Acute cardiovascular responses to leg-press resistance exercise in heart transplant recipients

Doug Oliver\textsuperscript{a}, Peter W. Pflugfelder\textsuperscript{b}, Neil McCartney\textsuperscript{a,\*}, Robert S. McKelvie\textsuperscript{c}, Neville Suskin\textsuperscript{b}, William J. Kostuk\textsuperscript{b}

\textsuperscript{a}Department of Kinesiology, McMaster University, 1280 Main St. West, Hamilton, Ontario, Canada L8S 4K1
\textsuperscript{b}Division of Cardiology, London Health Sciences Centre, London, Ontario, Canada
\textsuperscript{c}Division of Cardiology, McMaster University, Hamilton, Ontario, Canada

Received 6 January 2001; accepted 16 July 2001

Abstract

\textit{Background:} Reduced skeletal muscle strength is characteristic of individuals following heart transplantation. Weight lifting exercise has been demonstrated as an effective means by which to increase muscular strength in other cardiac patients but the appropriateness of this form of exercise in heart transplant patients has not been investigated. The purpose of this study was to describe the cardiovascular responses of heart transplant patients to a single, prolonged bout of weight lifting training. \textit{Methods:} Twenty-three heart transplant recipients were stratified into early (Early; 3 months; \textit{n}=6), intermediate (Intermediate; 1–3 years; \textit{n}=7) and late (Late; 5–14 years; \textit{n}=10) post transplant groups and studied in four experimental conditions: supine rest, upright rest, single leg-press exercise (28 repetitions over 2 min 20 s at 50\% 1 repetition maximum) and recovery. Swan-Ganz catheterization allowed measurement of right heart pressures and cardiac output by thermodilution. Systemic arterial pressures and heart rate were measured continuously using a non-invasive finger cuff. \textit{Results:} Cardiac output increased by 30, 40 and 54\% during exercise in Early, Intermediate and Late, respectively. Heart rate increased by 4.5\% in Early compared to 11 and 16\% increases in Intermediate and Late. At peak exercise, systolic blood pressures reached average values of 179±9, 180±14 and 176±8 mmHg in Early, Intermediate and Late, respectively. Average mean pulmonary artery pressure did not exceed 30 mmHg and average pulmonary wedge pressure did not exceed 15 mmHg in any group during the exercise. \textit{Conclusions:} These observations indicate that a lengthened set of single leg-press exercise at a moderate lifting intensity can be performed within safe and acceptable physiological limits in patients following heart transplantation. To better address the specific rehabilitation needs of heart transplant recipients, future research should focus on developing training programs which include weight lifting exercise. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Heart transplantation; Weight lifting; Hemodynamics; Safety

1. Introduction

Orthotopic heart transplantation is an effective treatment option for individuals with end-stage heart failure. Almost 3500 people worldwide benefit from this procedure each year and because of continuing surgical, pharmacological and diagnostic advances, over 70\% can expect to live an additional 5 years after the time of their surgery [1]. Although survival outcomes have been well studied in the past several years, less attention has been directed to the issue of post transplant functional capacity. Often overlooked as a major source of morbidity in transplant recipients are severe losses in

\*Corresponding author. Tel.: +1-905-525-9140; fax: +1-905-525-7629.
\textit{E-mail address:} mccartne@mcmaster.ca (N. McCartney).
skeletal muscle mass, strength and trabecular bone mineral density which accompany long periods of inactivity and long-term prednisone use [2–4]. A recent report has suggested that muscular weakness and fatigue are the primary limiting symptoms in the day to day activities of many transplant patients [5]. It is estimated that the skeletal muscle strength of transplant recipients is 60–70% of that in age-matched controls [6].

Dynamic resistance training (weight lifting) has been shown in other cardiac patients [7–10] and the elderly [11,12] to result in strength increases of 20–50% in trained muscle groups, as well as a 15% increase in peak power output on incremental exercise tests [13]. Furthermore, studies indicate light–moderate intensity resistance exercise can be performed safely, with clinically acceptable blood pressure responses [14–16], fewer ischemic episodes [17] and fewer ECG abnormalities [18] than aerobic exercise on a treadmill or cycle ergometer. The combined results of acute and chronic response studies such as these has led to the expansion of many cardiac rehabilitation programs to include dynamic resistance exercise in weekly routines for post myocardial infarction patients.

At the present time, dynamic resistance exercise is not commonly recommended for transplant patients, perhaps because of the complete absence in the literature of any functional assessment of the transplanted heart during this type of stress.

