Exercise capacity in adult patients with congenitally corrected transposition of the great arteries

P M Fredriksen, A Chen, G Veldtman, S Hechter, J Therrien, G Webb

Abstract

Objective—To examine cardiopulmonary values, static lung function, and ejection fraction in adult patients with congenitally corrected transposition of the great arteries (CCTGA).

Patients and methods—41 patients who had undergone static lung function testing and cardiopulmonary exercise tests with measurements of ejection fraction were identified at the Toronto Congenital Cardiac Centre for Adults.

Results—Aerobic capacity in patients with CCTGA was severely diminished, varying from 30–50% of the results achieved by healthy subjects. Normal values of right ventricular and left ventricular ejection fraction were found. However, the systemic right ventricular ejection fraction increased by 2% from rest to exercise, as opposed to the expected >5% increase in a healthy population. The pulmonary left ventricular ejection fraction decreased by 2% at peak exercise. Diminished values of heart rate, forced expiratory volume in one second (FEV1), forced vital capacity, and systolic blood pressure compared to the predicted values may contribute to the reduced maximal oxygen uptake (VO2max) found in patients with CCTGA. In addition, a limited increase in systolic right ventricular ejection fraction and a decrease in pulmonary left ventricle contractility suggest a dysfunction of both ventricles.

Conclusion—Diminished values of heart rate, forced expiratory volume in one second (FEV1), forced vital capacity, and systolic blood pressure compared to the predicted values may contribute to the reduced maximal oxygen uptake (VO2max) found in patients with CCTGA. In addition, a limited increase in systolic right ventricular ejection fraction and a decrease in pulmonary left ventricle contractility suggest a dysfunction of both ventricles.

Keywords: aerobic capacity; ventricular dysfunction; lung function; congenitally corrected transposition of the great arteries
Twenty seven patients (65.8%) were in sinus rhythm and four patients (9.8%) had atrial fibrillation. Fourteen patients (34.2%) used angiotensin converting enzyme (ACE) inhibitors which were given because of deteriorating systemic ventricular function or documented episodes of systemic ventricular failure. To estimate the effect of surgery, the patients were divided into a surgery group (29 patients, 70.7%) and a non-surgery group (12 patients, 29.3%). The patients without surgery did not have any significant residual left to right or right to left shunts. Patients with a conduit between the pulmonary left ventricle and the pulmonary artery (18 patients, 43.9%) were also analysed in comparison to patients without a conduit (23 patients, 56.1%). Some of the patients with conduits had residual obstruction assessed by two dimensional transthoracic echocardiogram with Doppler. Four patients had a gradient less than 20 mm Hg, eight patients had a mild obstruction (20–40 mm Hg), two had moderate obstruction (40–80 mm Hg), and none had severe obstruction (> 80 mm Hg).

**CARDIOPULMONARY TEST**

Cardiopulmonary tests were performed at Toronto General Hospital on an ergometer cycle (Elema, Sweden). Continuous measurements of expired gas values were analysed every 30 seconds (Amtech VO₂ Oxygen Analyzer S-3A/I). The analyser was calibrated before testing using known values of oxygen and carbon dioxide. During the test, measurements of blood pressure, heart rate, ventilation, and oxygen saturation (SaO₂) were taken continuously. All patients started at 20 W for warm-up in the first minute. Workload was increased by 20 W every two minutes until the patient experienced unacceptable fatigue or other symptoms. The American College of Sport Medicine guidelines for ending an exercise test were followed. Before the exercise tests, spirometry (SensorMedics, USA) tests were conducted according to American Thoracic Society standards with measurements of forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC). Measurements of ejection fraction were performed using radiopharmaceutical 750 MBq 99mTcO₄, which was injected before exercise. The results of VO₂ max from the CCTGA patients were compared with a healthy population in Canada over different age groups. Results of FEV₁ and FVC were compared to predicted values calculated from equations set out by Jones.

**STATISTICS**

Data were analysed using SPSS 9.0 for Windows. Median values with range were used descriptively to compare VO₂ max in patients with CCTGA to a healthy population. Differences in the FVC and FEV₁ between CCTGA patients and predicted values were analysed with the Student t test. Analysis over different age groups was done with analysis of variance (ANOVA). Multivariate linear regression modelling (stepwise backward elimination selection procedure) was used to examine the relation between age at test, type of associated defect, ACE inhibitors, sex, heart rate, type of heart rhythm, systolic blood pressure, diastolic blood pressure, surgery, conduit, FVC, and outcome variable of VO₂ max. Pearson correlation was used to determine the relation between VO₂ max and maximal heart rate (HRmax). A probability value of p < 0.05 was regarded as significant.

