Cardiorespiratory Responses of Cardiac Transplant Patients to Graded, Symptom-limited Exercise

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SUMMARY The electrocardiographic and ventilatory responses of 15 denervated heart patients who had undergone cardiac transplantation and 14 age-matched, normally innervated men were compared to assess the pattern of response to graded treadmill exercise. A 5-minute postexercise venous lactate sample was also obtained. Respiratory exchange ratio and ventilation (VE) were higher in denervated patients than in normals during submaximal exercise. Peak values (normals vs denervated) for heart rate (172 vs 159 beats/min), blood pressure (189 vs 167 mm Hg), oxygen uptake (37 vs 25 ml/kg/min), oxygen pulse (0.22 vs 0.16 ml/kg/beat) and work time (26.2 vs 18.0 minutes) were higher in normals than in cardiac transplant recipients. Peak ventilatory equivalent (2.14 vs 3.13 l/min/kg) and lactate values were higher for transplants than for normal subjects, but there were no significant intergroup differences in peak VE or in the respiratory exchange ratio. In cardiac transplant recipients, work time correlated inversely with a measure of rejection history ($r = -0.59, p < 0.01$). The response of cardiac transplant recipients to treadmill work differs from that of normal men and reflects a diminished ability to meet the oxygen demands of the exercising periphery.

Numerous investigators have reported the effects of chronic denervation on the exercise response of laboratory animals and men. During dynamic exercise, the denervated dog has cardiac output and oxygen consumption responses similar to those before denervation, though the capacity for maximal exercise is slightly diminished. In the normal dog, cardiac output during exercise is increased largely through elevation of heart rate, while in the denervated dog, an equivalent increase in cardiac output is achieved through a gradual and attenuated increase in heart rate and an increase in stroke volume subsequent to an increased venous return. This ability to increase heart rate gradually persists in the denervated, adrenalectomized dog, bringing to mind Blinks's report of a positive chronotropic effect of increased right atrial pressure (i.e., venous return).

Supine exercise studies in human cardiac transplant recipients have shown a pattern of response similar to that seen during submaximal exercise in animals. Cardiac output is increased during exercise by an initial elevation of stroke volume followed by a gradual rise in heart rate. Clarke et al. reported that during dynamic exercise in the denervated human, cardiac output increases, first by stroke volume augmentation due to the Starling mechanism and later by enhancement of contractility by circulating catecholamines. In the innervated heart these two mechanisms occur simultaneously. Reports of a diminished cardiac output response for a given level of work accompanied by an elevated arteriovenous oxygen difference suggest that maximal oxygen uptake and exercise tolerance after transplantation may be restricted. To document the cardiorespiratory response and exercise capacity of cardiac transplant recipients during symptom-limited treadmill exercise, the following study was performed.

Methods

Subjects

To assess the effect of cardiac transplantation upon exercise capacity, 15 cardiac transplant recipients (12 men and three women) and 14 normal men performed graded, symptom-limited treadmill exercise. The transplant recipients were patients returning to Stanford for their annual evaluation, while the controls were volunteers, similar in age to the cardiac transplant patients, who were asymptomatic for car-
diovascular and respiratory disease. To obtain normal subjects with activity habits similar to the transplants, we solicited men who considered themselves physically active but who were not vigorously training.

Testing Procedure

All subjects performed 3-minute work loads on the treadmill, starting at a 2.5% grade and 2 mph and progressing to a 2.5% grade and 3 mph at the next stage; the grade was increased by 2.5% every 3 minutes thereafter. Throughout exercise the subject's expired air was routed from a low-resistance Daniel's valve through a 5-foot length of respiratory tubing past a Fleisch pneumotach head interfaced to a Vertek VR 4000 pneumotachometer, into a Plexiglas mixing chamber. Gas was continuously sampled from the mixing chamber into 2-liter anesthesia bags, as described by Wilmore and Costill.14 One-minute aliquots were dried and then analyzed for O₂ (Beckman OM-11) and CO₂ (Godart Capnograph), allowing calculation of oxygen uptake (VO₂), ventilation (VE), respiratory exchange ratio (RER), ventilatory equivalent for oxygen (VE/VO₂) and oxygen pulse. A 12-lead ECG was monitored at rest, before exercise, throughout the exercise period, and for at least 7 minutes of recovery. Blood pressure was measured by sphygmomanometer before exercise and at the end of each work load. One milliliter of blood was obtained from the antecubital vein 5 minutes after exercise for lactate analysis by a modification of the method of Hohorst.16 The work tests for an additional 13 cardiac transplant recipients done without measurement of VO₂ were included in the graphic presentation of heart rate recovery. Subjects were told to continue exercising as long as possible and give a "maximal" effort.

