Cardiorespiratory responses to exercise training after orthotopic cardiac transplantation

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ABSTRACT  We have tested the feasibility and effectiveness of a 2 year (average 16 ± 7 months) walk/jog exercise program on 36 male orthotopic cardiac transplant patients (21 to 57 years old) seen initially 2 to 23 months after surgery. Comparison of initial exercise test results with those in 45 age-matched normal men showed the patients to have a lesser lean body mass (56 ± 7 vs 63 ± 8 kg, p < .001), with a higher resting heart rate (104 ± 12 vs 77 ± 14 beats/min, p < .001) and systolic (138 ± 16 vs 129 ± 17 mm Hg, p < .001) and diastolic (95 ± 14 vs 84 ± 10 mm Hg, p < .001) blood pressures. Peak power output was less than normal (101 ± 27 vs 219 ± 41 W, p < .001), as was peak heart rate (136 ± 15 vs 176 ± 13 beats/min, p < .001), peak oxygen intake (VO2max) (22 ± 5 vs 34 ± 6 ml·kg·min⁻¹, p < .001), and absolute anaerobic threshold (1.18 ± 0.40 vs 2.04 ± 0.40 liters·min⁻¹, p < .001). Peak ventilatory equivalent was higher (48 ± 9 vs 37 ± 6 1.1⁻¹, p < .001). Cardiac output (Q), as estimated by the CO2 rebreathing method, was slightly above normal at rest (p < .01), but below normal at two submaximal work rates. The group's average weekly training distance was 24 km, with eight highly compliant patients progressing to 32 km or more weekly. After training, lean tissue increased (+2.4 ± 3.1 kg, p < .001), and resting values were reduced for heart rate (−4 ± 11 beats/min, p < .05), systolic (−13 ± 20 mm Hg, p < .001), and diastolic (−9 ± 17 mm Hg, p < .001) blood pressures. There were significant reductions in submaximal values for minute ventilation (V̇E), ratings of perceived exertion, and diastolic blood pressure at equivalent workloads. Peak values increased for power output (+49 ± 34 W, p < .001), VO2max (+4.0 ± 6.0 ml·kg·min⁻¹, p < .001), V̇E (±20 ± 20 1·min⁻¹, p < .001), and heart rate (±13 ± 17 beats/min, p < .001), and decreased for diastolic blood pressure (−8 ± 15 mm Hg, p < .001). In the eight highly compliant patients a greater decrease occurred in resting heart rate (−11 ± 5 beats/min, p < .001) and submaximal heart rate (range 5 to 10 beats/min less at each power output), with a greater increase in peak power output (+68 ± 42 W, p < .001), and VO2max (+11 ± 6 ml·kg·min⁻¹, p < .001). The slope of the Q/VO2 line was unchanged by training. There was no evidence of cardiac reinnervation in any patient. We conclude that exercise rehabilitation is justified because of its ability to increase working capacity and thus quality of life in cardiac transplant patients.


CARDIAC TRANSPLANTATION is now an accepted treatment for end-stage cardiac disease, with actuarial survival rates of 78% for the first 2 years1 and greater than 60% for the first 5 years after operation.2,3 Nevertheless, to date there have not been any reports on the effect of a long-term endurance-type exercise training program on the cardiorespiratory function of a large group of such patients.

Consequently, the functional status of 36 male orthotopic cardiac transplant recipients was assessed at entry to and at the end of a 16 month training program. The initial status of the patients was compared with the findings in 45 age-matched male volunteers.

Methods

Because only 44 patients were entered into the study, and because they were taking a variety of immunosuppressive and other drugs, it was not feasible to randomize them into intervention and control cohorts. Averaged changes in measurements for the entire group thus provided the basis for our conclusions.

To encourage compliance with a lengthy exercise training program in patients already obligated to frequent invasive reassessments, only noninvasive testing was used.

Patients. A total of 44 patients (all but one male) were initially enrolled. Two of the group died during the study, one...
after repeated bouts of allograft rejection, and one during an acute rejection episode. Initial findings in these two individuals were unremarkable. One underwent initial assessment, but never started to exercise, dying 8 months after assessment and 31 months after transplantation. The other was active in the exercise program when he died (4 months after the initial test, and 21 months after the transplantation), having attained an average walking distance of 13 km/week.

Five men and one woman dropped out after the initial test, all for nonmedical reasons that were typical of those encountered in a long-term training program. Their average age was 47.2 ± 8.0 years, the mean time from initial test to dropout was 8.2 ± 3.3 months, and the initial findings were unremarkable. Our data are therefore restricted to 36 men, representative of an average of 7 months after transplantation, who exercised for 16.3 ± 6.9 months.