The purpose of the present study was to document the cardiovascular response during a set of single leg-press resistance exercise in patients following orthotopic heart transplantation. In addition, the effects of time post transplant on the cardiovascular response was investigated by comparing early (3 months), intermediate (1–3 years) and late (5–14 years) post transplant groups.

2. Methods

2.1. Patient population

Twenty-four transplant recipients agreed to participate in the present study. Patients were recruited at the time of a regularly scheduled endomyocardial biopsy and grouped according to time post transplant as early (Early, n=6), intermediate (Intermediate, n=7) and late (Late, n=11). Patients in Early were all 3 months post transplant, Intermediate averaged 2.1±1.1 years post transplant (range 1–3 years) and Late averaged 8.6±1.1 years post transplant (range 5–14 years). One patient in Late had angiographic evidence of accelerated graft vascular disease at the time of the study and was excluded from the analysis. In Early, there were three men and three women with a mean age of 48±12 years (range, 30–60 years), Intermediate had six men and one woman with a mean age of 47±11 years (range, 28–61 years) and Late had 10 men with a mean age of 53±11 years (range, 35–67).

None of the transplant recipients in the present study were experiencing episodes of acute allograft rejection as demonstrated by negative endomyocardial biopsy at the time of testing. Coronary angiograms were performed on all Intermediate and Late patients on the day of the study and within 2 months on all Early patients. Each patient followed a typical regimen of post transplant immunosuppressant medical therapy, including cyclosporine (all patients), prednisone (14 patients; six in each of Early and Intermediate and two in Late) and azathioprine (six patients; two in Intermediate and four in Late). Eighteen patients were taking calcium channel antagonists, four were taking diuretics and two were taking angiotensin converting enzyme inhibitors. Informed, written consent was obtained from each participant on the day of testing. All testing was performed in the cardiac catheterization laboratory at University Campus, London Health Sciences Centre (London, Ontario, Canada). The protocol was approved by the Health Sciences Standing Committee on Human Research of the University of Western Ontario.

2.2. Assessment of 1 repetition maximum

The leg-press apparatus (Global Gym, Downsview, ON) was wheeled into the cardiac catheterization laboratory just prior to each patient’s endomyocardial biopsy for assessment of single leg-press 1 repetition maximum. The 1 repetition maximum is the heaviest weight an individual can lift once through a complete range of motion. Determination of the 1 repetition maximum was initiated by having each patient lift
and lower a light load (20 kg) once with the right leg only.

Weight was gradually added on successive attempts until each patient could no longer lift the weight within a 3 s period. Two minute rest periods were provided between each attempt. Patients were instructed to keep their arms relaxed at their sides during lifting to avoid performing isometric contractions with the upper limbs. The entire 1 repetition maximum procedure took approximately 7–10 min, after which the endomyocardial biopsy and right heart catheterization were performed. Right-sided heart catheterization was performed by advancing a flow-directed thermodilution catheter through the right internal jugular vein until the tip was situated in a branch of the right pulmonary artery. Hemodynamic measurements were obtained using a Siemens Cathcor computer assisted pressure recording and monitoring system interfaced with Cathcor fluid-filled pressure transducers. The pressure transducers were calibrated and adjusted to the level of the mid-axillary line in the supine position and the fourth intercostal space in the upright exercise position.

Total time for endomyocardial biopsy and right heart catheterization was approximately 20 min.

All procedures were uneventful.

2.3. Study protocol

Following endomyocardial biopsy, hemodynamic measurements were taken in four experimental conditions: supine rest, upright rest (in the exercise position), single leg-press exercise and recovery from exercise. The supine resting condition began after insertion of the right heart catheter. Patients had been lying in this position for approximately 20 min at the time pressure measurements were initiated. Right atrial pressure and mean pulmonary artery pressure were acquired first, followed by pulmonary capillary wedge pressure and cardiac output by thermodilution. Thermodilution cardiac outputs were measured in duplicate or triplicate using a 10 ml, 5% dextrose and water, iced injectate, to obtain two values in agreement by 10%. Cardiac output values were calculated immediately after administration of the injectate using a Baxter Com-2 Cardiac Output computer.

Systolic, diastolic and mean arterial systemic pressures were measured using the FINAPRES 2300 pressure acquisition system (Ohmeda, BOC Health Care Inc., Englewood, CA, USA). This technique allows beat-by-beat measurement of blood pressure and heart rate by placing a pressure cuff around the middle phalanx of the middle finger on the left hand.

Systemic pressures were acquired and stored on computer disc for off-line analysis using WINDAQ software (Version 1.18; DATAQ Instruments, Inc., Akron, OH, USA).