Statistical Analysis

Unless otherwise noted, all statistical comparisons were done using the unpaired t test; p ≤ 0.05 was considered significant.

Results

Subject Characteristics

The characteristics of transplant recipients, transplant donors and normal controls are listed in table 1. Transplant recipients were tested an average of 39 months after transplantation (range 12–95 months). Six had been diagnosed as having coronary artery disease before transplantation, while the other nine had cardiomyopathies. All patients are still living; one has been retransplanted as a result of recurrent coronary artery disease. The mean age of recipients was higher than that of donors (p < 0.001), but body masses did not differ significantly (0.05 < p < 0.10). Transplant recipients and normal controls did not differ in mean age, height or mass.

Electrocardiographic Results

Results of the exercise ECGs were unremarkable. Two-thirds of the transplant recipients and no controls had sinus tachycardia at rest. No transplants and two normal subjects exhibited sinus dysrhythmia and bradycardia. Six normal subjects and four transplant recipients had dysrhythmias during exercise and recovery. No one in either group had signs of ischemia or hypertrophy on the ECG, though one patient had marked ST-segment elevation during recovery from an exercise thallium scan the day after his treadmill test reported here. The ST changes were interpreted to have resulted from coronary spasm; the patient was subsequently retransplanted after being resuscitated after cardiac arrest several months later.

Pattern of Response to Exercise Stress

Figure 1A shows that mean heart rate increased from 72 to 172 beats/min in normals and from 107 to 162 beats/min in transplant recipients. Normals had an exponential rate-recovery curve (r² for exponential fit was 0.82) and transplant recipients had a more gradual, linear diminution in heart rate (fig. 2). Transplant recipients ventilated more for a given level of oxygen uptake than did controls (fig. 1B). RER was higher for transplant recipients than for controls throughout exercise, while the oxygen pulse was lower in transplant recipients than in controls (fig. 1). Figure 3 shows that transplant recipients tend to consume less oxygen for a given work load than normals who attain the same peak speed and grade on the treadmill.

The rate at which transplant recipients and controls found themselves unable to finish successive work loads was similar, though the patients from the transplant group started stopping earlier than controls (fig. 4).

Peak Values

Mean peak exercise values for the 15 transplant recipients and 14 controls are listed in table 2. Controls had higher peak heart rate, systolic blood pressure, rate-pressure product, VO₂, oxygen pulse and work time. Transplant recipients did not differ significantly from controls in VE or RER, while VE/VO₂ and postexercise lactate were significantly higher in transplant recipients. Controls and transplant recipients stopped exercising for similar reasons: Fatigue limited exercise in over 50% of each

<table>
<thead>
<tr>
<th>Table 1. Subject Characteristics</th>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Transplant recipients (n = 15)</td>
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<tr>
<td>Transplant donors (n = 15–39)</td>
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<tr>
<td>Normal controls (n = 14)</td>
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Values are mean ± sd, with the range in parentheses.
group. Other reasons for test cessation included leg discomfort in six, throat discomfort in three, dyspnea in one, dizziness in one and heart rate above 200 beats/min.

**Discussion**

In this study we compared the cardiorespiratory responses of cardiac transplant patients and normal controls. Transplant recipients and controls were well matched with respect to age, height and mass, and an attempt was made to select normal subjects with routine activity levels similar to those of transplant recipients. Contrary to experience with laboratory animals after denervation, previous workers have failed to document reinnervation in human cardiac transplant recipients. Patients in the present study did not exhibit evidence of reinnervation. While normals showed a significant mean increase in heart rate of 12 beats/min ($p < 0.01$, paired t test) when comparing the erect with the supine posture, transplant recipients had no rise in mean heart rate. The high resting heart rate and diminished chronotropic reserve in the transplant patients is characteristic of the denervated state. The lack of ischemia and relatively normal rate of arrhythmias seen in transplant recipients at rest as well as during exercise and recovery provide confirmation that these patients were well controlled regarding rejection at the time of the study. The heart rate response of cardiac transplants to graded exercise (fig. 1) is similar to that in dogs when compared with normal animals, though there was a much greater disparity in maximal heart rates of denervated and innervated dogs than in humans. The transplanted human heart has an impaired chronotropic ability to respond to sudden increases in work, because it must rely solely upon intrinsic rate regulation and circulating catecholamines. Small work increments were selected in this study to allow a gradual accommodation to increasing exercise levels. Thus, when comparing the similar slopes of heart rate increase vs work load exhibited by normals and transplant patients in our study with the dissimilar slopes in dogs shown by Donald and Shepherd, one may postulate that the work increments were low enough to allow for substantial nonneural rate augmentation. One may suppose that the inotropic state of the heart was enhanced by circulating catecholamines as well, based upon the reports of McLaughlin et al. regarding maximal supine exercise in cardiac transplant recipients. The
exponential decline of heart rate in normals after exercise compared with the linear decline of transplanted donor heart rate (fig. 2) prompted us to wonder whether the rapid phase of heart rate decrease after exercise in normals is due to sympathetic withdrawal or to enhanced parasympathetic tone. Venipuncture for lactate analysis was performed between minutes 5 and 6 of recovery, when heart rate increased suddenly in normal subjects but not in transplant recipients.