**RESULTS**

**AEROBIC CAPACITY**

As shown in fig 1, aerobic capacity in patients with CCTGA was severely diminished, VO₂ max ranging from 11–22 ml/kg/min, corresponding to 30–50% of results achieved by normal subjects. None of the patients fall within the lower 15 centile range for normal values. Multiple linear regression model showed a positive effect of FVC (p = 0.002), HRmax (p < 0.0001), and systolic blood pressure (p = 0.001). No effect was found with regard to age at test, sex, ACE inhibitors, associated effects, surgery, conduits or heart rhythm.

Normal values were found at rest for SaO₂ (table 2). During exercise however, a decrease was displayed (table 3).

**HEART RATE**

A normal mean resting value was found for heart rate in the CCTGA patients, but a diminished increase with exercise was revealed, as 79% of predicted values were obtained. No differences were found between patients with pacemakers and patients in sinus rhythm.

**BLOOD PRESSURE**

Significantly higher values were demonstrated in males with respect to resting systolic and diastolic blood pressure (table 2). There was a
significant increase in systolic and diastolic blood pressure from rest to maximal exercise (p ≤ 0.0001 and p = 0.0003, respectively). The mean maximal systolic blood pressure, however, was lower than the expected values for normal subjects (table 3). Patients on ACE inhibitors (68 mm Hg) had a significantly lower diastolic blood pressure at rest compared to the patients without ACE inhibitors (76 mm Hg, p = 0.003). The same trend was found for systolic blood pressure at rest, and for diastolic and systolic blood pressure at maximal exercise, but no significant difference was shown.

EJECTION FRACTION
Normal resting values were found for both systemic right ventricular (48%) and pulmonary left ventricular (46%) ejection fractions (table 2). Systemic right ventricular ejection fraction only rose by 2% on exertion, less than the 5% or more expected in a normal population. Pulmonary left ventricular ejection fraction decreased by 2% on exertion (table 3). A multivariate linear regression model was used to examine the relation between sex, surgery, associated defects, ACE inhibitors, and outcome of maximal systemic right ventricular ejection fraction. Surgery turned out to have a negative effect on the systemic right ventricular ejection fraction. A t test showed that patients without surgery achieved a significantly higher systemic right ventricular ejection fraction (62%) on exertion than the surgery group (46%) (p = 0.033).

A similar multivariate linear regression model was used to examine the outcome of maximal pulmonary left ventricle ejection fraction. The results showed that patients treated with ACE inhibitors showed a significantly lower ejection fraction at maximal exercise (34%) in the pulmonary left ventricle compared to the non-ACE group (58%) (p = 0.014). In addition, the pulmonary left ventricular ejection fraction decreased for the ACE group from rest to maximal workload (37% to 34%), but increased for the non-ACE group (55% to 58%).

LUNG FUNCTION
Patients with CCTGA achieved significantly lower values of FVC (p = 0.005) and FEV1 (p = 0.003) compared to the predicted values. Patients without surgery (95%) achieved predicted values of FVC more frequently than the surgery group (79%, p = 0.008). A similar trend was also shown for FEV1 (p = 0.087) (fig 2).

Discussion
Diminished aerobic capacity and lung function of adult patients with CCTGA when compared to predicted values for healthy individuals was shown in the present study. In addition, low values of maximal systolic blood pressure, maximal heart rate, and SaO2 at maximal exercise were found. A reduced increase in ejection fraction with exercise in the systemic right ventricle was displayed. Also a decrease in ejection fraction with exercise was demonstrated in the pulmonary left ventricle.

AEROBIC CAPACITY
In patients with CCTGA, an important issue has been the performance of the morphologic right ventricle when executing systemic pumping over decades. It has been suggested that systemic ventricular dysfunction in CCTGA is uncommon before the age of 35 years.

