Cardiopulmonary adaptation at rest and during exercise 10 years after Mustard atrial repair for transposition of the great arteries


ABSTRACT Discordance exists between apparently reduced systemic right ventricular function and the reported asymptomatic state of many patients after atrial repair for transposition of the great arteries. To evaluate this clinical observation, cardiopulmonary response to exercise in 17 asymptomatic patients with no significant postoperative hemodynamic abnormalities was assessed by upright bicycle ergometry according to a modified James protocol 11.5 ± 1.5 years after Mustard atrial repair. Seventeen age- and sex-matched normal adolescents constituted the control group. Incremental exercise was performed to determine maximum work capacity, heart rate, blood pressure, oxygen saturation, and minute ventilation. Cardiac output was computed at rest and during steady-state exercise by a carbon dioxide rebreathing method at 50% of the maximum workload achieved during incremental exercise. Height and weight were similar in patients and controls (p > .05). Resting pulmonary function variables were normal in all subjects. At peak exercise, respiratory quotient was greater than 1 in both patients and controls (1.12 ± 0.09 and 1.09 ± 0.08 respectively, p > .05). Patients achieved a lower peak heart rate (172 ± 14 vs 185 ± 11 beats/min, p < .01), lower maximum work capacity (2.3 ± 0.6 vs 3.3 ± 0.7 W/kg, p < .01). The ratio of minute ventilation at peak exercise to maximum resting voluntary ventilation was normal (≤ 80%) in both groups. The ventilatory equivalent for oxygen was similar at rest, but significantly higher in patients than in control subjects at peak exercise (42 ± 7 vs 36 ± 5, p < .006). Cardiac output was in the normal range for age at rest, and increased appropriately during steady-state exercise, with peak values remaining in the normal range, in all but one patient. Ten years or more after atrial repair for transposition of the great arteries, asymptomatic patients have reduced maximum aerobic capacity; cardiac output and stroke volume responses to submaximal exercise are, however, normal when compared with those of normal peers, in part explaining the lack of symptoms with daily activity in these patients. Circulation 77, No. 5, 1055–1061, 1988.

ABNORMAL right ventricular function both at rest and during exercise has been documented in the majority of patients with transposition of the great arteries after atrial repair. Despite this, and the reported high incidence of other postoperative sequelae, some children are asymptomatic and report normal exercise tolerance during regular daily activities. When objectively measured by graded exercise testing, however, most patients show decreased endurance compared with normal subjects. The interpretation of these exercise tests has been complicated by the prevalence of multiple confounding variables such as arrhythmias, cyanosis, and systemic or pulmonary venous obstruction, each of which may contribute to a variable extent to the decreased exercise tolerance. Additionally, it is unclear in the asymptomatic patient how the decreased right ventricular ejection fraction frequently found in these exercise studies relates to clinical status and long-term prognosis.

The cardiopulmonary responses to exercise, in the absence of significant postoperative sequelae other than right ventricular dysfunction, have not been detailed late after the atrial repair. In an attempt to better understand postoperative cardiopulmonary adaptation to exercise, we studied maximum aerobic capacity during
graded incremental exercise and cardiac output response during steady-state submaximal exercise in a group of asymptomatic adolescent patients 10 years or more after surgery.

Patients and methods

The surgical records of patients with transposition of the great arteries (atrioventricular concordance, ventriculoarterial discordance) with or without a ventricular septal defect who had undergone Mustard atrial repair at the Hospital for Sick Children, Toronto, from 1972 to 1976 were examined. Patients were excluded from the study for the following reasons: out of country or province, symptomatic arrhythmias requiring drug or pacemaker therapy, significant pulmonary or systemic venous obstruction, significant residual ventricular septal defect (> 30% shunt), or left ventricular outflow tract obstruction (> 30 mm Hg) at postoperative cardiac catheterization. Of 50 randomly selected records, 18 patients (11 boys, and seven girls, age 12.8 ± 1.6 years) constituted the study group. All were in New York Heart Association class I, and took part in regular noncompetitive sporting activities both during and after school without apparent exercise limitation, as determined by careful questioning of patients and their parents during routine clinical follow-up and before participation in this study.