After obtaining resting supine measures, patients were assisted into the upright seated position in the leg-press machine. Patients rested comfortably for 10 min while measurement equipment was positioned for the exercise protocol. The FINAPRES transducer was positioned at heart level by having patients rest their left arm on a cart with the elbow bent and forearm pronated.

Resting upright hemodynamic measurements were obtained in the same order as described for the supine rest condition (pulmonary artery pressure, right atrial pressure, pulmonary capillary wedge pressure, followed by duplicate cardiac output measurements). Systemic blood pressure was monitored and collected continuously for 2 min.

For the exercise condition, patients placed their right foot onto the foot plate of the leg-press apparatus and let the right arm rest comfortably at their side to avoid upper limb isometric contractions. Each patient performed the single leg-press resistance exercise at 50% of 1 repetition maximum for 2 min and 20 s at a pace of 1 repetition every 5 s. Each repetition involved concentric contraction of the quadriceps to extend the knee, followed by a brief ‘lock-out’ phase at near full extension and finally an eccentric contraction of the quadriceps to bring the knee back to the flexed position. Verbal instructions were used to kept each subject on pace, so that at the end of the 2 min 20 s period, each subject had performed approximately 28 repetitions.

Subjects were instructed to breath comfortably and to avoid performing breath-hold manoeuvres.

Acquisition of continuous systemic pressure measurements began at the instant the subject started the exercise. Event markers were used to mark the start and completion times of the exercise.

Acquisition of pulmonary artery pressure and right atrial pressure were obtained at 60 s into the exercise protocol, followed approximately 15 s later by collec-
tion of pulmonary capillary wedge pressure. At 90 s into exercise the first measurement was made of cardiac output. The second measurement of cardiac output was made immediately after the first value was obtained, at approximately 2 min into exercise. After the second cardiac output was measured, subjects were instructed to stop exercising and to take the right foot off of the foot plate on the leg-press machine so that both legs were in a relaxed position.

Collection of continuous systemic blood pressures continued for 3.5 min into the recovery period. Hemodynamic data were acquired starting at 1 min post exercise with pulmonary artery pressure and right atrial pressure measures, followed by pulmonary capillary wedge pressure and duplicate cardiac output measurements, at approximately 2 min post exercise.

2.4. Blood collection and analysis

Mixed venous blood samples were collected and analyzed in 12 patients (n=5, 3, and 4 in Early, Intermediate and Late, respectively). Blood samples were taken from the pulmonary artery in the supine resting position, at the 28th repetition of single leg-press exercise and at 5 min into the recovery phase for catecholamine analysis. Vacutainers were prepared with EGTA and reduced glutathione and kept on ice during the entire protocol. Immediately after collection of the blood, tubes were spun in a centrifuge for 10 min for separation of plasma from cells. Plasma was pipetted into 1.5 ml Eppendorf tubes and frozen at −70°C until the analysis was performed.

Concentrations of epinephrine and norepinephrine were determined using high-performance liquid chromatography (HPLC).

2.5. Derived variables

Stroke volume was calculated by dividing cardiac output by heart rate. Systemic vascular resistance was calculated from the mean of the duplicate cardiac output measurements determined by thermodilution, right atrial pressure and mean arterial pressure obtained from the finger arterial blood pressure cuff. Systemic vascular resistance (Wood Units)=(mean arterial pressure−right atrial pressure)/cardiac output. Pulmonary vascular resistance was calculated in a similar fashion, using the pulmonary arterial pressure gradient (mean pulmonary artery pressure−pulmonary capillary wedge pressure) in place of the systemic arterial pressure gradient (mean arterial pressure−right atrial pressure). Pulmonary vascular resistance (Wood Units)=(mean pulmonary artery pressure−pulmonary capillary wedge pressure)/CO. Rate−pressure product was calculated by multiplying heart rate and systolic arterial pressure at a given time point and is reported at 14 repetitions and 28 repetitions in each subject. The majority of subjects in Early (n=4), Intermediate (n=5) and Late (n=9) performed progressive treadmill exercise tests (Bruce protocol) to exhaustion on the day prior to single leg-press testing. Arterial blood pressure and heart rate data were used to calculate rate−pressure product at the end of Stage I and at the point of exhaustion during the treadmill exercise, for comparison with the resistance exercise intervention.

2.6. Statistical analysis

Data are presented as mean±the standard error of the mean (S.E.M.). A separate one-way analysis of variance was performed on each of the following demographics: body weight, height, body surface area and age to uncover possible differences between groups on these variables. Differences between CONDITIONS (supine rest, upright rest, single leg-press exercise and recovery from exercise) or time points (as with the continuously measured variables) and GROUPS (Early, Intermediate and Late) were analysed using a two-way analysis of variance on each dependent measure.

