Cardiorespiratory Response to Exercise After Venous Switch Operation for Transposition of the Great Arteries*

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**Study objective:** This study reports on the cardiorespiratory response to graded exercise in patients after venous switch operation for transposition of the great arteries.

**Design:** Several small studies have documented a diminished exercise tolerance after Mustard repair for transposition of the great arteries; little information exists, however, about long-term cardiorespiratory exercise performance in patients who have had the Senning procedure.

**Patients:** This prospective study reports on the serial long-term (mean, 11±2.8 years) cardiopulmonary exercise performance of 43 patients (age, 12±3.1 years) who underwent a Senning procedure, with no significant postoperative abnormalities. Forty-three matched healthy children were also studied as a control group.

**Measurements and results:** All underwent exercise testing (Bruce protocol) with metabolic gas exchange to determine parameters at 3 min, anaerobic threshold, similar heart rate (150 beats/min), and peak exercise. Time of exercise was 10.5±1.9 min in patients and 13.4±2 min in control subjects (p=0.0001). Overall, patients reached 73% of peak oxygen uptake achieved by control subjects (32.6±5.6 vs 44.7±6 mL/kg/min). Chronotropic response (188±15.7 vs 166.5±19.6 beats/min [p=0.0001]) and oxygen pulse (7.4±2.9 vs 10.7±4.2 mL/beat [p=0.0002]) were lower in patients at peak exercise. Patients had a greater respiratory response to exercise: both respiratory rate and ventilatory equivalent for carbon dioxide were significantly higher at all stages of exercise. Exercise capacity assessed by peak oxygen uptake was correlated with time elapsed since surgical repair (r=0.48; p=0.001).

**Conclusions:** It is concluded that even in asymptomatic patients, exercise endurance and respiratory response are generally altered as much as 11±2.8 years after venous switch operation, although early surgical repair is predictive of a better long-term functional result.

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**Key words:** exercise testing; Senning; transposition of great vessels

**Abbreviations:** ASO=atrial switch operation; AT=anaerobic (ventilatory) threshold; RR=respiratory rate; TGA=transposition of great arteries; VCO₂=carbon dioxide output; VE=minute ventilation; VO₂=oxygen uptake; VT=tidal volume

Although the arterial switch operation is now frequently the procedure of choice for correcting transposition of the great arteries (TGA), most adolescents and young adults born with TGA owe their survival to the atrial switch operation (ASO). Mustard and Senning procedures result in low early morbidity and mortality, but long-term results have shown an increased incidence of arrhythmia, sudden deaths, and a decrease in functional capacity, probably because the morphologic right ventricle may be unable to function as successfully as a morphologic left ventricle in the systemic position for long periods of time. Previous investigators have described a limited cardiorespiratory response to exercise in patients who have had ASO. However, these series were limited in number, did not always analyze gas exchange, and included patients especially operated on with the Mustard technique. Therefore, the present study was undertaken to evaluate exercise tolerance in a larger series of 43 patients who had undergone a Senning procedure, with special attention to cardiopulmonary response.
Materials and Methods

Subjects

The forty-three patients (11 girls, 32 boys) underwent ASO at our cardiology hospital department between 1977 and 1988; after operation, they had yearly clinical, ECG, and echocardiographic examinations. All patients had at least one postoperative catheterization. Twenty-six patients had simple transposition, defined as TGA with an otherwise normal heart, whereas the remainder had additional associated defects, including ventricular septal defect (seven patients) or ventricular outflow obstruction (ten patients). At the time of the study, 11 patients had mild pulmonary stenosis (<40 mm Hg), 5 had atrial baffle obstruction, and 1 had important tricuspid regurgitation. Two patients had permanent pacemakers. All considered themselves asymptomatic and most of them took part in gym at school. Mean age at surgical repair was 9.6±5.6 months, and the postoperative interval ranged from 6.5 to 18.3 years (mean, 11±2.8 years). Two patients were taking cardiac medications at the time of their exercise study; these were diuretics (one patient) and beta-blockers (one patient). As a control group, 43 healthy voluntarily enrolled children from local schools were also studied; none had a sport activity elsewhere. They were matched for age, sex, height, and weight to TGA patients (Table 1).

Exercise Testing

This study was undertaken with the approval of the local ethics committee, and written informed consent from each subject's parents was obtained. Treadmill exercise testing was performed using a Bruce protocol. All children were encouraged by an experienced nurse to exercise to exhaustion.

Heart rate and rhythm were monitored continuously throughout exercise by an exercise ECG system (Marquette Cardiac; Marquette Electronics Inc; Milwaukee). A 15-lead ECG was obtained with the patient at rest, and at 1-min intervals for 5 min after exercise testing. BP was measured at each workload with a mercury sphygmomanometer.

