight ratio was not significant at 12 months. These data suggest that elevated exercise filling pressures in cardiac allograft recipients may result from multiple factors including volume status (resting pulmonary wedge pressure) and preload reserve (change in left ventricular end-diastolic volume), although an abnormal diastolic pressure-volume relation in some patients cannot be excluded. (Circulation 1989;80:525–532)

Past studies have documented an increase in left ventricular filling pressures with exercise in cardiac transplant recipients\(^1,2\) to levels that characteristically cause dyspnea in other patient populations. This rise in filling pressures may contribute to the decreased exercise tolerance evident in many of these patients. The rise in pressures has been ascribed to the need to use preload to increase exercise cardiac output because of the inadequate heart rate response in the denervated heart.\(^3\) More recently, an abnormal response to volume loading was described in the cardiac allograft recipient and an abnormality in diastolic function was postulated.\(^4,5\) An alternative hypothesis is that the transplanted heart does not maintain the normal pressure-volume homeostasis due to either a defect in systemic volume regulation by the cardiac transplant recipient or a mismatch between donor heart size and recipient body size, a situation certainly unique to cardiac transplantation. Prior studies have addressed size matching but only with respect to acute graft dysfunction,\(^6,7\) one of the studies showed an increased incidence of postoper-
ative right ventricular failure in recipients receiving a relatively small heart.\textsuperscript{7} We have previously shown that at 3 months after cardiac transplantation, the match between donor heart size and recipient body size influences resting hemodynamics with significant negative linear relations between resting heart rate, right atrial and pulmonary wedge pressures, and the donor to recipient body weight ratio.\textsuperscript{8} To further investigate potential mechanisms responsible for the abnormal exercise response and longer-term effects of donor heart size, cardiac pressure and volume changes during supine bicycle exercise were investigated in cardiac transplant recipients 1 year after transplantation.

**Methods**

**Patients**

Twenty-five patients completed 1 year of follow-up after transplantation at the time of this study. Of these, 23 patients were studied within 2 weeks of their 1-year anniversary. The two patients excluded from analysis included one with accelerated graft atherosclerosis and one with severe allograft dysfunction (ejection fraction, 0.29). There were 19 men and four women with a mean age of 41 years (range, 18–60 years). Maintenance daily immunosuppression included prednisone (0.1 mg/kg), azathioprine (1.5 mg/kg), and cyclosporine (4–8 mg/kg to achieve whole blood levels of 400–800 ng/ml). At the time of study, four patients had very focal areas of lymphocyte infiltration consistent with early moderate rejection on endomyocardial biopsy. The remaining 19 had no inflammation. Of those 19 patients, four had no evidence of rejection throughout their post-transplant course. Thirteen patients were receiving diuretics, and 11 were receiving antihypertensives for cyclosporine-induced hypertension. Antihypertensives included captopril (three patients), clonidine (one patient), nifedipine (five patients), and low-dose atenolol (25 mg/day, two patients). Blood pressures were moderately well controlled (systolic blood pressure, 128±10 mm Hg; diastolic blood pressure, 89±7 mm Hg).