The age of the compliers at enrollment was 47.3 ± 8.6 years (21 to 57 years). Before surgery, their clinical status had deteriorated to New York Heart Association functional classification IV, with causes including cardiomyopathy, coronary artery disease, myocarditis, valvular disease, and bacterial endocarditis. The time from transplantation to initial assessment was 7.4 ± 6.1 months; the distribution was slightly skewed (median 4.8, range 2 to 23 months). All patients were taking cyclosporine and azathioprine, with six on maximal quantities of oral steroids initially, and five finally. None required β-blocking agents, initially or finally. Other medications included nifedipine, (three initially, four finally), hydralazine (six initially, six finally), and furosemide (nine initially, six finally). The 45 age-matched volunteers were physically active, but not athletic individuals. None were taking medications of any type.

**Body composition.** Measurements were made of height, body mass, and three standard skin folds (triceps, subscapular, and suprailliac). Body fat and lean body mass were derived from appropriate age-specific equations.7

**Exercise testing.** Assessment included two cycle ergometer tests, performed approximately 24 hr apart. The first (stage I) test habituated patients to the laboratory procedures, measured peak heart rate, power output, and oxygen consumption (VO₂), and provided guidelines for the exercise prescription; loadings were increased by 16.7 W each minute until the patient could no longer pedal at 60 rpm. At each load the patient indicated his perception of effort with reference to the Borg scale.8 The electrocardiogram (leads III, V₁, and CM₄₆) was monitored throughout, with the use of a computer-assisted system (Marquette case II). Blood pressures were taken by sphygmomanometer in the final 15 sec of each minute of exercise. Metabolic data were analyzed by a SensorMedics Horizon II Metabolic Cart. The ventilatory anaerobic threshold was determined from the inflection of the minute ventilation (Vₑ)/VO₂ line, supplemented where necessary by information from the ventilatory equivalent and excess CO₂ production. Indications for halting a test before the demonstration of an VO₂ plateau were as follows:

1. Adverse symptoms (recognizing that the transplanted heart does not sense anginal pain); e.g., severe dyspnea, light-headedness and faintness, confusion, severe fatigue.
2. Adverse signs; e.g., facial pallor, heart rate or blood pressure fall, or failing to rise with increasing effort, systolic blood pressure exceeding 280 mm Hg, or diastolic blood pressure exceeding 140 mm Hg.
3. Adverse electrocardiographic changes; e.g., frequent complex ventricular extrasystoles, ventricular tachycardia, sustained supraventricular tachycardia, atrial fibrillation, second- or third-degree heart block, severe ST segment depression (horizontal or downsloping greater than 4 mm).9

**TABLE 1**

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (yr)</th>
<th>Height (cm)</th>
<th>Body mass (kg)</th>
<th>Excess mass(^A) (kg)</th>
<th>Skin folds (average of 3, mm)</th>
<th>Body fat (%)</th>
<th>Lean mass kg</th>
<th>kg·cm(^{-1}) of stature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac transplant</td>
<td>47.3 ± 8.6</td>
<td>172.8 ± 6.1</td>
<td>69.9 ± 11.5</td>
<td>3.1 ± 10.4</td>
<td>15.4 ± 6.8</td>
<td>19.1 ± 5.0</td>
<td>56.2 ± 7.3</td>
<td>0.325 ± 0.06</td>
</tr>
<tr>
<td>recipients (n = 36)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-matched normal</td>
<td>45.4 ± 7.2</td>
<td>176.4 ± 6.5</td>
<td>80.7 ± 10.9(^C)</td>
<td>10.1 ± 9.0(^C)</td>
<td>17.0 ± 4.6(^C)</td>
<td>22.1 ± 3.5(^C)</td>
<td>62.6 ± 7.6(^C)</td>
<td>0.355 ± 0.07(^C)</td>
</tr>
<tr>
<td>subjects (n = 45)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

\(^B\) p < .01; \(^C\) p < .001.

**TABLE 2**

<table>
<thead>
<tr>
<th>Group</th>
<th>Body mass (kg)</th>
<th>Body fat (%)</th>
<th>Lean mass (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Final</td>
<td>Change</td>
</tr>
<tr>
<td>All patients (n = 36)</td>
<td>69.9 ± 11.5</td>
<td>73.9 ± 12.4</td>
<td>+4.0 ± 6.7(^A)</td>
</tr>
<tr>
<td>Highly compliant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>patients (n = 8)</td>
<td>67.6 ± 11.6</td>
<td>68.9 ± 9.6</td>
<td>+1.3 ± 5.9</td>
</tr>
<tr>
<td>Moderately compliant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>patients (n = 28)</td>
<td>70.3 ± 11.6</td>
<td>75.3 ± 12.9</td>
<td>+5.0 ± 6.8(^A)</td>
</tr>
</tbody>
</table>