The difference in ventilatory response to exercise in denervated patients and normals is not attributable to a difference in states of training. When plotted (fig. 5), data from Saltin et al.20 show a "normal" ventilatory response to submaximal exercise after both bed rest and training. Our transplant recipients had elevations in $V_E$ at submaximal and peak exercise.

The ventilatory data presented indicate an earlier onset of anaerobiosis in the transplant recipients than in normals. $V_E$, RER, and $V_E/V_O_2$ were higher for transplant patients throughout exercise, reflecting increased CO$_2$ production during submaximal work, while lower $V_O_2$ at higher levels of work, as well as a diminished oxygen pulse throughout exercise, points

![Figure 3](http://circ.ahajournals.org/)

**FIGURE 3.** Oxygen uptake ($V_O_2$) is shown during the third minute of each treadmill workload for cardiac transplant recipients (solid dots) and controls (open dots) able to complete a maximum of 21, 24, 30 and 33 minutes of the protocol. (During the first 3 minutes of exercise, subjects walked at 2 mph up a 2.5% grade. The second stage was 3 mph and 2.5% grade. The grade was increased by 2.5% for each subsequent 3-minute work load.) Peak lactate values ($\mu$mol/ml) are shown in parentheses.

![Figure 4](http://circ.ahajournals.org/)

**FIGURE 4.** The percentages of cardiac transplant recipients and controls able to complete each successive work load are shown with the estimated energy requirement (mets) and test duration that correspond to each work load.

![Table 2](http://circ.ahajournals.org/)

**TABLE 2. Peak Values**

<table>
<thead>
<tr>
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<th>Normal controls</th>
<th>Transplant recipients</th>
<th>$p$</th>
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<tbody>
<tr>
<td>Heart rate (beats/ min)</td>
<td>172 ± 11</td>
<td>159 ± 16</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td>189 ± 22</td>
<td>167 ± 27</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Rate-pressure product (beats/ min × mm Hg × 10$^2$)</td>
<td>313.9 ± 45.2</td>
<td>256.0 ± 66.6</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td>$V_E$ (l/min, BTPS)</td>
<td>80.6 ± 15.7</td>
<td>76.6 ± 21.2</td>
<td>NS</td>
</tr>
<tr>
<td>$V_O_2$ (ml/kg/min, STPD)</td>
<td>37 ± 5</td>
<td>25 ± 6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>RER</td>
<td>1.03 ± 0.07</td>
<td>1.08 ± 0.11</td>
<td>NS</td>
</tr>
<tr>
<td>Oxygen pulse (ml/kg/beat)</td>
<td>0.22 ± 0.05</td>
<td>0.16 ± 0.04</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>$V_E/V_O_2$ (l/ml/kg)</td>
<td>2.14 ± 0.23</td>
<td>3.13 ± 1.03</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Lactate value 5 minutes after exercise ($\mu$mol/ml)</td>
<td>5.04 ± 1.60</td>
<td>7.29 ± 2.25</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Work time (min)</td>
<td>26.2 ± 3.9</td>
<td>18.0 ± 7.4</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