**Studies of Cardiac Function and Exercise Hemodynamics**

As part of a routine 1-year postoperative clinical evaluation, cardiac transplant recipients underwent right heart catheterization at rest and during supine two-leg bicycle exercise (400 kpm in 22 patients and 200 kkm in one patient). Measurements obtained included right atrial, pulmonary artery, and pulmonary wedge pressures, and thermodilution cardiac outputs (average of three determinations at each physiologic state). Left ventriculography, coronary angiography, and endomyocardial biopsy were also performed immediately after the right heart catheterization. Angiographic volumes were calculated from biplane oblique images corrected for magnification by the area-length method. No correction was subsequently applied for the known overestimation of ventricular volume by this method.\textsuperscript{9} Within 24 hours, patients underwent radionuclide ventriculography at rest and two-leg supine bicycle exercise at the identical workload performed during the right heart catheterization. Studies were performed as follows. After in vivo red blood cell labeling with 25 μCi \textsuperscript{99m}Tc, the cardiac blood pool was imaged with an Elscint Apex 415M mobile gamma camera (Elscint, Waltham, Massachusetts). The image acquisition was gated to the QRS complex of the electrocardiogram to obtain 28 images during the cardiac cycle in a 64 × 64 image matrix. Rest and exercise images were acquired in the left anterior oblique projection that displayed the interventricular septum most homogeneously. Rest images were acquired for 300,000 counts in the end-diastolic image, whereas exercise images were acquired during the last 3 minutes of the exercise period. Left ventricular ejection fractions were calculated as the background corrected left ventricular end-diastolic minus end-systolic counts divided by end-diastolic left ventricular counts with a semiautomatic edge detection algorithm. Left ventricular end-diastolic volume was determined as the background subtracted end-diastolic image left ventricular counts divided by the decay corrected blood \textsuperscript{99m}Tc activity concentration. Correction for attenuation of the 140 keV photons from the left ventricle was performed with the method of Starling et al.\textsuperscript{10} Left ventricular end-diastolic activity was taken as the average of regions of interest drawn by three experienced observers. In our laboratory, this method correlates well with biplane contrast left ventriculography at cardiac catheterization (\(r=0.99, \text{SEE}=14 \text{ ml}\)).

Systemic vascular resistance (SVR) was determined with cardiac outputs (CO) and right atrial pressures (RA) during catheterization and with cuff blood pressures obtained during radionuclide ventriculographic studies (mean arterial pressure [MAP]=\(\frac{1}{3}\) pulse pressure + diastolic pressure) by the following equation: SVR (Wood units)=\(\frac{(\text{MAP}–\text{RA})}{\text{CO}}\).

Within 72 hours, all patients underwent a treadmill exercise test according to the standard Bruce protocol after a 5-minute warm-up period that consisted of exercise at 1 mph, 0 grade. Functional capacity was calculated by the formula, \(\text{VO}_2\) (ml/kg/min)=3.88+0.056 × exercise duration (seconds), and expressed as a percentage of expected \(\text{VO}_2\) based on age and a sedentary activity level.\textsuperscript{11} Exercise was symptom limited and stopped when the patient could not continue.

Data are expressed as mean±standard deviation unless otherwise noted. Differences between rest and exercise data were determined with Student’s \(t\) test for paired data. Correlation was performed with Pearson’s correlation coefficient (\(r\)), and the significance of \(r\) was calculated with the Student’s \(t\) test. Significance was considered to be present at a \(p\) value of less than 0.05.\textsuperscript{12}
Results

Standard exercise testing with the Bruce protocol showed a peak heart rate of 147±17 beats/min (maximum predicted based on age and fitness 177±10 beats/min, peak systolic blood pressure of 151±19 mm Hg, exercise duration of 417±127 seconds, and calculated functional capacity of 79±16% of predicted (based on sedentary lifestyle). Symptoms that limited exercise were fatigue (nine patients), dyspnea (10 patients), and leg pain or weakness (four patients).

Figures 1 and 2 show the individual right atrial and pulmonary wedge pressures at rest and during exercise. In all patients, pulmonary wedge pressure rose with exercise, and in most patients, this pressure rose into the abnormal range (>12 mm Hg). All but two patients had abnormal elevations in right atrial pressure.

Mean pressures and flows are shown in Table 1. As noted in the prior figures, filling pressures increased almost twofold with exercise. Cardiac output doubled with exercise. This was accomplished by a combination of increased heart rate (38% above resting) and increased stroke volume (45% above resting). Mean arterial pressures increased slightly with exercise, whereas calculated systemic vascular resistances fell to almost 50% of their resting levels.