Table 2 Resting data (mean (SD)) for patients with CCTGA. The p values refer to the differences between males and females

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>CCTGA</th>
<th>Males</th>
<th>Females</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SaO2</td>
<td>24</td>
<td>96 (4)</td>
<td>13</td>
<td>96 (5)</td>
<td>0.544</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>27</td>
<td>71 (10)</td>
<td>15</td>
<td>72 (9)</td>
<td>0.515</td>
</tr>
<tr>
<td>Sys BP (mm Hg)</td>
<td>37</td>
<td>116 (13)</td>
<td>18</td>
<td>111 (13)</td>
<td>0.013</td>
</tr>
<tr>
<td>Dia BP (mm Hg)</td>
<td>37</td>
<td>73 (8)</td>
<td>18</td>
<td>70 (8)</td>
<td>0.015</td>
</tr>
<tr>
<td>MRVEF sys (%)</td>
<td>21</td>
<td>48 (15)</td>
<td>10</td>
<td>46 (19)</td>
<td>0.573</td>
</tr>
<tr>
<td>MLVEF pulm (%)</td>
<td>17</td>
<td>46 (19)</td>
<td>7</td>
<td>47 (15)</td>
<td>0.02</td>
</tr>
<tr>
<td>FVC obtained</td>
<td>32</td>
<td>3.66 (1.12)</td>
<td>14</td>
<td>3.81 (0.97)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>FVC % predicted</td>
<td>32</td>
<td>84 (15)</td>
<td>14</td>
<td>85 (12)</td>
<td>0.792</td>
</tr>
<tr>
<td>FEV1 obtained</td>
<td>32</td>
<td>2.99 (0.92)</td>
<td>14</td>
<td>3.62 (0.89)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>FEV1 % predicted</td>
<td>32</td>
<td>84 (17)</td>
<td>14</td>
<td>85 (19)</td>
<td>0.692</td>
</tr>
</tbody>
</table>

Table 3 Exercise data (mean (SD)) in patients with CCTGA

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO2max (ml/kg/min)</td>
<td>29</td>
<td>19.6 (7.4)</td>
</tr>
<tr>
<td>VO2max (ml/min)</td>
<td>29</td>
<td>1374 (530)</td>
</tr>
<tr>
<td>SaO2 (%)</td>
<td>24</td>
<td>92 (8)</td>
</tr>
<tr>
<td>HRmax (bpm)</td>
<td>29</td>
<td>150 (49)</td>
</tr>
<tr>
<td>Maximal systolic BP (mm Hg)</td>
<td>27</td>
<td>153 (19)</td>
</tr>
<tr>
<td>Maximal diastolic BP (mmHg)</td>
<td>27</td>
<td>82 (13)</td>
</tr>
<tr>
<td>Maximal MRVEF sys (%)</td>
<td>19</td>
<td>50 (14)</td>
</tr>
<tr>
<td>Maximal MLVEF pulm (%)</td>
<td>14</td>
<td>44 (20)</td>
</tr>
</tbody>
</table>

Figure 2 Percent of predicted values (12) in CCTGA patients with regard to forced expiratory capacity (FVC) and forced expiratory volume in one second (FEV1).
However, resting values may be of limited interest as ventricular dysfunction often is first shown during exercise.\(^5\) As shown in fig 1, patients with CCTGA have severely diminished values of VO\(_{2}\text{max}\) at all age groups. In addition, a significant fall off in VO\(_{2}\text{max}\) with age is apparent (p = 0.003). This may suggest a decrease in systemic right ventricular function with age. Hornung and colleagues have suggested a high prevalence of myocardial defects in unoperated patients with CCTGA with consequent abnormalities of region, wall motion and thickening, and impaired ventricular contractility.\(^6\) Ischaemia and infarction may therefore be important contributors to ventricular failure. Alternatively, a left ventricular outflow tract obstruction, as in patients with conduits, or a dynamic left ventricular outflow tract obstruction because of exercise induced systolic anterior motion of the mitral valve, may also serve as a hypothesis for changes in ventricular performance with exercise.

The lower lung function values found in CCTGA patients compared to the predicted values may also have had an impact on patients’ aerobic capacity. To support this suggestion the results from the multiple linear regression model showed that high FVC correlated with high VO\(_{2}\text{max}\) (p = 0.002).

**HEART RATE**

The mean maximal heart rate in the present study was 79% of the predicted value, and the low value is in accordance with a previous report.\(^7\) This chronotropic incompetence may be an important factor that contributes to the diminished VO\(_{2}\text{max}\); thus the HRmax could explain 64% of the increase in oxygen uptake (ml/kg/min). A significant impairment of the chronotropic response has previously been shown to correlate with abnormally low VO\(_{2}\text{max}\) values.\(^8\) The regression model in the present study revealed a similar pattern, since the high HRmax values are correlated with a high VO\(_{2}\text{max}\). The fact that 10 patients were paced may also have influenced the results of HRmax. However, only five patients needed rate-responsiveness and it is therefore less likely that this would have a major impact on the average values of HRmax.