If statistical significance was evident in the initial analysis of variance, Tukey’s HSD post hoc test was performed to investigate differences between selected means. A value of P<0.05 was considered significant.

3. Results

Table 1 provides a detailed description of all pertinent patient information for the three groups of heart transplant recipients. The groups did not differ significantly on any of the demographic variables (age, height, weight, body surface area).
Table 1
Subject characteristics

<table>
<thead>
<tr>
<th>EARLY (Early)</th>
<th>INTERMEDIATE (Intermediate)</th>
<th>LATE (Late)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.0 ± 11.7</td>
<td>46.6 ± 11.4</td>
</tr>
<tr>
<td>n (male/female)</td>
<td>3/3</td>
<td>6/1</td>
</tr>
<tr>
<td>Time post transplant</td>
<td>3 months</td>
<td>2.1 ± 1.1 years</td>
</tr>
<tr>
<td>Donor age (at time of OHT) (years)</td>
<td>41.6 ± 4.6</td>
<td>27.1 ± 9.2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174 ± 9.2</td>
<td>175 ± 4.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78 ± 19</td>
<td>92 ± 20</td>
</tr>
<tr>
<td>Maximum SLP (1 RM) (kg)</td>
<td>28.3 ± 6.1</td>
<td>43.6 ± 9.0</td>
</tr>
</tbody>
</table>

Reason for OHT

<table>
<thead>
<tr>
<th>IHD</th>
<th>n = 3</th>
<th>n = 3</th>
<th>n = 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDC</td>
<td>n = 3</td>
<td>n = 3</td>
<td>n = 4</td>
</tr>
<tr>
<td>Valvular</td>
<td>–</td>
<td>n = 1</td>
<td>n = 1</td>
</tr>
</tbody>
</table>

OHT, orthotopic heart transplantation; IHD, ischemic heart disease; IDC, idiopathic dilated cardiomyopathy. Data presented as mean ± S.D.

3.1. Cardiac output, heart rate and stroke volume

Cardiac output (Fig. 1) increased significantly in early, intermediate and late post transplant groups from upright rest to peak leg-press exercise ($P < 0.001$). Early increased cardiac output from 6.6 ± 0.7 l/min during upright rest to 8.6 ± 1.4 l/min after 2 min of single leg-press exercise. Intermediate increased cardiac output from an average of 6.8 ± 0.5 l/min at rest to 9.5 ± 0.7 l/min after single leg-press and Late from 5.4 ± 0.3 l/min to 8.4 ± 0.5 l/min following single leg-press. Percent increases in cardiac output from upright rest to peak single leg-press are 30, 40 and 54% in Early, Intermediate and Late, respectively.

Fig. 1 illustrates heart rate changes measured continuously across the four testing conditions. A significant GROUP×TIME interaction effect was revealed in the analysis of variance ($P < 0.001$). The average heart rate in Early was significantly lower than the average heart rate in Intermediate and Late after 60 s of single leg-press exercise (14 repetitions) and at the end of the exercise set (28 repetitions) ($P < 0.05$). Percent increases in heart rate from upright rest to peak single leg-press were 4.8, 10.5 and 16% in Early, Intermediate and Late, respectively.

Stroke volume (Fig. 1) increased significantly in all three groups of heart transplant recipients during the exercise intervention ($P < 0.001$). Mean values for stroke volume in Early were 79.4 ± 8.8 ml/beat (upright rest) and 99.6 ± 15.5 ml/beat (peak leg-press exercise). For Intermediate and Late, these respective means were 71.4 ± 5.1 ml/beat (Intermediate upright rest) and 93.0 ± 6.5 ml/beat (Intermediate peak exercise) and 62.2 ± 3.1 ml/beat (Late upright rest) and 82.8 ± 5.4 ml/beat (Late peak exercise). Relative increases from upright rest to peak single leg-press were very similar in all three groups (Early, 26%; Intermediate, 31%; and Late, 33%).

3.2. Arterial blood pressure and systemic vascular resistance

Fig. 2 depicts systolic arterial pressure, diastolic arterial pressure, mean arterial pressure and systemic vascular resistance during single leg-press. Each point plotted on the blood pressure graphs is the group mean of the average pressures over a 20-s period (i.e. every systolic or diastolic pressure was included in each patient’s 20 s average; the mean of these 20 s averages was then taken for the entire group and plotted as shown).