Gas was measured directly through open-circuit spirometry (Medical Graphic Corporation CPX System, St. Paul, Minn) by a first-responding oxygen analyzer and an infrared carbon dioxide analyzer. Minute ventilation (\(\text{Ve}\)), oxygen uptake (\(\text{Vo}_2\)), carbon dioxide output (\(\text{VCO}_2\)), and derived variables were measured for each breath. Before each exercise study, the system was calibrated with known volumes of airflow and precise gas mixtures. Gas exchange and flow measurements were corrected for ambient temperature, barometric pressure, and water vapor. Peak \(\text{Vo}_2\) was defined as the maximal value of \(\text{Vo}_2\) obtained during the last 30 s of exercise. Oxygen pulse was calculated as the ratio of \(\text{Vo}_2\) to the concomitant heart rate. Anaerobic threshold was determined mainly by the V slope method, in addition to the following conventional criteria: an increase, after a period of stability or reduction in ventilatory equivalent for oxygen (Ve/\(\text{Vo}_2\)) and a steeper increase in the gas exchange ratio. \(\text{Vo}_2\) at anaerobic threshold was also expressed in percent of the maximal oxygen consumption. The relationship between both respiratory rate (RR) and ventilation (Ve) against carbon dioxide production (\(\text{VCO}_2\)) was calculated as indexes of the ventilation response.

All parameters were examined at four reference time points, ie, the third minute of the test, anaerobic threshold, 130 beats/min if reached, and peak exercise.

Statistical Methods

The analyses were performed using software (Mac Statview 512). Data are reported as mean values ±SD. Differences between mean values were calculated by analysis of variance with repeated measurements. Differences were considered statistically significant at the p<0.05 level. Linear regression analysis was used to study the correlation between exercise time or age of surgery and the different indexes of cardiopulmonary tolerance.

Results

Characteristics of the patients and control groups are summarized in Table 1. No significant differences were found between patients and control subjects with respect to age, sex, weight, height, and body surface area. Compliance with the study exercise was excellent for all children. Fatigue or breathlessness were the only reasons to stop exercise.

Mean heart rates at rest on ECG were 87±15.1 beats/min in patients and 99.2±14.9 beats/min in the normal group (p=0.0001). All normal subjects and 36 of 43 patients were in sinus rhythm at rest; 5 patients had intermittent junctional rhythm; 2 patients were paced because of sinus node dysfunction. All patients but one developed sinus tachycardia with exercise; 6 patients had significant atrial (n=3) or ventricular (n=3) arrhythmias during exercise. At peak exercise, control subjects achieved a significantly higher heart rate (187.8±16.1 vs 166.5±19.6 beats/min; p=0.0001). Twenty-one patients were unable to reach 80% of their theoretical maximal heart rate, and 6 patients did not achieve 150 beats/min at the end of exercise; the relationship between chronotropic response and \(\text{Vo}_2\) was \(y=3.1 x+47.2\) in control subjects and \(y=4.2 x+31.3\) in patients, where \(y=\text{heart rate (beats/min)}\) and \(x=\text{Vo}_2\) in mL/min/kg (Fig 1). Maximal exercise heart rate showed no correlation with either age at the time of operation or age at the time of exercise testing. However, maximal heart rate was weakly correlated with peak \(\text{Vo}_2\) in patients (r=0.29, p=0.05). Systolic BP was also different at rest (pa-
patients, 100±10 mm Hg; control subjects, 109±13 mm Hg; p=0.002) and at peak exercise (patients, 122±15 mm Hg; control subjects, 140±23 mm Hg; p=0.0001).

Exercise duration, VO₂, and work capacity were significantly greater in control subjects than in patients (Table 2). Overall, patients achieved 73% of peak VO₂ obtained by control subjects (32.6±5.6 vs 44.7±6 mL/kg/min; p=0.0001). Time of exercise was 10.5±1.9 min in patients and 13.4±2 min in control subjects (p=0.0001). The anaerobic (ventilatory) threshold (AT) could be determined in 38 of the 43 patients and in 39 control subjects. VO₂ at AT was 24.6±4.2 mL/kg/min in patients and 34.7±6.1 mL/kg/min in control subjects (p=0.0001). Compared with normal control subjects, the AT was surpassed sooner (6±1.8 vs 8.6±2 min; p=0.0001). The mean values of VO₂ at AT were 75±11% of peak VO₂ in patients and 78±8% in control subjects (p=NS). VO₂ was also lower in patients at all levels of exercise: 19.5±3.6 vs 24.6±5.9 mL/kg/min; p=0.0001; at 3 min, 26.6±5.2 vs 33.1±7.3 mL/kg/min; p=0.0003; at an identical heart rate of 150 beats/min (Fig 2).