\(^A\) p < .001.
TABLE 3

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (yr)</th>
<th>Weeks after surgery</th>
<th>Heart rate</th>
<th>Systolic pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rest (beats/min)</td>
<td>Peak (beats/min)</td>
</tr>
<tr>
<td>All patients (n = 36)</td>
<td>47.3 ± 8.6</td>
<td>29.4 ± 24.4</td>
<td>103.9 ± 11.8</td>
<td>135.5 ± 15.2</td>
</tr>
<tr>
<td>Age-matched normal subjects</td>
<td>45.4 ± 7.2</td>
<td>---</td>
<td>76.8 ± 13.7(^a)</td>
<td>176.2 ± 12.8(^a)</td>
</tr>
<tr>
<td>(n = 45)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highly compliant patients</td>
<td>42.1 ± 11.5</td>
<td>25.5 ± 25.7</td>
<td>116.6 ± 9.2</td>
<td>145.6 ± 12.2</td>
</tr>
<tr>
<td>(n = 8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately compliant patients</td>
<td>48.8 ± 6.7(^a)</td>
<td>30.5 ± 24.5</td>
<td>100.3 ± 9.9(^a)</td>
<td>132.6 ± 14.9(^a)</td>
</tr>
<tr>
<td>(n = 28)</td>
<td></td>
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</tbody>
</table>

\(^a\) p < .001, all patients vs normal subjects and eight highly compliant patients vs 28 moderately compliant patients.

In the second (stage II) test, steady-state cardiac output was measured at rest and approximately one- and two-thirds of the previously determined peak power output with the CO\(_2\) rebreathing technique of Jones and Campbell.\(^b\)\(^c\) Arterial carbon dioxide pressures were estimated from the end-tidal CO\(_2\) and tidal volume and the standard downstream correction was applied to the mixed venous figure, always based on a true plateau.

**Exercise training regimen.** Workouts were preceded by a 20 min muscle-stretching routine. The main prescribed activity was walking, initially 1.6 km five times weekly, at an intensity based on the results of the stage I test with respect to 60% to 70% peak oxygen intake (VO\(_2\)max), the ventilatory anaerobic threshold, and a perception of effort of 14 on the Borg scale. The initial average pace varied between 11 and 14 min/km. The distance was then increased by 1.6 km every 2 weeks, maintaining the same pace until, by 6 weeks, the patient was walking 4.8 km five times weekly. The pace was then quickened by 1 min per 1.6 km until the 4.8 km was accomplished in 45 min (typically within 4 months of starting the program). Thereafter, 45 m bouts of slow jogging paced at 7.5 min/km were introduced every 800 m, 400 m, 200 m, and so on until ultimately the entire 4.8 km was completed in 36 min. The distance was then extended in stages by 400 m, the aim being to have the patient jogging 6.4 km in 48 min five times weekly by the eighth month of the program.\(^1\)\(^1\)\(^2\)

The training regimen recognized that angina could not warn of myocardial ischemia and that the sluggish response of the denervated heart to effort rendered pulse counting less accurate as a measure of exercise intensity. Thus, accurate pacing, thorough familiarity with the Borg concept of perceived exertion, and correct interpretation of such symptoms as excessive dyspnea, unusual fatigue, lightheadedness, and extrasystoles were of paramount importance. The possibility of episodes of rejection or infection retarding progress was an additional concern.

**Statistical methods.** Because the normal subjects were age- and sex-matched, differences in response to exercise between them and the patients could be evaluated by t tests for groups of unequal size. Training responses were evaluated by paired t tests. Since our experience has shown differences in responses between patients covering longer and shorter distances,\(^13\)\(^14\) we subdivided data for the 36 patients on this basis.

**Results**

**Compliance.** Few workouts were missed because of injuries or other medical setbacks. The average length of time on the program was 16 ± 7 months. All patients progressed to walk/jogging an average distance of 24 km/wk, at an average pace of 8.5 min/km. The eight most highly motivated achieved 32 km or more a week, at an average pace of 6.5 min/km. One of these entered and finished the 42 km Boston marathon 12 months after joining the program and 15 months after undergoing the transplantation procedure.\(^16\) The findings for the eight were compared with the results in the remaining 28 patients.

**Body composition.** Body masses of the patients were lighter than those of the age-matched controls, even allowing for the latter’s greater height (table 1). The patients had a lower percentage of body fat, but the differences in body mass were largely attributable to a lesser lean mass.

After training, the patients had increased their body mass by 4 kg without significant increase in body fat, implying an increase in lean mass (table 2).

**Exercise test results.** A total of 250 exercise tests were performed without incident; all stage I tests were continued to voluntary exhaustion.

