Cardiovascular responses to incremental and sustained submaximal exercise in heart transplant recipients

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Scott JM, Esch BT, Haykowsky MJ, Warburton DE, Toma M, Jelani A, Taylor D, Paterson I, Poppe D, Liang Y, Thompson R. Cardiovascular responses to incremental and sustained submaximal exercise in heart transplant recipients. Am J Physiol Heart Circ Physiol 296: H350–H358, 2009. First published December 5, 2008; doi:10.1152/ajpheart.01100.2008.—The cardiovascular response to exercise in heart transplant recipients (HTR) has been compared with that of healthy individuals matched to the recipient age (RM controls). However, no study has compared HTR with donor age-matched (DM) controls. Moreover, the cardiovascular response to sustained submaximal exercise in HTR requires further evaluation. We therefore examined cardiovascular responses during incremental exercise and sustained (1 h) submaximal aerobic exercise in 9 clinically stable HTR [63 ± 10 yr of age, 24.2 ± 10.9 ml·kg⁻¹·min⁻¹ peak O₂ uptake (V˙O₂peak)] and 11 healthy age-matched controls [60 ± 11 yr of age and 36.3 ± 10.7 ml·kg⁻¹·min⁻¹ V˙O₂peak for 6 RM controls and 35 ± 8 yr of age and 51.1 ± 10.4 ml·kg⁻¹·min⁻¹ V˙O₂peak for 5 DM controls]. Heart rate (HR) and left ventricular systolic and diastolic volumes (2-dimensional echocardiography) indexed to body surface area [end-systolic and diastolic volume indexes (EDVI and ESVVI)], cardiac output (CI), ejection fraction (EF), systemic vascular resistance (SVRI), end-systolic elastance index, and arterial elastance index were determined. Although systolic function was maintained during incremental exercise, peak CI was significantly reduced (6.7 ± 2.4 vs. 11.6 ± 1.4 l·min⁻¹·m⁻²), secondary to blunted HR, EDVI, and increased peak SVRI, in HTR compared with DM controls. The sustained activities of everyday living, nor do they take into account the fact that the overall duration of exercise incorporated in most cardiac rehabilitation programs is ~1 h (22). Because few HTR exercise at maximal intensities, it is particularly important to expand the understanding of preload, heart rate (HR), and vascular responses to sustained submaximal exercise in this population. An additional limitation is that cardiovascular performance has been compared only between HTR and healthy individuals matched to the recipient age (1, 4, 21, 32, 33). Given that the mean donor age is nearly two decades lower than the recipient age (45), the interaction of the heart with the systemic vasculature (ventricular-vascular coupling) may be a significant determinant of cardiovascular exercise performance. Furthermore, although abnormalities in ventricular-vascular coupling are well documented in HTR at rest (1, 32, 33), no investigation, to our knowledge, has compared the effects of exercise on ventricular-vascular coupling in HTR. In particular, by contrasting the exercise responses of HTR with those of donor age-matched individuals, insight into the limitations of coupling a younger, transplanted cardiac allograft with an older, foreign circulation in HTR can be obtained (30, 31, 43). The primary aim of this investigation was to compare the cardiovascular responses to incremental exercise and sustained submaximal aerobic exercise (1 h) in HTR and healthy individuals matched to the age of the recipient and the age of the donor heart. Our primary hypothesis was that HTR would have impaired preload, HR, and vasodilator reserve during incremental and sustained submaximal exercise compared with the recipient-matched group and that the magnitude of these differences would be markedly greater than in the donor-matched group.

METHODS

Participants. The participants included 9 clinically stable male HTR [63 ± 10 yr] and 11 controls [6 male recipient age-matched (RM) and 5 male donor age-matched (DM) healthy controls]. HTR were recruited from the University of Alberta Heart Transplant Clinic, and controls were recruited from the surrounding area. This investigation was approved by the University of Alberta Health Research Ethics Board, and informed consent was obtained before study participation.