Systolic arterial pressure in Early increased ($P < 0.001$) from a mean of 156 ± 6 mmHg in upright rest to 179 ± 9 mmHg at peak single leg-press (15% increase). Intermediate demonstrated a mean increase ($P < 0.001$) in systolic arterial pressure from 142 ± 8 mmHg in upright rest to 180 ± 14 mmHg at peak single leg-press (27% increase). In Late, average systolic arterial pressure increased ($P < 0.001$) from a mean of 138 ± 8 mmHg in upright rest to 176 ± 8 mmHg at peak single leg-press (28% increase). No significant difference existed between the groups for the systolic arterial pressure response.
Fig. 1. Plots of cardiac output, stroke volume and heart rate at rest and during single leg-press (SLP) weight lifting exercise in heart transplant recipients who are early (G1, ○), intermediate (G2, ▲) and late (G3, □) post transplant. Data for supine rest, upright rest, SLP exercise and recovery from exercise are plotted as mean±S.E.M. Some error bars have been omitted for clarity. * Significant main effect of CONDITION (CO and SV graphs) or TIME (HR graph) (P<0.001, peak leg-press exercise vs. upright rest). Significant GROUP×TIME interaction effect (P<0.001 G1 vs. G2 and G3).

Increases in diastolic arterial pressure from upright rest to peak single leg-press were 96±7 to 103±8 mmHg in Early (P<0.05); 91±4 to 105±5 mmHg in Intermediate (P<0.05); and 98±7 to 116±7 mmHg in Late (P<0.05). Percent increases were 7, 15 and 18% in the three groups, respectively.

Mean arterial pressure in Early increased from 116±8 mmHg in upright rest to 130±8.4 mmHg at peak single leg-press (P<0.05). Mean arterial pressure in Intermediate increased from 108±5 mmHg in upright rest to 132±7 mmHg at peak single leg-press (P<0.05). Late increased mean arterial pressure from 114±7 mmHg in upright rest to 139±7 mmHg at peak single leg-press (P<0.05). Percent increase in mean arterial pressure was 12% in Early and 22% in both Intermediate and Late.
Fig. 2. Plots of systolic (SBP), diastolic (DBP), mean arterial blood pressure (MABP) and systemic vascular resistance (SVR) at rest and during single leg-press (SLP) weight lifting exercise in heart transplant recipients who are early (G1, ○), intermediate (G2, △) and late (G3, □) post transplant. Values are plotted as mean±S.E.M. Some error bars have been omitted for clarity. * Significant main effect of time (for SBP, DBP and MABP graphs) or CONDITION (for SVR graph) (P<0.001, SLP exercise vs. upright rest).

Systemic vascular resistance differed significantly between testing conditions in all three groups (P<0.001). Post hoc analysis demonstrated a significant difference between mean systemic vascular resistance in supine rest and mean systemic vascular resistance in upright rest (P<0.001) and between mean upright rest and mean peak leg-press exercise (P<0.001). Early, Intermediate and Late had decreases in systemic vascular resistance from upright rest to peak leg-press exercise of 18, 18 and 21%, respectively.

3.3. Pulmonary pressures and pulmonary vascular resistance

In Fig. 3 mean pulmonary artery pressure, right atrial pressure, pulmonary capillary wedge pressure and pulmonary vascular resistance are plotted.

Average mean pulmonary artery pressure increased significantly in all groups during single leg-press. Analysis of variance demonstrated a significant main effect of CONDITION (P<0.001) with specific
Fig. 3. Plots of mean pulmonary artery pressure, pulmonary capillary wedge pressure, right atrial pressure and pulmonary vascular resistance during rest and single leg-press (SLP) weight lifting exercise in heart transplant recipients who are early (G1, ○), intermediate (G2, △) and late (G3, □) post transplant. Data are presented as mean±S.E.M. Some error bars have been omitted for clarity. * Significant main effect of CONDITION (P<0.001, SLP vs. upright rest). † Significant GROUP×CONDITION interaction effect (P<0.003, G1 vs. G2 and G3).

differences between supine and upright rest (P<0.001) and upright rest and single leg-press (P<0.001). A significant GROUP×CONDITION interaction effect was observed (P<0.05) with Early showing a significantly higher mean pulmonary artery pressure during single leg-press compared to Intermediate and Late (P<0.05). Early had an average upright resting mean pulmonary artery pressure of 18±1 mmHg and an average exercise value of 26±2 mmHg (48% increase).

Intermediate showed an increase from 13±1 to 20±2 mmHg (53% increase) and Late increased mean pulmonary artery pressure from a mean of 15±2 to 23±2 mmHg (52% increase).