**Initial assessment (stage I test).** Initial cardiorespiratory responses before training were typical of the denervated heart.\(^17\)\(^19\) Resting heart rates were higher (p < .001) and peak exercise heart rates lower (p < .001) than in the age-matched normal subjects (table 3).

Resting systolic and diastolic pressures were higher in the patients than in the normal subjects (p < .001), although the resting pulse pressure was essentially normal (41.7 ± 12.7 vs 44.8 ± 12.6 mm Hg in the normal subjects). The patients terminated exercise at a lower systolic pressure (p < .001) and double product (p < .001) (table 3).

A breakdown of information on the eight highly compliant and the 28 moderately compliant patients

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CIRCULATION
TABLE 3 (Continued)

<table>
<thead>
<tr>
<th>Diastolic pressure</th>
<th>Peak Double product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest (mm Hg)</td>
<td>Peak (mm Hg)</td>
</tr>
<tr>
<td></td>
<td>(beats-mm Hg(^{-1}))</td>
</tr>
<tr>
<td>95.3 ± 13.5</td>
<td>100.4 ± 12.5</td>
</tr>
<tr>
<td>83.8 ± 10.0</td>
<td>95.6 ± 12.1</td>
</tr>
<tr>
<td>86.3 ± 15.7</td>
<td>93.3 ± 13.2</td>
</tr>
<tr>
<td>97.9 ± 11.9</td>
<td>102.4 ± 11.7</td>
</tr>
</tbody>
</table>

showed that the former were 6 years younger (p < .001) and had a higher average resting (p < .001) and peak exercise (p < .001) heart rate. Nevertheless, their peak heart rates were lower than those of the age-matched normal subjects (p < .001), (table 3). No significant correlations were found between cardiovascular function and either age of patient, age of donor, or time elapsing between surgery and entry to program.

All exercise tests were terminated because of leg fatigue. Three of the highly compliant and 15 of the moderately compliant patients exercised to an oxygen plateau as classically defined (an increment in \(\dot{V}O_2\) of less than 2 ml·kg·min\(^{-1}\) for a further increment of power output), compared with 39 of the 45 age-matched controls. The absolute \(\dot{V}O_2\)max attained before training was 70% of that for the age-matched normal group (p < .001); there was no significant difference between high compliant and moderately compliant patients (table 4).

The average peak power output achieved by the patients before training was less than one-half that attained by the normal subjects (p < .001), showing that they were unable or unwilling to undergo substantial anaerobic metabolism. At peak effort, the patients also had a lower rating of perceived exertion (p < .001), respiratory exchange ratio (NS), and \(V\_E\) (p < .001). Peak ventilatory equivalent was, however, higher (p < .001) than in the normal subjects. The absolute ventilatory threshold was lower (p < .001) in the patients (table 4).

Final assessment (stage I test). After training, most test values approached those of healthy age-matched control subjects (table 5). There was no evidence of reinnervation, but the resting heart rate for all patients was reduced (p < .05), with the greatest reduction occurring in those who were highly compliant (p < .001).

FIGURE 1. Relationship of heart rate to power output in total patient group before and after conditioning (n = 36).

FIGURE 2. Relationship of heart rate to power output in highly compliant patients before and after conditioning (n = 8, mean ± SD). *p < .05; **p < .01; ***p < .001.

FIGURE 3. Relationship of oxygen intake to power output before and after conditioning (n = 36).
TABLE 4
Initial cardiorespiratory responses of cardiac transplant patients and age-matched normal subjects at stage I exercise test (mean values ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>VO₂ max 1·min⁻¹ STPD</th>
<th>VO₂ max ml·kg⁻¹·min⁻¹ STPD</th>
<th>Peak power (W)</th>
<th>Peak ventilation (1·min⁻¹ BTPS)</th>
<th>VE/VO₂ (1·l⁻¹)</th>
<th>Resp. exchange ratio</th>
<th>Rating of perceived exertion (units)</th>
<th>Ventilatory threshold (1·min⁻¹ STPD)</th>
<th>% of VO₂ max</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n = 36)</td>
<td>1.51 ± 0.33</td>
<td>21.7 ± 4.5</td>
<td>101 ± 27</td>
<td>70.5 ± 16.6</td>
<td>48.1 ± 9.3</td>
<td>1.14 ± 0.11</td>
<td>18.3 ± 2.1</td>
<td>1.18 ± 0.38</td>
<td>78</td>
</tr>
<tr>
<td>Age-matched normal subjects (n = 45)</td>
<td>2.74 ± 0.56</td>
<td>34.0 ± 5.9</td>
<td>219 ± 41</td>
<td>101.4 ± 23.8</td>
<td>37.3 ± 6.4</td>
<td>1.18 ± 0.10</td>
<td>19.4 ± 1.1</td>
<td>2.04 ± 0.44</td>
<td>75</td>
</tr>
<tr>
<td>Highly compliant patients (n = 8)</td>
<td>1.44 ± 0.40</td>
<td>21.3 ± 4.9</td>
<td>105 ± 34</td>
<td>70.7 ± 19.9</td>
<td>49.5 ± 9.5</td>
<td>1.14 ± 0.15</td>
<td>17.8 ± 1.7</td>
<td>1.18 ± 0.33</td>
<td>82</td>
</tr>
<tr>
<td>Moderately compliant patients (n = 28)</td>
<td>1.53 ± 0.32</td>
<td>21.8 ± 4.4</td>
<td>100 ± 25</td>
<td>70.4 ± 15.9</td>
<td>47.6 ± 9.4</td>
<td>1.13 ± 0.08</td>
<td>18.4 ± 2.2</td>
<td>1.19 ± 0.27</td>
<td>78</td>
</tr>
</tbody>
</table>