General protocol. Participants reported to the Alberta Cardiovascular and Stroke Research Centre exercise stress laboratory at the Mazankowski Alberta Heart Institute on two separate occasions to perform 1) an incremental exercise test and 2) 1 h of sustained submaximal exercise.
Incremental exercise test. On day 1, an incremental exercise test was performed on a semicircular cycle ergometer. After a brief rest period, the workload increased by 20 W every 2 min until the subjects reached ventilatory threshold (49); thereafter, power output increased by 20 W each minute until exhaustion. HR (12-lead ECG), blood pressure (cuff sphygmomanometer), expired gas analysis (Parvomedics, Salt Lake City, UT), and ventricular volumes (2-dimensional echocardiography; Vivid-i, GE Healthcare) were obtained at rest and during exercise for determination of O$_2$ uptake (V$_{O2}$), HR, end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), cardiac output, and ejection fraction (EF). All images were obtained by a single, experienced sonographer in accordance with the American Society of Echocardiography guidelines (27) at rest and during the last 30 s of each workload. Images were analyzed offline by a single experienced technician. A minimum of three consecutive cardiac cycles were measured and averaged.

Sustained submaximal exercise. On day 2, participants performed 1 h of sustained submaximal exercise at 80–90% of the ventilatory threshold determined from the incremental exercise test (day 1) (49). All the ventricular and ventricular data were obtained before and at 30 and 60 min of exercise. Images were obtained and analyzed as previously stated. Participants were encouraged to consume fluid ad libitum during exercise, and fluid loss was estimated by measurement of body mass before and after the exercise session.

Calculations. End-systolic pressure (ESP) was calculated as 0.9 × brachial systolic blood pressure, a noninvasive estimate that accurately predicts LV pressure-volume loop measurements of ESP (25). LV volumes were determined using the method of Teichholz et al. (46) and were normalized to body surface area (13) for calculation of ESV index (ESVI), EDV index (EDVI), SV index (SVI), and cardiac output index (CI). End-systolic elastance index (EesI) was calculated as EesI = ESP/ESVI, effective arterial index (EaI) was calculated as EaI = ESP/SVI, and ventricular-vascular coupling was determined as EaI/EesI (41). Systemic vascular resistance index (SVRI) was calculated as mean arterial pressure/CI × 80. Reserve function was defined as the difference in these variables between rest and peak exercise for incremental exercise, and submaximal reserve was defined as the difference in these variables between rest and 60 min for sustained submaximal exercise.

Statistical analysis. Repeated-measures ANOVA was initially used to compare means between groups. Because of the small sample size and large amount of variability in the data, nonparametric tests were carried out at each level of intensity and at each time of measurement. Comparisons among groups were performed using the Kruskal-Wallis test. When differences were determined to be significant, pairwise comparisons were made using the Mann-Whitney method, and the Bonferroni-adjusted significant level was applied. Associations between V0$_2$ and ventricular-vascular coupling were examined using Pearson’s correlation coefficient. Values are means ± SD; significance level was set at 0.05. Corrected P < 0.017 was considered statistically significant for Bonferroni-adjusted pairwise comparisons.

RESULTS

Participant characteristics are shown in Table 1. There were no statistical group differences in height, mass, body surface area, LV mass, or self-reported physical activity levels (201 ± 174, 210 ± 166, and 240 ± 228 min/wk for HTR, RM controls, and DM controls, respectively). By study design, HTR and RM controls were significantly older than DM controls. V0$_{2}$peak was lower in HTR than in RM and DM controls by 33% and 53%, respectively (Table 1).

Incremental exercise test. Resting and exercise cardiovascular responses during incremental exercise are summarized in Table 2. Resting HR, Eal, and Eal/EesI were significantly higher in HTR than in RM and DM controls. No significant difference was found between groups for any other resting parameter. In all groups, HR, EDV, EesI, SVI, and EF increased, while ESVI, SVRI, and Eal/EesI decreased, throughout the incremental exercise. Peak exercise HR, SVI, and CI were significantly lower and SVRI was significantly higher in HTR than in DM controls, while EDVI was lower in HTR than in RM and DM controls. There was no significant difference in peak HR between HTR and RM controls. Furthermore, no significant difference was found between groups for peak ESVI or EF. The reserve HR, SVI, and CI were significantly lower in HTR than in DM controls, while EDVI reserve was lower in HTR than in RM and DM controls (Fig. 1). Eal increased throughout incremental exercise in RM and DM controls, whereas it decreased in HTR, resulting in a significantly lower Eal reserve in HTR (Fig. 2). There were no differences between groups in EesI or EesI reserve (Fig. 2). In HTR, reserve HR was associated with time after transplantation and V0$_{2}$peak (Fig. 3).