![Figure 1. Plot of right atrial pressures from rest to supine bicycle exercise for the group. A more than twofold increase was seen in all but two patients. *Patients with mild or moderate rejection at the time of exercise; #patients never experiencing rejection.](image1)

![Figure 2. Plot of pulmonary wedge pressures from rest to supine bicycle exercise for the group. These pressures more than doubled for the group, and some degree of pulmonary wedge pressure elevation was seen in all patients. *Patients with mild or moderate rejection at the time of exercise; #patients never experiencing rejection.](image2)

| TABLE 1. Pressures and Flows at Rest and Exercise |
|---------------------------------|----------------|----------------|------|
| Parameter                        | Rest            | Exercise       | p    |
| Right atrial (mm Hg)             | 6±2             | 14±7           | <0.0001 |
| Pulmonary artery mean (mm Hg)   | 18±3            | 32±9           | <0.0001 |
| Pulmonary wedge (mm Hg)         | 10±3            | 20±6           | <0.0001 |
| Cardiac output (/min)            | 5.0±0.9         | 9.9±1.7        | <0.0001 |
| Cardiac index (l/min/m²)         | 2.5±0.5         | 5.0±0.8        | <0.0001 |
| Stroke volume (ml)               | 55±9            | 77±13          | <0.0001 |
| Stroke volume index (ml/m²)      | 28±6            | 39±7           | <0.0001 |
| Heart rate (beats/min)           | 90±11           | 122±18         | <0.0001 |
| Mean arterial pressure* (mm Hg) | 91±12           | 102±14         | <0.0003 |
| Systemic vascular resistance†    | 17.7±4.0        | 9.3±2.4        | <0.0001 |

*Calculated from cuff pressure during radionuclide study.
†Systemic vascular resistance was calculated with the mean arterial pressure listed in the table.

All data are consistent with the identical work loads used and suggest similar exercise responses in the two studies despite being 24 hours apart.

Table 2 shows the results from the radionuclide and angiographic left ventriculography. Angiographic volumes and ejection fractions were obtained in 22 patients, radionuclide ejection fractions were obtained for all. Radionuclide left ventricular volumes were obtained in 22 of the 23 patients studied at rest and in 20 of the 23 patients with exercise. Resting left ventricular ejection fractions by radionuclide ventriculography were normal (0.58±0.08) and increased normally with exercise (0.63±0.07, p=0.004). Right ventricular ejection fractions were also normal at rest (0.59±0.07).
Left ventricular end-diastolic volumes were small both by radionuclide and contrast angiography. Patients receiving diuretics or antihypertensives had greater radionuclide ventricular volumes (52±12 ml/m², 16 patients) compared with patients not receiving either type of medication (37±13 ml/m², six patients, *p*=0.022). There is no obvious explanation for this finding; however, it does effectively eliminate the possibility that diuretics or antihypertensives were responsible for the decreased volumes.

Mean left ventricular end-diastolic volume increased with exercise (100±31 increasing to 117±39 ml, *p*=0.001), but in three patients, left ventricular end-diastolic volume actually fell. Figures 3 and 4 show the correlation between change in left ventricular end-diastolic volume between rest and exercise and resting pulmonary wedge pressure or exercise pulmonary wedge pressure, respectively. A statistically significant negative correlation occurred between rest pulmonary wedge pressure and change in left ventricular end-diastolic volume, and a slightly weaker but still statistically significant correlation occurred between exercise wedge pressure and volume change. In addition, a statistically significant positive correlation was found between rest and exercise pulmonary wedge pressures (*r*=0.43, *p*=0.044). These data show that those patients with a greater increase in end-diastolic volume with exercise (utilized preload reserve) had lower resting and exercise filling pressures. In addition, as expected, those patients with lower resting pulmonary wedge pressures had lower exercise pulmonary wedge pressures. There was, however, no correlation between resting left ventricular end-diastolic volume or volume index and overall exercise tolerance as assessed by treadmill testing.