Abbreviations: $V_E$ = ventilation; $V_O_2$ = oxygen uptake; RER = respiratory exchange ratio; $V_E/V_O_2$ = ventilatory equivalent for oxygen; BTPS = body temperature and pressure, saturated with water vapor; STPD = O°C, 760 mm Hg, dry.
to decreased \( O_2 \) delivery to the exercising periphery. If the volitional fatigue for which most subjects stopped was the result of a buildup of anaerobic metabolic end products, then the different work times in transplant recipients and controls correlate well with their ventilatory data. The trend toward earlier fatigue in transplants (fig. 3) would be expected in light of their elevated RER and \( V_E \) values at these exercise levels. The fact that transplants and controls did not differ in their peak \( V_E \) or RER values, and the fact that transplants had a significantly higher peak lactate level despite a diminished work time when compared with normals, is further evidence for an inadequate \( O_2 \) supply to the exercising periphery throughout exercise. In contrast to the present findings in humans, Donald and Shepherd\(^9\) found no deterioration in maximal work capacity, cardiac output or maximal \( VO_2 \) in dogs after denervation, though cardiac output was largely increased by stroke volume augmentation in denervated dogs and cardioacceleration in normal dogs. Studies done on dogs\(^21,\ 22\) soon after cardiac transplantation have shown a relatively fixed stroke volume with pacing; however, the normal inverse relationship between heart rate and stroke volume has been observed later in the postoperative course of transplanted dogs\(^22,\ 23\) and in man.\(^24\) Stinson et al.\(^9,\ 10\) found that although cardiac transplant patients exhibit a normal increment of cardiac output per unit of external work during supine exercise, the absolute value of their cardiac output is below normal at rest and throughout submaximal exercise, while arteriovenous oxygen differences are above normal at any given work level. Our data are consistent with the pattern of elevated arteriovenous oxygen difference and diminished cardiac output reported by Stinson et al.

In attempting to resolve the differences between response of denervated animals and human cardiac transplant patients to exercise, one must consider the effects of graft rejection and interference from immunsuppressive or other medications. At Stanford, diagnosis of rejection is based upon myocardial biopsy results, summed QRS voltage changes, and changes in clinical cardiac status. Rejection episodes may be designated as mild, moderate or severe, based on the clinical evaluation of cardiac function.\(^9\) Though our patients were not experiencing diagnosed rejection at the time of their exercise test, we were able to examine the rejection history of 22 transplant patients who had performed fatigue-limited treadmills in our lab on the standard protocol. Using work time as a single indicator of exercise capacity, we examined the relationship between rejection history and exercise performance. Mean work times were associated with zero to six episodes of early, late and combined early and late rejection. (Early indicates rejection onset less than 90 days after surgery; late means onset more than 90 days after surgery.) To weight the severity of early rejection episodes, an arbitrary value of one was given to mild, two to moderate, and three to severe rejection episodes, and the totals were designated an "arbitrary early rejection score." There is a general, though not significant, trend toward a decrease in work time as the number of early, late, and total rejection episodes increases. A trend is also seen with increasing magnitude of arbitrary early rejection score. Figure 6 shows the linear regression of work time vs arbitrary early rejection score. It appears that there is a signif-

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**FIGURE 5.** Mean data from Saltin et al.\(^9\) Filled triangles with solid line represent control exercise test, open triangles represent response after 20 days of bed rest, and filled triangles with dashed line represent response after 53-55 days of training after bed rest. \( VO_2 = \) oxygen uptake; \( V_E = \) ventilation. BTPS = body temperature and pressure, saturated with water vapor; STPD = 0°C, 760 mm Hg, dry.

**FIGURE 6.** Regression of work time on arbitrary early rejection score.
cant relationship between rejection history and work performance, though other factors, such as degree of physical training and medication side effects, are also important.

Potential medication interference with exercise performance falls under two categories. First, one must consider the effects of potential muscle weakness, muscle mass loss, osteoporosis and steroid myopathy that can accompany prednisone administration. Loss of muscle mass has been a problem in this patient group and could provide a partial explanation for the decrease in work time relative to the control group. Were it not for the altered cardiac output and arteriovenous oxygen difference responses reported by Stinson et al.,9 as well as the evidence of excessive anaerobic work in the present study, steroid-induced alterations of peripheral muscle could explain the differences in work capacity of transplant recipients compared with normals. Second, the oxygen-carrying capacity of the blood could be compromised by the administration of the hematopoietic drugs azathioprine and cyclophosphamide. This does not appear to be a significant factor in the present study group; 87% of our transplant patients had normal hematocrits and 80% had normal hemoglobin values16 at the time of their exercise test. Linear correlations between both hemoglobin level and work time and hematocrit and work time were performed, and no relationship was found.

Conclusions

The response of cardiac transplant patients to graded, symptom-limited treadmill exercise is characterized by a decreased chronotropic reserve, altered ventilatory pattern, decreased work time and elevated postexercise lactate level. Our data point to a limited supply of oxygen to the exercising periphery, probably as a result of the cardiac output limitation noted by Stinson et al.9 It appears that there is some relationship between functional capacity and rejection history supporting the possibility that cardiac output is limited in transplant patients as a result of residual myocardial injury subsequent to rejection.

Acknowledgments

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