Sustained submaximal exercise. All participants successfully completed 1 h of submaximal exercise. Mean exercise V0$_2$ at 60 min corresponded to 85 ± 8% of ventilatory threshold for all groups (88 ± 8% for HTR, 82 ± 7% for RM, and 80 ± 8% for DM) and 60 ± 9% of V0$_{2}$peak (65 ± 8% for HTR, 59 ± 8% for RM, and 53 ± 7% for DM). Cardiovascular function at rest and during sustained submaximal exercise is shown in Table 3. Resting values were not different from day 1 (incremental exercise). In each group, all variables were significantly higher at 30 and 60 min than at rest, except Eal, Eal/EesI, and SVRI, which were significantly lower. At 1 h of sustained exercise, SVI, CI, and EF were lower and SVRI was significantly higher in HTR than in DM controls (Table 3). There were no significant differences between groups in submaximal reserve Eal.
controls, while SVI and EF reserve were lower in HTR than in RM and DM. EesI, or EaI/EesI (Fig. 2). Submaximal reserve HR, EDVI, and HTR (n = 9) | RM (n = 6) | DM (n = 5)
---|---|---
HR, beats/min
Rest | 90 ± 7† | 68 ± 16 | 69 ± 16
50% | 119 ± 24 | 117 ± 21 | 138 ± 19
75% | 139 ± 16† | 136 ± 20 | 161 ± 15
100% | 151 ± 19† | 152 ± 19† | 183 ± 6
ESP, mmHg
Rest | 107 ± 15 | 106 ± 11 | 101 ± 8
50% | 138 ± 19 | 154 ± 19 | 146 ± 20
75% | 150 ± 18 | 172 ± 23 | 168 ± 10
100% | 159 ± 24† | 193 ± 23 | 190 ± 2.8
EF, %
Rest | 61.0 ± 4.2 | 69.6 ± 4.7 | 67.9 ± 6.0
50% | 71.6 ± 8.5 | 76.6 ± 5.4 | 77.0 ± 6.6
75% | 77.7 ± 7.1 | 80.7 ± 5.6 | 82.4 ± 4.9
100% | 80.0 ± 7.4 | 83.3 ± 5.9 | 84.6 ± 4.8
EDVI, ml/m²
Rest | 45.5 ± 11.6 | 51.9 ± 4.3 | 56.9 ± 10.8
50% | 51.7 ± 13.1 | 59.0 ± 7.1 | 65.7 ± 12.3
75% | 53.0 ± 13.5† | 64.7 ± 7.3 | 72.8 ± 11.0
100% | 54.1 ± 13.2† | 68.6 ± 5.7 | 75.7 ± 11.4
ESVI, ml/m²
Rest | 18.5 ± 3.0 | 15.9 ± 3.8 | 18.6 ± 6.8
50% | 14.3 ± 4.4 | 13.8 ± 3.7 | 15.2 ± 6.1
75% | 11.6 ± 4.2 | 12.6 ± 4.5 | 13.0 ± 5.1
100% | 10.7 ± 4.4 | 11.7 ± 4.7 | 11.9 ± 5.1
SVI, ml/m²
Rest | 27.2 ± 9.1 | 36.0 ± 1.3 | 38.3 ± 5.0
50% | 37.4 ± 11.9 | 45.2 ± 5.8 | 50.5 ± 9.8
75% | 41.4 ± 11.6 | 52.1 ± 5.0 | 59.8 ± 8.2
100% | 43.4 ± 11.6 | 56.9 ± 3.7 | 63.8 ± 8.3
CI, l/min⁻¹·m⁻²
Rest | 2.5 ± 1.0 | 2.4 ± 0.6 | 2.6 ± 0.5
50% | 4.6 ± 2.0 | 5.3 ± 1.1 | 6.9 ± 1.3
75% | 5.8 ± 2.1† | 7.1 ± 1.3† | 9.5 ± 1.0
100% | 6.7 ± 2.4† | 8.7 ± 1.3† | 11.6 ± 1.4
Eal, mmHg·ml⁻¹·m⁻²
Rest | 4.21 ± 1.14† | 2.92 ± 0.30 | 2.66 ± 0.33
50% | 3.91 ± 0.92 | 3.50 ± 0.70 | 3.09 ± 0.81
75% | 3.84 ± 1.04 | 3.33 ± 0.53 | 3.87 ± 0.54
100% | 3.88 ± 1.03 | 3.40 ± 0.41 | 3.09 ± 0.50
EesI, mmHg·ml⁻¹·m⁻²
Rest | 6.02 ± 1.17 | 6.98 ± 1.79 | 5.88 ± 1.78
50% | 10.69 ± 2.34 | 12.08 ± 4.69 | 10.90 ± 4.44
75% | 15.25 ± 8.71 | 15.58 ± 7.20 | 14.45 ± 5.02
100% | 18.41 ± 10.52 | 19.94 ± 10.51 | 18.13 ± 6.57
Eal/EesI
Rest | 0.72 ± 0.14† | 0.44 ± 0.10 | 0.48 ± 0.13
50% | 0.41 ± 0.17 | 0.31 ± 0.10 | 0.31 ± 0.11
75% | 0.27 ± 0.10 | 0.24 ± 0.09 | 0.22 ± 0.07
100% | 0.26 ± 0.11 | 0.21 ± 0.09 | 0.19 ± 0.07
SVRI, dyn·s·cm⁻⁵·m⁻²
Rest | 3.34 ± 5.09 | 3.154 ± 648 | 2.912 ± 526
50% | 2.108 ± 626† | 1.703 ± 434 | 1.250 ± 185
75% | 1.691 ± 529† | 1.334 ± 252 | 965 ± 106
100% | 1.541 ± 506† | 1.148 ± 198† | 855 ± 99