Mean pulmonary capillary wedge pressure increased significantly in all three groups during single leg-press (P<0.001). Early showed an increase in pulmonary capillary wedge pressure from 6±2 in upright rest to 15±2 mmHg at peak single leg-press. Intermediate increased pulmonary capillary wedge pressure from 6±1 in upright rest to 12±1 mmHg at peak single leg-press and Late increased pulmonary capillary wedge pressure from 7±2 to 15±3 mmHg over the same conditions. Percent increases were 148,
95 and 119% in Early, Intermediate and Late, respectively.

Right atrial pressure decreased in each group upon movement from the supine resting position to the upright resting position and then increased significantly from upright rest to single leg-press ($P<0.001$).

Pulmonary vascular resistance across all three groups was similar during the single leg-press intervention to values observed during supine rest, although pulmonary vascular resistance in recovery ($1.6\pm0.1$ Wood Units) was significantly higher than both supine rest ($1.2\pm0.1$ Wood Units; $P<0.003$) and single leg-press values ($1.1\pm0.1$ Wood Units; $P<0.001$). A significant GROUP effect was also found with Early displaying a higher pulmonary vascular resistance across all four conditions compared to Intermediate ($P<0.05$).

3.4. Rate–pressure product

Fig. 4 summarizes the rate–pressure product results for single leg-press and treadmill exercise. Single leg-press values were calculated after 14 repetitions and 28 repetitions (reps) at 50% of 1 repetition maximum, while treadmill rate–pressure product was obtained from progressive exercise tests performed on the day prior to single leg-press testing. Analysis of variance demonstrated a significant main effect of EXERCISE TYPE ($P<0.02$, 14 reps vs. 28 reps of single leg-press; and $P<0.0001$, 28 reps of single leg-press vs. peak treadmill exercise). A significant main effect of GROUP ($P<0.01$ Late vs. Early and Intermediate) and a significant interaction effect were also evident. Post hoc analysis of the GROUP×EXERCISE TYPE interaction demonstrated that the rate–pressure product of Early was significantly lower ($P<0.001$) than the rate–pressure product of Intermediate and Late after 28 repetitions of single leg-press exercise.

3.5. Plasma catecholamines

Mean plasma concentrations of norepinephrine and epinephrine for 12 subjects are listed in Table 2. The increase in norepinephrine over the course of the single leg-press intervention was significant at $P<0.0001$. No significant difference between groups was evident. Epinephrine concentrations also increased significantly in all three groups ($P<0.0001$) during single leg-press and remained elevated above resting levels at 5 min into the recovery period ($P<0.005$).

4. Discussion

Exercise training is commonly recommended to patients following orthotopic heart transplantation. In recent years, extensive reviews have outlined guidelines for the prescription of aerobic exercises for transplant patients [19–21] but until very recently no mention has been made of the need for strength training exercise in this patient population [2,3]. The benefits of strength training seen in other cardiac patients have yet to be recognized in many cardiac transplant recipients. This is a noteworthy observation, given the severe losses in skeletal muscle strength [2] and bone mineral density [22] experienced by many transplant recipients.

There is currently no data available which documents the response of the transplanted heart to an acute bout of dynamic resistance exercise and this is
Table 2
Plasma catecholamine concentrations

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Condition</th>
<th>Supine rest</th>
<th>Peak SLP</th>
<th>5 min post SLP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>Early</td>
<td>2534±877</td>
<td>5782±1593</td>
<td>3967±1627</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>2987±541</td>
<td>4368±645</td>
<td>4169±148</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Late</td>
<td>3212±399</td>
<td>7811±2478</td>
<td>5622±918</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Condition Mean</td>
<td>2911</td>
<td>5987±913</td>
<td>4624±691</td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Early</td>
<td>81±19</td>
<td>189±36</td>
<td>144±38</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>184±74</td>
<td>258±108</td>
<td>251±69</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Late</td>
<td>83±25</td>
<td>204±57</td>
<td>146±54</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Condition Mean</td>
<td>116</td>
<td>217±22</td>
<td>182±46</td>
<td></td>
</tr>
</tbody>
</table>

Data presented as mean±S.E.M.

*P<0.001 vs. supine rest.

One possible explanation as to why many transplant centers do not prescribe this type of exercise to transplant recipients. The significance of the present study is that it provides the first description of the cardiovascular response in heart transplant patients during an acute bout of resistance exercise. To our knowledge, it also provides the first set of right atrial and pulmonary pressure measurements in any population during a set of dynamic resistance exercise.