Mean age at surgical repair was 1.6 ± 0.9 years. Three patients had ventricular septal defects closed at surgery, one closed spontaneously, and the rest had an intact ventricular septum. Surgery was performed with the use of hypothermia with circulatory arrest and cold cardioplegia. The results from one patient with left pulmonary vein stenosis requiring reoperation 3 years after repair were excluded from analysis due to severe abnormalities in resting respiratory function thought to be secondary to pulmonary vein restenosis.

At cardiac catheterization, performed at a mean age of 3.9 years in 15 patients, all had normal systemic oxygen saturations (95% or more). Mean resting right ventricular ejection fraction was 46 ± 5%, and the ratio of left to right ventricular systolic pressure was 0.27 ± 0.05. Tricuspid regurgitation of a mild degree was present in most patients. Two patients had small residual atrial shunts, and one a small residual ventricular septal defect. Routine electrocardiograms and 24 hr Holter monitoring performed during follow-up showed predominant sinus rhythm in 14, and frequent periods of intermittent junctional rhythm in three patients. No patient had ventricular ectopy. One patient had a history of intermittent atrial flutter treated with digoxin but had been arrhythmia free for several years before study.

Values for right ventricular radionuclide ejection fractions with exercise performed at a mean age of 11 ± 1.2 years were obtained in nine patients. Mean resting ejection fraction was 48% (range 42% to 60%), with abnormally low peak exercise response (< 5% increase) in all patients. Echocardiographic evaluation of ventricular function performed at a mean age of 12 ± 2 years was available in 13 patients. All patients had mildly diminished right ventricular wall motion, but none had moderate or severe impairment, based on a subjective assessment of free wall motion in the parasternal short- and apical four-chamber views. None had more than mild tricuspid regurgitation by Doppler ultrasound. As determined by a method validated in our laboratory,13 echocardiographic mean right ventricular ejection fraction at rest was 43 ± 7% in patients.

The control group consisted of 18 age- and sex-matched adolescents selected from a large group of normal children voluntarily enrolled in a concurrent exercise study in our laboratory. This study was undertaken with the approval of the Human Subjects Experimentation Committee of the Hospital for Sick Children, University of Toronto, and informed consent was obtained from each participant.

Exercise protocol. After height and weight measurements were obtained, spirometry was performed on all subjects before bicycle exercise. To assess pulmonary function, maximum voluntary ventilation, 1 sec forced expiratory volume, peak flow rate, and forced vital capacity were measured and expressed as a percent of predicted value for height and sex based on normal standards developed in our laboratory.14 Bicycle exercise was performed on an upright bicycle ergometer with an electronically adjustable load (Elema-Schonander, Stockholm) with the seat height adjusted to an appropriate level for each subject. Lead V1 of the electrocardiogram was monitored continuously during exercise. Blood pressure was measured from the right arm at rest and at peak exercise with use of a mercury sphygmomanometer. Systemic oxygen saturation was measured at rest and continuously during exercise with an ear oximeter (Hewlett-Packard 47201A).

During exercise, patients breathed through a low-resistance and low dead space directional two-way valve (Koege! Y-valve). Inspired minute ventilation was measured by a dry gas meter (Parkinson-Cowan). Oxygen and carbon dioxide concentrations in expired air were measured by rapid gas analyzers (Applied Electrochemistry oxygen, and Beckman LB-2 carbon dioxide analyzers). Measurements were performed at rest and in the last 10 sec of each minute during incremental exercise. An on-line computer then calculated tidal volume (VT), expired minute ventilation (VE), oxygen consumption (VO2), and carbon dioxide production, ventilatory equivalent for oxygen (VE/VO2), and respiratory exchange ratio (RQ) at rest and for each workload.