Values are means ± SD. HR, heart rate; ESP, end-systolic pressure; EF, ejection fraction; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; SVI, stroke volume index; CI, cardiac output index; Eal, effective arterial elastance index; EesI, end-systolic elastance index; SVRI, systemic vascular resistance index. *P < 0.017 vs. RM. †P < 0.017 vs. DM.

Ventricular-vascular coupling and V̇O₂. In all groups, a significant inverse linear relationship between Eal/EesI and V̇O₂ was observed (r = −0.69, P < 0.05 for HTR; r = −0.69, P < 0.05 for RM; r = −0.46, P < 0.05 for DM).

DISCUSSION
To our knowledge, this study is the first to examine the cardiovascular responses to incremental and prolonged sustained exercise in HTR compared with DM and RM controls. The major new findings of this investigation are as follows. 1) During incremental exercise, the lower peak and reserve CI observed in HTR than in DM controls is due to a lower peak and reserve HR and EDVI and higher peak SVRI; in contrast, the decreased peak and reserve CI in HTR compared with RM controls is primarily due to a reduced peak and reserve EDVI. 2) In HTR, the contribution of preload, systolic volume reserve, and vascular reserve was limited during sustained submaximal exercise. 3) The abnormal V̇O₂peak in HTR is due, in part, to impaired ventricular-vascular coupling.

Cardiovascular responses to incremental exercise in HTR. Kao and colleagues (20, 21), using invasive hemodynamic radionuclide angiography and expired gas analysis, demonstrated that the reduced V̇O₂peak in HTR compared with age-matched controls was primarily due to a lower peak CI. In turn, the blunted peak CI was the result of a lower peak HR and EDVI, as EF was similar between HTR and controls. Our data confirm and extend these findings by demonstrating that, despite preserved peak and reserve EF, V̇O₂peak in HTR remains 33% and 53% lower than in RM and DM controls, respectively. Compared with DM controls, the reduced peak CI in HTR was secondary to a blunted peak and reserve HR and EDVI. However, in contrast to the results of Kao et al., we found that the lower CI in HTR than in RM controls (P > 0.017) was primarily due to a lower peak and reserve EDVI, rather than a blunted HR response (which was similar in these groups).