All 24 heart transplant recipients tested in the present study were able to complete 28 repetitions of single leg-press exercise at 50% of their 1 repetition maximum without discomfort or visible signs of distress. The only symptom reported by patients during the extended set of single leg-press was that of localized quadriceps fatigue.

4.1. The cardiac output response

Perhaps the most intriguing question prior to single leg-press testing was, can the denervated heart effectively augment cardiac output during a 2 min and 20 s bout of single leg-press exercise at 50% of maximum lifting intensity? The initial belief was that this intensity and duration of exercise may not be sufficient to cause circulating catecholamine concentrations to increase significantly. With no direct sympathetic neural connections to the myocardium and insufficient time for catecholamine levels to increase, there would seem to be no immediate mechanism for increasing the chronotropic and inotropic state of the myocardium.

Previous research has shown that healthy individuals do not rely heavily on heart rate increases to augment cardiac output during a set of resistance exercise. A recent study [23] demonstrated that during extremely heavy leg weight lifting exercise, the heart does increase its state of contractility (presumably by increasing sympathetic neural activity to the myocardium) to help augment stroke volume. Although the bulk of the stroke volume increase during weight lifting is brought about by the muscle pump and the Frank–Starling mechanism, at least some of the increase is the result of direct neural influences on the heart as well. The early group of transplant recipients (complete sympathetic denervation) provided a unique model to test the degree to which cardiac output can be augmented during weight lifting exercise with the Frank–Starling mechanism alone.

All three groups in the present study showed average increases in cardiac output equal to or greater than 30% over the course of 28 repetitions of single leg-press exercise. Early had the lowest relative increase in cardiac output, primarily because of the inability of the denervated heart to augment heart rate. Intermediate and Late increased heart rate by an average of 10 and 14 beats/min (bpm), respectively. All three groups increased stroke volume in a nearly identical fashion.

While no definite conclusions can be made regarding the state of myocardial innervation of Intermediate and Late, the pattern of heart rate increase seen specifically in Late seems to be consistent with some degree of sympathetic reinnervation. There is a substantial body of research in both animals and...
humans which has provided evidence for functional sympathetic reinnervation in subjects who are greater than 3 years post transplant [24–26]. While reinnervation is a possible explanation for the difference between the heart rate responses in the early group of transplant recipients and the later two groups, alternative explanations must be considered.

The increase in heart rate that Intermediate and Late experienced during single leg-press may have been due to increased levels of circulating epinephrine from the adrenal medulla or norepinephrine spillover into the circulation from increased muscle sympathetic nerve activity and not norepinephrine release from intact sympathetic nerve endings in the myocardium. A limited sample set acquired in the present study on plasma catecholamine levels seems to support this theory by showing a significant increase in norepinephrine and epinephrine levels after only 2 min and 20 s of single leg-press exercise. Due to small sample size and infrequent drawing of samples from each subject, no certain conclusions can be made regarding the contribution of these norepinephrine and epinephrine increases to the observed heart rate increases. These norepinephrine and epinephrine data do reflect an earlier observation that the kinetics of catecholamine release during exercise in transplant recipients may be more rapid than those observed in normals [27].

Finally, the augmented heart rate in the late groups may be due to an increased sensitivity of the β1 receptors to the same level of circulating catecholamines. There is some debate in the literature as to whether changes in the sensitivity of β1 receptors or increases in β1 receptor density do actually take place over time in the transplanted heart [28,29].

4.2. The arterial blood pressure response

It has long been recognized that prolonged isometric exercise is associated with large increases in arterial and left-ventricular pressures [30,31]. These large increases in arterial pressure during isometric lifting have traditionally led to fears that cardiac patients may place too much stress on the damaged myocardium during any lifting activity. Subsequent studies investigating the pressor response to isometric exercise have demonstrated the safety of this type of activity at lower relative intensities [17].

Although healthy individuals lifting close to maximal loads until fatigue have been observed to have large increases in systolic and diastolic blood pressure [32], this has not been the case for cardiac patients lifting more moderate loads [7–9,18]. Dynamic resistance exercise has been found to be well tolerated, efficacious and safe in patients with coronary artery disease with either preserved or impaired left ventricular function [7–9,16,18].

Results from the present study indicate that single leg-press exercise at 50% of 1 repetition maximum in a select group of transplant recipients is associated with an arterial blood pressure response that is very similar to previously published accounts in healthy subjects [33] and patients with coronary artery disease [14]. In a study measuring the intra-brachial blood pressure response to single leg-press exercise at 60% of 1 repetition maximum in eight cardiac patients, SBP was found to increase by 13% from upright rest to the 15th repetition of single leg-press exercise [14]. This increase is almost identical to the 14% increase found in our combined subject sample (n=23) after 80 s (16 repetitions) of single leg-press exercise at 50% of 1 repetition maximum (Fig. 2).