STPD = standard temperature, pressure, dry; BTPS = body temperature, pressure, saturated.

* p < .001.

At the same time, the peak heart rate was significantly increased in both highly compliant (p < .001) and moderately compliant patients (p < .001; table 5). Nevertheless, the final resting heart rates remained higher (p < .001), and the final peak heart rates lower (p < .001), than in the age-matched normal subjects (table 5).

Resting systolic and diastolic blood pressures for all patients were significantly reduced (p < .001), as were peak diastolic pressures (p < .001), so that at the end of the conditioning program differences from normal were no longer significant. However, the peak systolic pressure and the peak double product did not change significantly, remaining less than in the normal subjects (p < .001; table 5).

At the final assessment, the average relationship of submaximal heart rates to midrange power outputs showed a small reduction in the group as a whole (figure 1). However, there was no change in the 28 moderately compliant patients, whereas in the eight highly compliant patients the effect was quite large (average, 7 beats/min, range 5 to 10; figure 2). Interestingly, the patient who completed the Boston marathon, averaging 65 km weekly in the final months of training, showed the response closest to a true training bradycardia. Since the relationship of VO₂ to power output in all patients, including the highly compliant eight, was unchanged during submaximal effort (figure 3), this reduction in submaximal heart rate could not have been due to an improvement in mechanical efficiency on the ergometer. There was also an overall and significant marked reduction in the rating of perceived exertion (figure 4), VE (figure 5), and diastolic blood pressure (figure 6) at equivalent power outputs.

TABLE 5
Final cardiovascular status of cardiac transplant patients (total group, highly compliant, and moderately compliant), with differences from initial values (stage I exercise test, mean values ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>Rest Heart rate (beats/min)</th>
<th>Peak Heart rate (beats/min)</th>
<th>Rest Systolic pressure (mm Hg)</th>
<th>Peak Systolic pressure (mm Hg)</th>
<th>Rest Diastolic pressure (mm Hg)</th>
<th>Peak Diastolic pressure (mm Hg)</th>
<th>Peak double product (beats·mm Hg⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n = 36)</td>
<td>100.3 ± 13.4</td>
<td>148.2 ± 17.2</td>
<td>125.2 ± 14.9</td>
<td>174.4 ± 20.1</td>
<td>86.3 ± 11.6</td>
<td>92.5 ± 12.1</td>
<td>25,336 ± 4,823</td>
</tr>
<tr>
<td>Change from initial value</td>
<td>-3.6 ± 10.7</td>
<td>+12.7 ± 16.7</td>
<td>-12.6 ± 20.2</td>
<td>-3.8 ± 30.9</td>
<td>-9.0 ± 16.5</td>
<td>-7.9 ± 15.4</td>
<td>+1,794 ± 6,611</td>
</tr>
<tr>
<td>Highly compliant patients (n = 8)</td>
<td>106.1 ± 8.7</td>
<td>157.8 ± 15.8</td>
<td>125.9 ± 16.8</td>
<td>175.0 ± 17.7</td>
<td>8.59 ± 10.8</td>
<td>91.0 ± 6.7</td>
<td>27,210 ± 4,331</td>
</tr>
<tr>
<td>Change from initial value</td>
<td>-10.5 ± 4.9</td>
<td>+12.1 ± 13.2</td>
<td>-6.0 ± 21.1</td>
<td>+10.0 ± 2.2</td>
<td>-0.4 ± 17.8</td>
<td>-2.3 ± 12.3</td>
<td>+3,919 ± 5,110^A</td>
</tr>
<tr>
<td>Moderately compliant patients (n = 28)</td>
<td>98.6 ± 14.2</td>
<td>145.5 ± 16.9</td>
<td>124.9 ± 14.6</td>
<td>174.3 ± 21.1</td>
<td>86.4 ± 12.0</td>
<td>93.3 ± 13.1</td>
<td>24,801 ± 4,894</td>
</tr>
<tr>
<td>Change from initial value</td>
<td>-1.7 ± 11.1</td>
<td>+12.7 ± 17.8</td>
<td>-14.5 ± 19.9</td>
<td>-7.7 ± 32.3</td>
<td>-11.5 ± 15.5</td>
<td>-9.1 ± 15.9</td>
<td>+1,187 ± 6,940</td>
</tr>
</tbody>
</table>