Figure 5 shows the negative correlation between donor to recipient body weight ratio and exercise pulmonary wedge pressure for the patients showing a weak and statistically insignificant relation. There was no correlation between donor to recipient body weight ratio and change in left ventricular end-diastolic volume with exercise. However, looking at mismatch extremes, three patients had donor to recipient body weight ratios above 1.2 and had an increase in left ventricular end-diastolic volumes of 34, 27, and 25 ml, respectively (mean, 29±5 ml). An additional four patients had ratios of less than 0.85, with increases in left ventricular end-diastolic volumes of 6, 0, 3, and 55 ml, respectively (mean, 16±26 ml; excluding outlier with a very thin donor: mean, 3±3 ml). There was a negative linear but insignificant relation between resting heart rate and donor to recipient body weight ratio present.
(r = -0.37, p = 0.06). In contrast to previously reported data obtained 3 months after transplantation, there were no significant relations between donor to recipient body weight ratio and right atrial or pulmonary wedge pressures (r = -0.12 and r = -0.25, respectively).

Discussion

It is clear that the denervated heart contributes to the exercise response by different mechanisms compared with a normally innervated heart. As early as 1970, Campeau and colleagues showed a reduced heart rate response to exercise associated with a dramatic increase in left ventricular end-diastolic pressure in transplant patients. Our results are similar 18 years later. Campeau et al interpreted their findings as evidence for myocardial dysfunction perhaps related to chronic rejection or catecholamine depletion secondary to the denervated state.

Alternative explanations were provided by Stinson and colleagues who defined the exercise response in patients 1 and 2 years after cardiac transplantation. They showed elevated resting heart rates, a very gradual increase in heart rate with exercise, a rapid increase in left ventricular end-diastolic pressure, and a substantial increase in cardiac output due to an increase in stroke volume. Thus, the transplanted heart relied heavily on the Frank-Starling mechanism for increased cardiac output because of a much attenuated heart rate response especially early after the onset of exercise. Later, the Stanford group measured end-diastolic volume directly at rest, during volume loading (leg lifting), and with graded supine bicycle exercise. As predicted, end-diastolic volume increased with end-diastolic pressure confirming the role of the Frank-Starling mechanism at least for early exercise. This finding was more recently substantiated with radionuclide ventriculography by others and is consistent with data presented here. However, in this later study, no intracardiac pressures were measured.

In contrast to the data presented above, the normally innervated heart responds quite differently to supine exercise. Heart rate at rest in normal hearts is substantially lower than for transplanted hearts. During exercise, heart rate in normal hearts increases promptly and in proportion to the amount of work. The increment in cardiac output during supine exercise is primarily due to increased rate, and stroke volume plays only a minor role in most studies. The mechanism by which supine exercise stroke volume is increased is unclear because studies have reported both a reduction in end-systolic volume presumably by increased contractility and decreased afterload, and no change in end-diastolic volume, or an increase in end-diastolic volume with no change in end-systolic volume.

Left ventricular filling pressure does increase slightly during supine exercise in normal hearts, although not to the degree seen in the transplanted heart. In normal supine individuals, the heart appears to operate at or near the "break point" (see Figure 6) of the function curve and uses preload minimally, if at all, to increase cardiac output. Our findings are consistent with prior observations that preload reserve or end-diastolic volume is used to augment cardiac output during supine exercise in patients after cardiac transplantation. Although the increased end-diastolic volume and increased ejection fraction effectively increase exercise stroke volume, the higher than normal filling pressures reach levels that may produce symptoms of dyspnea. Thus, the reduced functional capacity reported in this study and by others may be related more to abnormal filling pressure changes than to restriction of exercise cardiac output.