The arterial blood pressure response found during single leg-press exercise in our cohort of transplant recipients is not surprising because most of the afferent and efferent neural connections which determine the blood pressure response at rest and during exercise in healthy individuals, are still intact in transplant recipients. Central command and the exercise pressor reflex are the two major theories of blood pressure control during exercise [34]. The central command theory states that when a motor command is relayed from the motor cortex to the spinal cord and then on to the effector muscle, the cardiovascular control nuclei in the medulla are activated in parallel to initiate the appropriate blood pressure and heart rate response via the autonomic nervous system. The magnitude of the initial motor command determines the magnitude of the parallel autonomic activation.

The exercise pressor reflex is another very important input to the cardiovascular control centre in the medulla. This reflex involves feedback from working skeletal muscle via Type III and IV muscle afferents. As with the central command theory, the amount of exercise being performed helps to determine (by way of increased afferent feedback to the
medulla) the resulting arterial blood pressure and heart rate response. Again, the portion of the exercise pressor reflex loop involving BP control is still intact in transplant patients, while the efferent limb from the medulla to the myocardium (controlling heart rate) is absent.

4.3. Pulmonary pressures

Mean pulmonary artery, pulmonary capillary wedge and right atrial pressures are all typically elevated at rest and during submaximal exercise in heart transplant patients compared with age-matched control subjects [35]. These elevated pulmonary pressures show signs of normalization in most subjects as time post transplant increases beyond 1 year [36,37]. Subjects in the present study showed relatively normal mean pulmonary artery pressure, pulmonary capillary wedge pressure and right atrial pressure responses during supine rest as well as normal decreases in the transition from a supine to upright seated position (Fig. 3). As expected, mean pulmonary artery pressure, pulmonary capillary wedge pressure and right atrial pressure all increased with single leg-press exercise, with the highest mean exercise values for mean pulmonary artery pressure observed in the early post transplant group.

After 60 s of single leg-press exercise at 50% of 1 repetition maximum, subjects in the present study demonstrated average mean pulmonary artery pressure values of 26, 20 and 23 mmHg in Early, Intermediate and Late, respectively. An earlier study measuring mean pulmonary artery pressure in transplant patients during cycling exercise at a light intensity (25 Watts) reported values in early (<1 year) and late (>1 year) post transplant groups that were 30 and 27 mmHg, respectively [36]. This comparison with an accepted form of exercise (cycling) shows that pulmonary artery pressures during single leg-press in heart transplant recipients over a wide range of post transplant times are well within safe and acceptable physiological limits.

Due to the low resistance offered by the pulmonary vasculature, pulmonary capillary wedge pressure is a very close estimate of left atrial and therefore, left ventricular filling pressure [38]. According to the Starling relationship, increases in pulmonary capillary wedge pressure with continuing exercise are not only normal but very important for increasing stroke volume and thus cardiac output [39]. However, abnormally high filling pressures are often associated with symptoms of breathlessness (dyspnea), which can be extremely uncomfortable and are likely to cause an early stoppage of the exercise bout [40]. None of the subjects in the present study demonstrated mean pulmonary capillary wedge pressure values during single leg-press exercise that exceeded values reported during moderate–heavy cycling exercise in other transplant patients [36] and no subject showed signs or reported symptoms of respiratory distress during the exercise intervention.

4.4. Rate–pressure product

Rate–pressure product is accepted as a non-invasive estimate of myocardial oxygen demand during physical stress [41]. Previous studies measuring rate–pressure product in other cardiac populations during resistance exercise have demonstrated that the myocardial oxygen demand is typically lower during a set of resistance exercise compared to a bout of aerobic exercise at a similar relative intensity [42]. The results of the present paper show a similar trend. The rate–pressure product following 14 repetitions of single leg-press exercise was very similar to the rate–pressure product calculated after Stage I of the treadmill protocol and much lower than that at peak treadmill exercise for all three transplant groups.

5. Conclusions

Results from the present study indicate that a 2 min, 20 s bout of single leg-press resistance exercise at 50% of 1 repetition maximum can be performed within safe and acceptable physiological limits in patients following transplant. This conclusion is based on the effective hemodynamic adjustments and moderate blood pressure responses observed in all patients, regardless of time post transplant. This study provides support for the initiation of a training study
investigating the chronic effects of dynamic resistance exercise in transplant recipients.

References