After familiarization with the equipment, during which time each subject was allowed to breathe freely through the mouthpiece, incremental exercise was performed according to the protocol described by Jones and Campbell15 beginning with a load of 25 W at a steady pedal speed (60 rpm). The load was increased by 15 W at the end of each minute, and the final completed workload was taken as the maximum work capacity. All children were encouraged by an experienced technician to exercise to exhaustion.

A rest period of 1 hr was allowed, and steady-state exercise was then performed for 4 min at a constant load equivalent to 50% of maximum workload achieved during the incremental protocol. Cardiac output was measured by the Collier carbon dioxide rebreathing technique, in which a mixture of 12% to 16% carbon dioxide and oxygen was selected to achieve a plateau in carbon dioxide concentration during rebreathing depending on the patient’s body surface area.16 Subjects were initially instructed in the technique of deep rapid regular breathing necessary to achieve equilibrium in carbon dioxide concentration. Rebreathing was then performed at rest and again during the last minute of steady-state exercise. This technique has been validated for use in normal children and those with a variety of cardiac conditions, with results similar to those obtained by dye dilution techniques.16, 17

All curves were examined to ensure that a clear plateau in CO2 concentration was achieved during rebreathing. When this was not the case, rebreathing was repeated after appropriate adjustment of CO2 concentration. One patient showed extreme anxiety at rest and during exercise that was manifested by hyperventilation, resulting in absence of a plateau at steady state. Data from this patient and another showing exercise systemic arterial desaturation were not used for analysis of the submaximal state. Cardiac output and stroke volume were determined at rest and at the end of steady-state exercise in 15 patients. Comparisons were made with normal data obtained in our laboratory by the same technique.
**Results**

**Anthropometric and respiratory variables at rest.** No significant differences were found between patients and controls with respect to height, body surface area, maximum voluntary ventilation, 1 min forced expiratory volume, or forced vital capacity (table 1).

**Rest.** Resting respiratory rate, VT, VE, and VO\textsubscript{2} were not significantly different in the two groups (table 2). Although VE at rest tended to be higher in patients than control subjects, the slightly higher respiratory rate in patients was offset by their lower VT and the differences did not achieve significance.

**Peak exercise response.** Exercise duration, VO\textsubscript{2}, and work capacity were significantly greater in control subjects than in patients, while the other variables were not significantly different in the two groups. Overall, patients performed 70% of the maximal work achieved by control subjects. Ventilation at maximum exercise related to resting maximum voluntary ventilation was 76 ± 16% for the control group and 67 ± 14% for the patients (p < .05). VE/VO\textsubscript{2} at rest and at peak exercise is shown in figure 1. Although similar between groups at rest, this value remained unchanged at peak exercise in patients, while as expected, it decreased in control subjects. Mean RQ at maximum work was greater than 1.0 and similar in both groups (table 2). Systemic arterial saturation at rest was normal (≥ 94%) in all but one patient who had a saturation of 87% at rest. The saturation in this patient decreased further with exercise, despite the finding of only trivial residual atrial shunting at postoperative cardiac catheterization. All other patients and control subjects had normal systemic arterial oxygen saturations during exercise.

**Heart rate and blood pressure response.** Sinus rhythm could not always be documented during exercise due to low P wave amplitude in most patients. However, no atrial arrhythmias were encountered and only one patient had a ventricular arrhythmia consisting of a single ventricular couplet near peak exercise. Exercise was not stopped due to arrhythmia in any patient. There were no arrhythmias in the control group. Both patients and control subjects had similar heart rates at rest, but controls achieved a significantly higher heart rate at peak exercise. During incremental exercise patients had higher heart rates than controls at the same workload (figure 2), this difference achieving significance between 50 and 80 watts. The relationship between heart rate response and oxygen consumption was similar in both groups, represented by the regression equations: y = 46.6x + 95 in patients, and y = 36.3x + 94 in controls, where y = heart rate in beats/minute, and x = VO\textsubscript{2} in liters/minute. However, while the y intercepts were virtually identical, the slopes were