^A p < .05; ^b p < .001.
FIGURE 4. Relationship of rating of perceived exertion to power output before and after conditioning (n = 36, mean ± SD). *p < .05; **p < .01; ***p < .001.

While six of the highly compliant patients reached an oxygen plateau after training, only 15 of the remaining 28 patients did so. Nevertheless, there was a notable overall increase of 27% in VO₂max (change of +4.2 ± 5.9 ml·kg·min⁻¹, p < .001), which was again larger (54%) in the eight highly compliant patients (change of +10.9 ± 5.6 ml·kg·min⁻¹, p < .001) than in the remaining 28 patients (change of +2.7 ± 5.1 ml·kg·min⁻¹ or 20%, p < .001) (table 6). Gains in peak power output were even more marked, 64% and 43% for the subgroups, respectively (changes of +68 ± 42 W, p < .001; and +43 ± 30 W, p < .001), with all patients exercising to a larger respiratory VE and a higher maximum heart rate after training.

FIGURE 5. Relationship of VE responses to power output before and after conditioning (n = 36, mean ± SD). *p < .05; **p < .01; ***p < .001.

Since change in respiratory gas exchange ratio (NS), and peak rating of perceived exertion (p < .05) were quite small, it is unlikely that greater voluntary effort was responsible for improved performance (table 6). Stage II test (initial and final). The initial resting cardiac outputs of the transplant patients (average cardiac index of 2.94 ± 0.73 liters·min⁻¹·m²), were slightly larger than those of the age-matched control subjects (2.55 ± 0.48 liters·min⁻¹·m², change of 0.39, SE of change 0.14; p < .01). At the two submaximal workloads, the patients' average cardiac outputs were less than those for the normal subjects (table 7).

For the whole patient group, the initial linear regression relating cardiac output (Qt) to VO₂ was Qt = 6.1 (VO₂) + 3.29 (r = .88), with no difference between highly and moderately compliant groups. The

FIGURE 6. Relationship of diastolic blood pressure responses to power output before and after conditioning (n = 36, mean ± SD). *p < .05; **p < .01; ***p < .001.

FIGURE 7. Relationship of individual cardiac output responses to VO₂ before and after conditioning (n = 36).
corresponding equation for the age-matched normal subjects was \( Q_l = 6.0 \cdot (VO_2) + 3.87 \) \((r = .94)\). After training, the line for the patients remained essentially unchanged \((Q_l = 5.9 \cdot (VO_2) + 3.17, r = .94; \) figures 7 and 8).

**Discussion**

Human physical work performance is impaired after cardiac transplantation,\(^{20}\) in contrast to the performance of the denervated dog heart.\(^ {21}\) Improvement by exercise training seems a reasonable approach. However, correct interpretation of any improvement apparently associated with training must be viewed in the light of initial baseline responses of the transplanted human heart to exercise, as well as the possibility that any such changes are due to spontaneous recovery.

**Initial pretraining exercise responses.** Several investigators have commented on the high resting heart rate after transplantation,\(^ {17, 18, 22}\) attributing this to a revelation of the intrinsic rate of the sinoatrial node. In the absence of autonomic reinnervation, the resting rate has remained quite high, with figures from the literature ranging from an average of 107 beats/min at age 29 to 80 beats/min at age 52 years.\(^ {23, 24}\) Given that the average age of the donors in this study was 24 years, and that care was taken to familiarize our patients with the exercise test protocol, it seems reasonable to assume that the high resting heart rates we observed are nodal and not due to anxiety. Assuming a normal peripheral demand for blood flow, the resting tachycardia implies a small stroke volume, and therefore during light exercise the Frank-Starling mechanism can produce a substantial increase of cardiac output. However, during more vigorous activity any further increase in cardiac output depends on circulating catecholamine-induced chronotropic and inotropic responses.\(^ {18, 21, 25}\) This