One potential explanation for the elevation in filling pressures with exercise in this transplant population is an abnormal or inappropriate peripheral response to exercise resulting in an increase in afterload, especially because these patients have hypertension secondary to their cyclosporine immunosuppression. Three factors make this explanation less likely. First, the exercise elevation in filling pressures was initially reported in cardiac allograft recipients not receiving cyclosporine. Second, in our patients, resting mean arterial pressures were
normal, with only a slight increase with exercise, and systemic vascular resistance fell to almost 50% of resting levels. These changes are similar to those reported for a normal population undergoing supine bicycle exercise. Finally, ejection fraction rose significantly with exercise.

Consistent with and supporting the original hypothesis of abnormal pressure-volume homeostasis in cardiac transplantation is the inverse relation between rest and exercise left ventricular filling pressures and the ability to increase left ventricular end-diastolic volume with exercise. These findings suggest that some cardiac transplant recipients are not operating on the "break point" of the left ventricular function curve but may be operating anywhere along it. Normal individuals operate near the "break point" (Figure 6, point 1, Panels A and B). At this point, a small increase in left ventricular volume causes a substantial increase in filling pressures as intravascular volume is shunted centrally with the onset of exercise. Little increase in stroke volume results. Cardiac transplant recipients who receive relatively smaller hearts may be operating at or beyond point 1. Recipients receiving relatively larger hearts, presumably with "preload reserve," may be operating on the ascending limb of the function curve (Figure 6, point 2, Panels A and B), where an increase in left ventricular volume causes a smaller increase in left ventricular filling pressure and a larger increase in stroke volume.

Why then can the cardiovascular system of the normal individual carefully regulate cardiac filling pressures and volumes and why does the cardiovascular system of the transplant patient appear unable to do likewise? One solution to this puzzle is suggested by the donor to recipient matching of heart size. The guidelines used by our center involve matching the donor and recipient body weights within a range of approximately 20–30%. The average maximal weight discrepancy used nationally is 29%. This is clearly a very inaccurate means of matching donor heart size to recipient body size because recipient volume overload is frequent, and there are differences in body habitus--and in sex-related cardiac mass. Nevertheless, body weight matching is the standard method.

Because of the above problems, one may expect a significant donor heart to recipient body size mismatch in some transplant recipients, a problem certainly unique to the transplant circulation. We previously investigated resting hemodynamics in transplant recipients 3 months after transplantation. Those patients who received a relatively small heart in proportion to their body size required greater resting heart rates and higher resting left and right ventricular filling pressures to maintain their cardiac outputs. All of the 23 patients of the current investigation were also studied at 3 months. Serial investigation of this cohort reveals that the highly significant negative correlation between donor to recipient body weight ratio and resting right atrial or pulmonary capillary wedge pressure ($r = -0.48$, $p = 0.020$ and $r = -0.47$, $p = 0.022$, respectively) is no longer present at 12 months. These data are consistent with an alteration in donor to recipient matching and cardiac allograft hemodynamics over time and could represent alterations in filling characteristics, blood volume, venous capacitance, or cardiac chamber volume. These alterations in the allograft may not be necessarily favorable "adaptations" because the study cohort at 3 months had resting heart rates (92±12 beats/min), right atrial pressures (5±3 mm Hg), pulmonary wedge pressures (9±3 mm Hg), and cardiac outputs (5.0±1.4 l/min) that were not different from their hemodynamics at 12 months. Nevertheless, the inverse relations between donor to recipient body weight ratio and resting heart rate or exercise pulmonary wedge pressure, the differences in the available preload reserve (change in end-diastolic volume) in the extreme cases of body size mismatch, and our previously reported data obtained at 3 months after transplant would support the concept that those patients who received smaller hearts are already optimally or excessively filled at rest, and hence, no preload reserve is available for exercise. The converse would be the case for those patients receiving larger hearts.