### Table 1

**Comparison of anthropometric and spirometric variables in patients and control subjects**

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>12.8 ± 1.6</td>
<td>13.0 ± 1.6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>45.5 ± 12</td>
<td>47.2 ± 10</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>153.5 ± 11</td>
<td>157 ± 11.5</td>
</tr>
<tr>
<td>MVV (% predicted)</td>
<td>87.2 ± 18</td>
<td>93.5 ± 16</td>
</tr>
<tr>
<td>FEV₁ (% predicted)</td>
<td>96 ± 9</td>
<td>98 ± 13</td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>88.5 ± 8</td>
<td>91 ± 8</td>
</tr>
</tbody>
</table>

Data are mean ± SD. No difference between groups were significant at p ≤ .05.

FEV₁ = 1 min forced expiratory volume; FVC = forced vital capacity; MVV = resting maximum voluntary ventilation.

### Table 2

**Cardiopulmonary variables at rest and peak exercise**

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Control subjects</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endurance time (min)</td>
<td>6.0 ± 1.5</td>
<td>9 ± 2.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Maximum work capacity (W/kg)</td>
<td>2.3 ± 0.6</td>
<td>3.3 ± 0.7</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>R 88 ± 14</td>
<td>89 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Ex 172 ± 14</td>
<td>185 ± 11</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>R 115 ± 8</td>
<td>111 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Ex 145 ± 15</td>
<td>143 ± 18</td>
<td>NS</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>R 23 ± 6</td>
<td>20 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Ex 47 ± 8</td>
<td>49 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>VT (ml)</td>
<td>R 455 ± 123</td>
<td>513 ± 266</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Ex 1270 ± 388</td>
<td>1453 ± 448</td>
<td>NS</td>
</tr>
<tr>
<td>VE (liters/min/kg)</td>
<td>R 0.24 ± 0.08</td>
<td>0.21 ± 0.1</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Ex 1.3 ± 0.3</td>
<td>1.5 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>VO\textsubscript{2} (ml/kg/min)</td>
<td>R 5.8 ± 2.0</td>
<td>4.9 ± 1.6</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Ex 31 ± 7</td>
<td>45.3 ± 10.5</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>VE/VO\textsubscript{2}</td>
<td>R 43 ± 19</td>
<td>43 ± 12</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Ex 42 ± 7</td>
<td>36 ± 5</td>
<td>&lt;.006</td>
</tr>
<tr>
<td>RQ</td>
<td>Ex 1.12 ± 0.09</td>
<td>1.09 ± 0.08</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are mean ± 1 SD.

Ex = peak exercise; R = rest.
divergent, although not significantly different, with patients having a slightly higher heart rate than control subjects for the same VO₂. Systolic blood pressure was similar at rest and at peak exercise in both groups (table 2).

Steady-state submaximal exercise. At 50% of maximum workload, patients achieved a mean heart rate equivalent to 93 ± 4% of the value obtained at peak exercise during the incremental protocol, while for control subjects this proportion was 84 ± 5% (p < .001). Similarly, the ratio of steady-state to peak incremental VO₂ was 86 ± 10% for patients and 68 ± 9% for control subjects (p < .001). The RQ determined immediately before CO₂ rebreathing at the end of steady-state exercise was 0.99 ± 0.05 in patients, indicating that they were still below anaerobic threshold. Use of CO₂ rebreathing for the estimation of cardiac output at this level of work was therefore considered valid. With one exception, the cardiac output response was within the 95% confidence limits of normal at rest and during steady-state submaximal exercise (figure 3).