**TABLE 6**

Final cardiorespiratory responses of cardiac transplant patients (total group, highly compliant, and moderately compliant), with differences from initial values (stage I exercise test, mean values ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>VO(_2) max (ml·kg·min(^{-1}))</th>
<th>Peak power (W)</th>
<th>Peak ventilation (1·min(^{-1}))</th>
<th>VE/VO(_2) (1·l·l(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1·min(^{-1}) STPD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients (n = 36)</td>
<td>1.92 ± 0.47</td>
<td>150 ± 40</td>
<td>90.9 ± 23.4</td>
<td>48.1 ± 9.2</td>
</tr>
<tr>
<td>Change from initial value</td>
<td>+ 0.41 ± 0.44&lt;sup&gt;a&lt;/sup&gt;</td>
<td>+ 49 ± 34&lt;sup&gt;a&lt;/sup&gt;</td>
<td>+ 20.4 ± 20.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.0 ± 9.6</td>
</tr>
<tr>
<td>Highly compliant patients (n = 8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from initial value</td>
<td>+ 0.77 ± 0.43&lt;sup&gt;b&lt;/sup&gt;</td>
<td>+ 68 ± 42&lt;sup&gt;b&lt;/sup&gt;</td>
<td>+ 23.1 ± 20.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>− 6.9 ± 12.6</td>
</tr>
<tr>
<td>Moderately compliant patients (n = 28)</td>
<td>+ 0.31 ± 0.39&lt;sup&gt;b&lt;/sup&gt;</td>
<td>+ 43 ± 30&lt;sup&gt;b&lt;/sup&gt;</td>
<td>+ 19.6 ± 21.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>+ 2.2 ± 7.4</td>
</tr>
</tbody>
</table>

Abbreviations as in table 4.

<sup>a</sup>\( p < .05; \) <sup>b</sup>\( p < .001\).

**TABLE 7**

Responses of cardiac transplant patients and age-matched normal subjects to stage II testing before and after conditioning

<table>
<thead>
<tr>
<th>Group cardiac transplant recipients (n = 36)</th>
<th>VO(_2) (1·min(^{-1})) STPD</th>
<th>Cardiac output (1·min(^{-1}))</th>
<th>SV (ml)</th>
<th>AVD (ml·l(^{-1}))</th>
<th>VO(_2) (1·min(^{-1})) STPD</th>
<th>Cardiac output (1·min(^{-1}))</th>
<th>SV (ml)</th>
<th>AVD (ml·l(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>0.34 ± 0.06</td>
<td>5.4 ± 1.3</td>
<td>2.94 ± 0.73</td>
<td>52.0 ± 14.0</td>
<td>65.8 ± 16.5</td>
<td>0.85 ± 0.16</td>
<td>8.6 ± 1.9</td>
<td>74.0 ± 21.0</td>
</tr>
<tr>
<td>Final</td>
<td>0.29 ± 0.04</td>
<td>4.8 ± 0.74</td>
<td>2.54 ± 0.44</td>
<td>48.1 ± 11.1</td>
<td>63.1 ± 11.3</td>
<td>0.87 ± 0.15</td>
<td>8.6 ± 1.4</td>
<td>77.4 ± 16.0</td>
</tr>
<tr>
<td>Age-matched normal subjects (n = 45)</td>
<td>0.30 ± 0.04</td>
<td>5.0 ± 0.84</td>
<td>2.55 ± 0.48</td>
<td>69.2 ± 13.5</td>
<td>61.8 ± 10.5</td>
<td>1.16 ± 0.19</td>
<td>11.3 ± 1.6</td>
<td>106.0 ± 24.0</td>
</tr>
</tbody>
</table>

SV = stroke volume; AVD = arteriovenous difference; STPD = standard temperature, pressure, dry.
explains the sluggish heart rate response and delayed recovery rates seen on the incremental exercise test.

Both cardiac and peripheral vascular components probably contribute to changes in resting and exercise blood pressure responses. The resting hypertension may reflect preoperative congestive heart failure and a resultant chronic elevation of plasma norepinephrine, or it may be a side effect of cyclosporine. Loss of sympathetic stimulation and resultant impairment of myocardial contractility could account for the low peak exercise systolic pressure. Chronically elevated levels of serum catecholamines may also induce down-regulation of the peripheral arterial \( \alpha \)-receptors. This blunted systolic blood pressure response to exercise may compound the peripheral limitations described below.

Our previous exercise radionuclide studies have also noted that the transplanted heart develops impairment of diastolic function at moderate levels of supine exercise (45 W). Contributing factors here include impaired myocardial compliance, ischemia from accelerated coronary artery narrowing, or the side effects of immunosuppressive drugs.

The patients had 6 kg less lean tissue mass than the age-matched normal subjects, which was likely the result of prolonged preoperative physical inactivity. This reduction in muscle mass undoubtedly plays a major role in limiting maximum exercise performance. Partly because of this peripheral limitation and partly because of low peak heart rate and peak blood pressure, the \( \text{VO}_2\text{max} \) of our patients was only about two-thirds of that in the normal age-matched population. Consequently, early fatigue is experienced during exercise, thus discouraging future effort and leading to a vicious circle of further loss of lean tissue and more fatigue.