The average left ventricular end-diastolic volume index for our patients was only 68 ml/m² by contrast angiography and 48 ml/m² by radionuclide angiography. Although the average donor to recipient ratio was 0.97 for the group, many patients received smaller hearts than may be optimal based on body size. Although the volumes noted above are within the normal range for our laboratory, they are distinctly at the lower range of normal. Furthermore, in two studies that also assessed normal subjects, left ventricular volumes were smaller in the transplanted patient. The radionuclide study by Pflugfelder et al gave left ventricular end-diastolic volume indexes for 18 transplant patients that were remarkably similar to the values reported here. Thus, left ventricular volumes remote from transplantation are smaller than expected when viewed in relation to recipient body size or control subjects. One must therefore conclude that the transplanted heart does undergo change over time but does not appear to achieve the normal relation between end-diastolic volume and body size in the recipient. It is unclear whether or not other factors such as persistently elevated resting heart rates play a role in reducing heart size.

Finally, rejection and scar formation may produce a small stiff ventricle, and in fact, cases of myocardial restrictive physiology have been reported after cardiac transplantation. In these studies, however, assessment of initial cardiac size was not taken into account, and it is not clear from the data whether or not true muscle dysfunction was present. We and others have reported increased filling pressures, diastolic abnormalities, and evi-
dence of myocardial tissue edema early after transplant, but these changes appear to be reversed by 3 months after transplantation. Finally, abnormalities in diastolic function have been reported associated with acute episodes of rejection.26–29 In reports supporting this association, the correlation with rejection appeared to occur early after transplantation26,27 at a time when increased tissue edema may already be present, and in all cases, the changes were subtle with substantial overlap with patients without rejection. In almost all series with cyclosporine immunosuppression reported to date, systolic function was not affected,25–27 and in at least one study,25 filling pressures were unchanged. We feel that it is difficult, however, to attribute our findings to prior rejection and scarring or even to the early rejection occurring in four of our patients. This hypothesis is unattractive for two reasons because of the presence of normal filling pressures at rest in most patients and because of the identical hemodynamic responses in patients who have never experienced a rejection episode. Another reason is that at least one measure of diastolic function, the peak diastolic filling time (by radionuclide ventriculography), was different in the four patients with early rejection compared with the entire group (153±14 vs. 170±20 msec, p=NS). We cannot, however, completely exclude abnormal diastolic pressure-volume relations in a number of these patients.

Other factors involved in the optimal filling of the heart may relate to potential donor and recipient atrial interactions and cardiac innervation. The contraction of the recipient heart’s atrial remnants after orthotopic heart transplantation augments atrial and ventricular pressures (if appropriately timed) by 2–4 mm Hg.30 During exercise, the recipient’s atrial rate usually exceeds the donor heart rate, and therefore, recipient atrial contraction will occur more frequently against a closed ativoventricular valve. This could augment right atrial and pulmo-

dary wedge pressures in excess of ventricular filling pressures. Although potentially contributing, it is unlikely that this entirely explains the increase in atrial pressures noted in this study because similar increases in left ventricular end-diastolic pressure have been reported.1,30

Although the absence of efferent innervation has been emphasized in the literature, the absence of afferent innervation may be very important in the regulation of vascular reflexes.31 In addition, cardiac afferents have been well-documented to be important for renin release,32,33 which would presumably influence both volume regulation and vascular tone. Finally, current immunosuppressive therapy, specifically cyclosporine, may directly alter sodium and water handling by the kidney.34

In conclusion, cardiac transplantation, now a well established clinical modality for the treatment of severe heart failure, imposes unique alterations on the cardiovascular system. Despite normal rest-

ing hemodynamics, most patients have some degree of exercise intolerance. These data suggest that abnormalities in exercise filling pressures (which may be exercise limiting) are determined by the presence or absence of “preload reserve.” We speculate that inappropriate intracardiac volume regulation and donor heart to recipient body size mismatching in patients after cardiac transplantation may play an important role in this phenomenon, although abnormal diastolic properties have not been excluded in these studies. Because of the cardiac allograft recipient’s unique reliance on pre-

load (with its associated increase in filling pressures) for increasing cardiac output, it may be necessary to “oversize” the transplanted heart for optimal recipient exercise performance.

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