The cardiac output in one 11-year-old female patient fell into the lower percentile at rest, and dropped slightly below normal during exercise. Her reported activity level and exercise tolerance were similar to those in all the other patients. All patients increased their cardiac output from rest to submaximal exercise. There were no significant differences in cardiac output responses in male and female patients. The stroke volume response from rest to submaximal exercise is shown in figure 4, where a statistically significant increase during exercise was observed (p < .05). Compared with our normal data, patients’ stroke volume responses were within the normal range.

Discussion

Our results demonstrate that, in asymptomatic patients without significant postoperative sequelae 10 years or more after Mustard repair for transposition of the great arteries, maximum aerobic capacity is significantly decreased in comparison with that of an age-matched control group of healthy nonathletic peers. However, when cardiac output response to submaximal exercise, a situation that simulates that of normal daily activity, is examined, no significant difference is found between groups. While subjects in this study were
specifically selected to exclude those with symptomatic postoperative residua or arrhythmias, it is difficult to determine from the literature what proportion of survivors of this procedure this group of patients represents, although our own experience would suggest that more than 50% fall into this category.18

Right ventricular dysfunction, characterized by decreased contractility, abnormally low resting ejection fractions,2-5, 10 and diminished exercise response as assessed by radionuclide techniques,6-9 has been repeatedly documented after atrial repair in this setting. Indeed, in some patients, right ventricular dysfunction precedes surgical repair.2 Variable degrees of impairment of left ventricular function have also been found in these patients. While it is difficult to objectively assess the degree of cardiovascular functional status, particularly in children,19 some patients are reported to be asymptomatic even in the presence of significant postoperative residual abnormalities8, 9 and arrhythmias.11

Although controversy still exists regarding what constitutes normal ventricular ejection variables in a systemic right ventricle, the paradox of abnormal exercise ventricular ejection fraction in the setting of apparently normal daily exercise tolerance has not been adequately explained.

Exercise studies after the Mustard repair have also yielded varying results, with one study reporting normal exercise performance in young patients, but decreased performance in older patients.12 The high incidence of postoperative abnormalities such as caval, pulmonary venous, and left ventricular outflow obstruction, residual atrial baffle leaks, and significant arrhythmias encountered in many patients in these studies further complicates interpretation of the results with regard to the role of right ventricular dysfunction in limiting exercise tolerance.

In this study, we evaluated cardiorespiratory function both at maximum and submaximal exertion, with measurement of cardiac output at submaximal exercise by a validated method of carbon dioxide rebreathing. The major limitations of this method, however, are the need for cooperation during CO2 rebreathing, which restricts its use to older children, and the presence of significant left to right shunting, which invalidates the results.16 Neither of these situations were encountered in this study population. This type of evaluation can be repeated frequently, and may be useful as an adjunct to
measurement of right ventricular performance because of its ability to quantitate functional status after surgery, as has been demonstrated by others\textsuperscript{20-22} using similar techniques in patients with different forms of postoperative congenital heart disease.

**Respiratory function.** The resting respiratory function in patients was not significantly different from normal. At maximum exertion, however, patients had a higher VE. Pulmonary function was not a limiting factor in the level of work performed, as shown by the normal ratio of maximum VE to maximum resting voluntary ventilation (50% to 80\%)\textsuperscript{15} in both groups.

The ventilatory equivalent for oxygen, an indicator of respiratory work required to achieve a particular level of VO$_2$ was similar at rest in both groups. This ratio should normally decrease with exercise, and was found to increase in the patient group. Similar findings have been reported in patients with univentricular hearts after the Fontan operation.\textsuperscript{20}

**Aerobic capacity.** The finding of reduced maximum aerobic capacity is consistent with previously published reports of patients of comparable age.\textsuperscript{12} In one study using radionuclide techniques and patients similar in age to those in this study,\textsuperscript{8} however, peak exercise capacity was found not to differ significantly from normal. In contrast, both right ventricular ejection variables and the cardiac output response to exercise were grossly abnormal in the patient group. The paradox of an abnormal cardiac output response to maximum stress in association with normal exercise tolerance is difficult to explain, although VO$_2$ and its relation to cardiac output was not determined. It seems unlikely that the explanation for these results was that patients were more physically fit than control subjects or that they had above normal capacity for oxygen extraction.