The difference between the exercise HR response we found and that reported by others (14, 20, 21, 23) may be due to the length of time after transplantation and subsequent partial cardiac reinnervation, or differences in fitness levels of study participants. In our study, the average time after transplantation was 8 ± 6 yr compared with 29.4 ± 24.4 wk (23), 9 ± 4 mo (21), and 41 ± 8 mo (14) in other studies. A number of studies reported partial and nonuniform sympathetic reinnervation of the allograft 1–8 yr after transplantation (2, 12, 50). Our finding of functional evidence of cardiac reinnervation (i.e., >36 beat/min increase in exercise HR; Fig. 3A) (38, 48) in eight of nine of our HTR may account for the similar peak HR between HTR and RM controls. Also, the fact that HTR may only have partial and nonuniform reinnervation (2) could explain why HTR have a significantly lower peak HR than DM controls.

A second contributing factor related to HR responsiveness may be underlying differences in fitness of HTR between studies. Pokan et al. (38) examined the effects of high-volume and -intensity endurance training in HTR and, similar to our findings, reported that the peak HR of trained reinnervated HTR was not significantly different from that of healthy controls. They also demonstrated that the peak HR of sedentary reinnervated HTR was significantly lower than that of healthy controls.
age-matched controls (142 ± 10 vs. 164 ± 17 beats/min) (38). The HTR in our study were more aerobically fit than those in the study of Kao et al. (21) (24.2 ± 10.9 vs. 12.3 ± 3.5 ml·kg⁻¹·min⁻¹ VO₂peak) and, in fact, were as fit as the healthy age-matched controls in the previous study (22.9 ± 4.0 ml·kg⁻¹·min⁻¹ VO₂peak). We additionally found that HR reserve was correlated with VO₂peak in HTR (Fig. 3B; P < 0.05). Taken together, these results suggest that time after transplantation and exercise training could be major factors contributing to reinnervation and, consequently, improvements in cardiovascular performance.

A second main finding of the present study was that the reduced CI during incremental or sustained submaximal exercise in HTR compared with RM and DM controls was due to impaired peak and reserve EDVI (Table 2, Fig. 3). Previous investigators demonstrated that cardiac allograft diastolic dysfunction is not associated with the number of rejection episodes, immunosuppressive medication, or the interval after transplantation (15, 18, 44). We also found that EDVI reserve was not related to time after transplantation (r = −0.15, P > 0.05), suggesting that other mechanisms may contribute to diastolic impairments. As previously mentioned, it appears that the majority of our HTR were functionally reinnervated. Thus, if sympathetic reinnervation is regionally heterogeneous (2, 3), adrenergic stimulation of the LV through neural release of catecholamines may also be nonuniform. This nonuniformity...
has been shown to slow LV relaxation, as select infusion of isoproterenol in the mid-left anterior descending coronary artery increased the time constant of isovolumic LV pressure fall (28). Limited reinnervation could also result in alterations in cardiac Ca\(^{2+}\) homeostasis. Paulus et al. (37) observed a slow relaxation with downward convexity of the dP/dt signal in the cardiac allograft after postextrasystolic potentiation with nitroprusside infusion, which could be due to delayed sarcoplasmic reticulum Ca\(^{2+}\) reuptake (29), alterations in myocardial Ca\(^{2+}\) sensitivity (11), or decreased sarco(endo)plasmic Ca\(^{2+}\)-AT-Pase (SERCA2a) expression (42). To understand why diastolic volume is so impaired during exercise in HTR compared with RM and DM controls, future investigations should address the issue of heterogeneous reinnervation and abnormal lucitropy in HTR.

The blunted peak exercise and reserve CI in HTR could also be due to an increased afterload associated with pre- and posttransplant vascular dysfunction. Indeed, Scherrer et al. (39) demonstrated that cyclosporin therapy is associated with sympathetic neural activation and plays a key role in the damage to the microvasculature leading to hypertension. Milani et al. (33) also reported significantly elevated arterial elastance and arterial elastance/end-systolic elastance in HTR compared with patients with uncomplicated hypertension and normal controls at rest. Consistent with this, we found significantly higher Eal in HTR than in RM and DM controls at rest (+44% and +58%, respectively, \(P < 0.017\)), resulting in significantly elevated Eal/Ees (+27% vs. RM and +41% vs. DM, \(P < 0.017\)). These vascular abnormalities apparent at rest are also present during exercise. In support of previous findings (20,
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HTR reached the same EDVI and submaximal exercise found at peak exercise when exercising at 80% of ventilatory threshold, a response for which changes in ESVI, HR, or EF did not fully compensate. There may be several explanations for the different responses between exercise protocols. 1) HTR were working at a lower absolute workload than DM and RM controls. However, HTR were able to decrease ESVI and increase EF during incremental exercise, despite reaching a lower absolute workload. Furthermore, because all groups exercised at an identical percentage of their ventilatory threshold by study design, the blunted HR, ESVI, and EF response in HTR cannot be explained by a lesser relative effort. 2) It is possible that HTR rely on relatively greater increases in plasma catecholamines to decrease ESVI and augment EF and HR during sustained submaximal exercise. It has been reported that plasma norepinephrine levels were not different between HTR and controls at 40% of peak power output but were significantly higher in HTR during exercise at 70% of peak power