**Exercise responses after training.** Since the incidence of rejection episodes or coronary atherosclerosis was minimal or absent in our group, we believe we are justified in disregarding these factors as playing any significant part in our findings.

The changes observed in association with training included an increase of lean tissue, peak power output, peak heart rate, peak \( V_E \), and \( \text{VO}_2\text{max} \), together with a reduction in resting systolic and diastolic blood pressures and resting heart rates, the latter more marked in those patients who attained a regular weekly training distance of 32 km or more. There was also a significant reduction in peak diastolic blood pressure.

At all levels of submaximal effort, there was an overall reduction in diastolic blood pressure, \( V_E \), and rating of perceived exertion, but no change in mechanical efficiency or submaximal cardiac output. Submax-

![FIGURE 8. Relationship of cardiac output responses to \( \text{VO}_2 \) before and after conditioning (n = 36).](image-url)
imal heart rates were reduced only in those who attained the greatest training distances.

Since it was not possible to organize a matched-control series, it could be argued that part of the changes were due to natural recovery. However, we do not believe this to be the case. Previously published reports\textsuperscript{17, 18} have not shown any spontaneous change in cardiac function after cardiac transplantation. Moreover, our initial and final data do not show any significant correlation with the interval between operation and entry into the study.

There are several possible explanations for these responses. In normal subjects, training increases vagal inhibitory tone at rest, while sympathetic tone is decreased at submaximal effort.\textsuperscript{32} Such a mechanism for bradycardia cannot occur in the denervated heart, as substantiated by observations in the trained cardiac denervated dog\textsuperscript{33} and in exercise-trained human cardiac transplant patients.\textsuperscript{22, 34} Reinnervation has not been reported to occur in association with the human orthotopic transplant, and there was no evidence of reinnervation in our patients. It has been shown, however, that the denervated heart develops an increased sensitivity to circulating catecholamines.\textsuperscript{35} The mechanism seems to be an increase in myocardial $\beta$-receptor density and/or affinity.\textsuperscript{36–38} There is also evidence that vigorously exercise-trained normal subjects and even postmyocardial infarction patients develop a significant reduction in effort-induced levels of serum norepinephrine.\textsuperscript{39, 40} Measurements of circulating catecholamines were not made in the present study, but if such a reduction occurred as a result of our training regimen, it could explain the training bradycardia seen in the eight highly compliant subjects. Another possibility is that the high compliers experienced a “down-regulation” in sensitivity of cardiac $\beta$-adrenoreceptors. This occurs in both rats and humans exposed to vigorous training,\textsuperscript{41–43} and correlates closely with increases in VO$_2$max.

The entire group’s increase in peak exercise heart rate could largely be due to a strengthening of the leg muscles. This peripheral adaptation would account for the improved power output, and because of a later onset of anaerobiosis, the reduced perception of effort and $V_{E}$ during submaximal exercise. The lack of change in cardiac outputs over the period of training argues against any central improvement, although it is tempting to infer that the reduction in peak and submaximal diastolic blood pressures toward normal values is an indication of improved myocardial compliance.

In conclusion, while it seems that a number of mechanisms interacted to varying degrees in bringing about a training effect in our transplant patients, strengthening of the peripheral muscles appeared to play the major role, and it achieved this by allowing the healthy transplanted heart to realize its full physiologic and functional potential. In the final analysis, the ability of the cardiac transplant patients to attain jogging distances of between 24 and 32 km/week and power outputs of up to 170 W on the cycle ergometer implies that exercise training has considerable potential for improving the quality of life of such patients.

We gratefully acknowledge the invaluable assistance of Salah Qureshi. Chief Cardio-Respiratory Technician, Rawlins Mohammed, Cardio-Respiratory Technician, and Manuscript Secretary Anna Ceci, all from the Toronto Rehabilitation Centre, and Fiona Robinson, Exercise Program Liaison Secretary from Harefield Hospital. We also thank Ken Lee of Cardiokinetics for the loan of the MMC Horizon Metabolic Measurement Cart, and Ian Eddy of Marquette Electronics (GB) for the loan of the Marquette ECG system.

References

7. Durnin JVGA, Womersley J: Body fat assessed from total body density and its estimation from skinfold thickness measurements on 481 men and women from 16 to 72 years. Br N Nutr 32: 77, 1974
THERAPY AND PREVENTION–CARDIAC TRANSPLANTATION


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*Circulation.* 1988;77:162-171
doi: 10.1161/01.CIR.77.1.162

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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