Other factors besides cardiac performance, such as psychological or emotional status, and thigh muscle mass,\textsuperscript{23} may influence exercise endurance on the bicycle ergometer. The subjects in this study were weight and height matched, thus diminishing the possibility of a strong influence on performance as a result of discrepancies in muscle mass. Additionally, RQs at peak exercise were similar in both groups, confirming the subjective impression that patients and control subjects alike exercised to maximum voluntary effort.

The reduced aerobic capacity seen in our group of patients appears therefore to be due to cardiopulmonary compromise unrelated to arrhythmias or residual surgical abnormalities. The contribution to decreased exercise performance of abnormal chronotropic response of the sinus node to exercise after the Mustard repair\textsuperscript{24} remains an unknown variable that may, however, not be as significant at submaximal exercise as it might be at maximum stress.

**Steady-state exercise.** While performance at maximum exertion was clearly subnormal, when submaximal response was evaluated, cardiac outputs and stroke volumes were within the normal range with one exception. Godfrey\textsuperscript{16} has reported that the slope of the relationship between cardiac output and VO$_2$ is fairly constant in normal individuals throughout childhood. In this study, in addition to all individual data being within the 95\% confidence limits for normal, the slopes and y intercepts of this relationship were not significantly different for patients and controls (figure 3). When the heart rate response and the VO$_2$ achieved at submaximal work were compared with those at peak exercise, however, patients were working at a higher fraction of their maximum capacity. Although it would be ideal to compare these variables in patients and control subjects at the same levels of submaximal work, our results imply that while patients maintain normal cardiac outputs at submaximal levels of work, their reserve is significantly less than that of normal individuals. It would appear therefore that the systemic right ventricle in this setting is capable of increasing output appropriately to at least meet the demands of submaximal exertion. An increase in stroke volume and heart rate is one of the mechanisms involved in achieving this increased cardiac output. The relatively flat stroke volume slope (figure 4) suggests that patients depend more on an increase in heart rate than stroke volume to achieve increased output.

The higher heart rates noted in patients at similar levels of work (figure 2) and higher VO$_2$ when compared with control subjects during incremental exercise, along with the reduced right ventricular exercise fraction response characteristic of the postoperative patient, support the concept of a limitation in stroke volume augmentation during exercise. In normal subjects, it is well documented that during exercise stroke volume rises to only approximately 40\% to 50\% of maximum VO$_2$, and does not change much thereafter,\textsuperscript{25} or may even fall.\textsuperscript{26} The relative contribution of stroke volume and heart rate to increased cardiac output in patients can only be determined by examination of both these variables at several different levels of steady-state exercise, below and above approximately 40\% of maximum VO$_2$. In this setting of limited cardiovascular exercise response it is encouraging that even in the presence of major postoperative residual abnormalities such as arrhythmias requiring pacemaker implantation, other investigators\textsuperscript{27} have
shown that aerobic capacity can be significantly improved by a short intensive exercise program in adolescent patients many years after atrial repair.

In conclusion, although subnormal results may be obtained at maximum exertion in asymptomatic patients with no significant postoperative sequelae many years after atrial repair, cardiac output responses to submaximal exercise may be well within normal limits.

These observations bring into perspective the finding of reduced systemic ventricular ejection fraction seen so frequently with maximum exercise radionuclide angiographic evaluation. Further long-term exercise studies (> 20 years after repair) may show declining submaximal performance, and perhaps an increasing frequency of symptoms in this group of patients.

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Cardiopulmonary adaptation at rest and during exercise 10 years after Mustard atrial repair for transposition of the great arteries.

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