Table 3. Cardiovascular responses at rest and during 30 and 60 min of sustained submaximal exercise

<table>
<thead>
<tr>
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<th>HTR (n = 9)</th>
<th>RM (n = 6)</th>
<th>DM (n = 5)</th>
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<tr>
<td>HR, beats/min</td>
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<tr>
<td>Rest</td>
<td>91 ± 10+†</td>
<td>67 ± 13</td>
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<td>30 min</td>
<td>120 ± 8</td>
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<td>60 min</td>
<td>115 ± 23</td>
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<td>139 ± 15</td>
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<td>EF, %</td>
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<td>EDV1, ml/m2</td>
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<tr>
<td>Rest</td>
<td>45.5 ± 12.3</td>
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<td>57.0 ± 13.1</td>
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<tr>
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<td>54.8 ± 15.0</td>
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<tr>
<td>Rest</td>
<td>16.8 ± 3.8</td>
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<td>CI, l/min/1·m-2</td>
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<tr>
<td>Rest</td>
<td>2.6 ± 1.1</td>
<td>2.3 ± 0.5</td>
<td>2.3 ± 0.4</td>
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<td>30 min</td>
<td>4.6 ± 1.6</td>
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<td>60 min</td>
<td>4.5 ± 1.5†</td>
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<td>EaI, mmHg·ml⁻¹·m⁻²</td>
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<tr>
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<td>4.06 ± 1.28+†</td>
<td>3.11 ± 0.26</td>
<td>2.81 ± 0.60</td>
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<td>2.63 ± 0.54</td>
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<td>3.26 ± 0.90</td>
<td>2.85 ± 0.23</td>
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<td>EesI, mmHg·ml⁻¹·m⁻²</td>
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<tr>
<td>Rest</td>
<td>6.35 ± 1.72</td>
<td>6.59 ± 1.5</td>
<td>5.13 ± 1.43</td>
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<td>8.15 ± 2.97</td>
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<td>0.49 ± 0.14</td>
<td>0.51 ± 0.11</td>
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<tr>
<td>30 min</td>
<td>0.44 ± 0.15</td>
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<td>0.31 ± 0.07</td>
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<td>60 min</td>
<td>0.45 ± 0.13</td>
<td>0.33 ± 0.10</td>
<td>0.28 ± 0.05</td>
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<td>SVRI, dyn·s·cm⁻²·m⁻²</td>
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<td>3.227 ± 667</td>
<td>2.622 ± 903</td>
</tr>
<tr>
<td>30 min</td>
<td>1.824 ± 537†</td>
<td>1.453 ± 184†</td>
<td>1.059 ± 330</td>
</tr>
<tr>
<td>60 min</td>
<td>1.821 ± 535†</td>
<td>1.412 ± 161</td>
<td>964 ± 277</td>
</tr>
</tbody>
</table>

Values are means ± SD. *P < 0.017 vs. RM. †P < 0.017 vs. DM.

21), we found that peak SVRI was higher [34% vs. RM (P > 0.017) and 80% vs. DM (P < 0.017)] and reserve SVRI was lower (10% and 12%, P > 0.017) in HTR than in RM and DM controls. Additionally, whereas RM and DM controls increased EaI in a typical response during incremental exercise (10), HTR had an abnormal response and decreased EaI (Table 2). Because HTR and RM controls achieved the same maximal HR, the decrease in EaI in HTR was not due to chronotropic incompetence. Previous investigations demonstrated impaired blood pressure responses to maximal exercise in HTR (6, 20, 21), and it is likely that the decrease in EaI was due to a disproportionate increase in SVI vs. ESP. This idea is supported by the fact that EaI also decreased during sustained submaximal exercise in all three groups when blood pressures were lower (Fig. 2). Taken together, these findings suggest that the lower Vo2peak in HTR may be secondary to an impaired CI and vascular abnormalities, resulting in a reduction of O2 delivery to exercising muscles.