**BLOOD PRESSURE**

A significant increase in both systolic and diastolic blood pressure was found with exercise; however, the maximal systolic blood pressure was lower than expected. This may support the assumption of an exercise induced deterioration of the systemic right ventricle, as the inability to increase blood pressure may influence the aerobic capacity.\(^9\)

**EJECTION FRACTION**

**Systemic right ventricle**

As previously mentioned, there is an increase in systemic right ventricular ejection fraction with exercise which, however, is less than the expected 5%.\(^9\) A deterioration of the systemic ventricle may to a greater extent influence aerobic capacity than the pulmonary ventricle, and may be the main reason for the diminished values of VO\(_{2}\text{max}\) shown in the present study. Parrish and colleagues suggested that for most patients, abnormality of ventricular function is not clinically important in childhood.\(^10\) The present data indicate that for adults, a deterioration of systemic right ventricular function has an impact on physical ability, in agreement with others.\(^11\)

**Pulmonary left ventricle**

Previous papers have suggested normal function in the systemic ventricle, but an impaired pulmonary ventricular function.\(^12\) Others have reported normal ejection fraction in the pulmonary left ventricle, but no increase in the systemic right ventricular ejection fraction with exercise.\(^13\) The data in the present study show a small mean decrease of the ejection fraction in the pulmonary left ventricle. The explanation for the decrease in pulmonary ejection fraction is unclear. A hypothesis may be that pacing and arrhythmia could affect exercise intolerance in the CCTGA group; however, analyses show no differences in VO\(_{2}\text{max}\) between patients with pacemakers and patients in sinus rhythm. A possible explanation may be that the systemic atrioventricular valvar regurgitation may worsen during exercise, resulting in a relatively higher systemic ventricular ejection fraction, and thus raising pulmonary venous pressures and pulmonary capillary wedge pressures in turn. This would result in exercise intolerance as reported to occur with the systemic mitral valve in patients with mild rheumatic mitral valve disease at rest.\(^14\) In addition, the diastolic pressure overload of the morphological right ventricle may be at the expense of pulmonary left ventricular volume as the septum is bulging into the ventricle. This may result in impaired diastolic filling of the left ventricle as suggested in previous studies of ventricular interdependence, and a lower ejection fraction on the pulmonary side.\(^15\)

The lower values found in patients on ACE inhibitors have a selection bias, as these patients have poorer ventricular function than patients without ACE. The fact that ejection fraction decreases with exercise in patients treated with ACE probably emphasises this. Unfortunately, there were no data available before and after the introduction of ACE inhibitors; thus the present data do not reveal the effect of ACE inhibitors in patients with CCTGA.

**MORTALITY**

Both early and late mortality in patients with CCTGA is quite high. In 1976, Bjurke and Kidd reported a 25% early paediatric mortality in patients with CCTGA including death during surgery.\(^16\) The results are based on data from the Hospital for Sick Children in Toronto, the same hospital as the patients in the present study attended before they were transferred to TCCCA. The treatment of these patients has improved since the 1970s, although the late mortality of 21% in our study showed that this still is a high risk group at all ages and should be followed with special attention.\(^17\)
LIMITATIONS OF THE STUDY
This study is limited by the follow up constraints inherent in caring for adults with congenital heart disease. Many of our patients reside outside Toronto, and those that are well may be less interested in returning to our centre for cardiopulmonary testing. Our 41 of 84 patients may therefore represent a biased sample towards patients with more medical problems and poorer exercise capacity. There were too few patients with measurements of ejection fraction at maximal exercise to include these variables in a linear regression model with VO2max as the dependent variable. A continuous follow up of these patients with ejection fraction measurements would give additional information for future research. The limited number of patients available implies that failure to regret a hypothesis does not necessarily imply equality.

CONCLUSION
Diminished values of heart rate, FEV1, FVC, and systolic blood pressure compared to the predicted values may contribute to the reduced VO2max found in patients with CCTGA. In addition, a limited increase in systemic right ventricular ejection fraction and a decrease in pulmonary left ventricle contractility suggest a dysfunction of both ventricles. A larger prospective study should be carried out in order to confirm the present data.

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