Cardiovascular responses to sustained submaximal exercise in HTR. The cardiovascular responses noted above are also limiting during sustained submaximal exercise in HTR. However, in sharp contrast to incremental exercise, HTR demonstrated diverse LV volume and EF responses during sustained submaximal exercise compared with DM and RM controls.
output and at peak exercise (5, 6). Our participants were exercising at ~40% of peak power output throughout sustained submaximal exercise, and HTR may consequently not have achieved the “critical point” in catecholamine concentration necessary to decrease ESVI and increase EF and HR. 3) An increased vascular load could also contribute to lower systolic function in HTR during submaximal exercise. Exercise SVRI was higher in HTR than in RM (P > 0.017) and DM (P < 0.017) controls during sustained exercise, which would increase ESVI and decrease SVI. Taken together, these results suggest that HTR relied on the Frank-Starling mechanism to enhance exercise cardiac performance during sustained submaximal exercise. 

Ventricular-vascular coupling and \( \dot{V}O_2 \) in HTR. Although the importance of central and peripheral limitations to \( \dot{V}O_2_{peak} \) has been described in detail (19–21), few studies have examined the impact of ventricular-vascular coupling on exercise capacity. Najjar et al. (35) examined the association between \( \dot{V}O_2 \) and ventricular-vascular coupling in men and women and found no significant associations between \( \dot{V}O_2_{peak} \) and \( E_aI \), \( E_{esI} \), and \( E_aI/E_{esI} \). In contrast, given our finding of an inverse linear relationship between \( \dot{V}O_2 \) and \( E_aI \) in all groups (\( P < 0.05 \)), our results suggest that coupling of ventricular and vascular properties may be an important aspect of exercise tolerance. 

Clinical implications. Our investigation demonstrated decreased ESVI reserve and vascular reserve during sustained
submaximal exercise compared with incremental to peak exercise in HTR. If we consider that the overall duration of aerobic exercise incorporated in most cardiac rehabilitation programs is ~1 h at submaximal intensities (22), alternate exercise therapies may be of significant benefit for improving functional capacity in HTR. High-intensity interval exercise training has recently been shown to significantly improve exercise performance in HTR to levels comparable to, or even exceeding, that of sedentary or moderately trained healthy subjects (38). Thus high-intensity exercise may be essential for achieving the critical concentration of catecholamines (5, 6) necessary to augment HR, EesL, and EF. Additionally, because resting and exercise EesL and SVRI were found to be impaired in HTR, therapies that target the vasculature, such as minor muscle mass training and/or interval training, would allow for close-to-maximal skeletal muscle work with beneficial peripheral adaptations (47). Taken together, these forms of exercise training could improve ventricular-vascular coupling in HTR, a limitation to exercise tolerance confirmed in the present study. Study limitations. The present study must be examined in the light of several potential limitations. 1) Although we did not assess catecholamines, the catecholamine response to submaximal and peak exercise in HTR has been reported previously (5, 6). 2) Because the present study included only men, our findings cannot be generalized to women. Previous studies demonstrated sex differences in the cardiovascular response during cycle exercise (17, 35). 3) Use of two-dimensional ultrasound to quantify ventricular volumes has its limitations; however, it has previously been used for volume measurement during submaximal and maximal exercise in numerous populations (16, 36, 41). Because this technique was applied across all groups, any errors were systematic in nature. 4) We used the functional consequences of reinnervation (HR response to exercise) to infer reinnervation. This technique assesses sympathetic reinnervation only, and autonomic regulation involving parasympathetic and sympathetic innervation may be more accurately inferred from dobutamine stress testing with atroventricle and coronary arteries after orthotopic cardiac transplantation in cardiac transplant patients. Med Sci Sports Exerc 25: 191–196, 1993.


27. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology, J Am Soc Echocardiogr 18: 1440–1463, 2005.