Exercise capacity assessed by peak VO₂ was correlated with time elapsed since surgical repair (r=0.48; p=0.001) (Fig 3).

As a result of VO₂ and heart rate decreases at each stage of exercise, the oxygen pulse was lower in patients at the third minute of exercise (6.7±2.6 vs 8.6±3 mL/beat; p=0.001), at AT (7.1±2.6 vs 10.2±4.1 mL/beat; p=0.0007), and at the end of exercise (7.4±2.9 vs 10.7±4.2 mL/beat; p=0.0002) (Fig 4).

As in normal subjects (r=0.85; p=0.001), oxygen

**Table 2—Cardiopulmonary Variables in Patients (p) and Control Subjects (c)**

<table>
<thead>
<tr>
<th></th>
<th>3 min</th>
<th>AT</th>
<th>150 Beats/min</th>
<th>Peak Exercise</th>
</tr>
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<tbody>
<tr>
<td>VE, L/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>21.8±7</td>
<td>29.8±9.7</td>
<td>35±11.7</td>
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<td>c</td>
<td>27.5±7</td>
<td>41.3±12.8</td>
<td>38.9±13.1</td>
<td>69.3±20.1</td>
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<tr>
<td>RR, min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>33±6</td>
<td>37±8</td>
<td>40±8</td>
<td>49±9</td>
</tr>
<tr>
<td>c</td>
<td>31±7</td>
<td>38±8</td>
<td>37±9</td>
<td>51±9</td>
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<tr>
<td>VT, mL/min</td>
<td></td>
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<td></td>
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<tr>
<td>p</td>
<td>680±280</td>
<td>830±330</td>
<td>900±330</td>
<td>960±440</td>
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<tr>
<td>c</td>
<td>940±380</td>
<td>1,150±430</td>
<td>1,070±402</td>
<td>1,420±720</td>
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<tr>
<td>VO₂, mL/min/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>19.5±3.6</td>
<td>24.6±4.2</td>
<td>26.6±5.2</td>
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</tr>
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<td>33.1±7.3</td>
<td>44.7±6.1</td>
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<td>VO₂, L/min</td>
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</tr>
<tr>
<td>p</td>
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<td>0.85±0.35</td>
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<tr>
<td>c</td>
<td>0.94±0.29</td>
<td>1.60±0.65</td>
<td>1.46±0.6</td>
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<td>Ve/VO₂</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>37.4±8.5</td>
<td>36.6±8</td>
<td>35.5±6.1</td>
<td>36.9±11.5</td>
</tr>
<tr>
<td>c</td>
<td>29.7±4.1</td>
<td>27.4±4.1</td>
<td>27.1±4.5</td>
<td>31.4±5.3</td>
</tr>
<tr>
<td>O₂ pulse, mL/beat</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>6.6±2.6</td>
<td>7.1±2.6</td>
<td>7.2±2.8</td>
<td>7.4±2.9</td>
</tr>
<tr>
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<td>10.2±4.1</td>
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<td>10.7±4.2</td>
</tr>
</tbody>
</table>

*Ve/VO₂=respiratory equivalent for carbon dioxide; O₂ pulse=oxygen pulse.
1p<0.001.
2p<0.0001.
3p<0.01.
4p<0.05.
pulse at the end of exercise was strongly correlated with body surface area in the patient group ($r=0.89$; $p=0.0001$) but with a lower slope relationship (control subjects, $y=11.2 x-4.78$; patients, $y=8.3 x-2.8$, where $y$=oxygen pulse and $x$=body surface area).

During exercise, the patient group had a $V_{E}$/lower than control subjects (46±18.7 vs 69.3±30.1 L/min; $p<0.0001$) at the end of exercise. However, the ventilatory pattern was very different between the two groups: the increase of tidal volume ($V_{T}$) was lower during exercise in patients. Patients had a greater respiratory response to exercise with RR/ $V_{E}CO_2$ and $V_{E}/V_{CO}_2$ showing significant increases at all stages of exercise. Figure 5 shows the $V_{T}$-RR relationship for each group. We found no significant correlation between $V_{E}/V_{CO}_2$ and $V_{O}_2$ at the end of exercise.

All these differences in cardiopulmonary parameters were also present for the Senning subgroup with or without additional defects.

**DISCUSSION**

Comparisons of cardiopulmonary function in patients having undergone venous switch operation

![Figure 2. Box plots of the values of $V_{O}_2$ during exercise in control subjects and patients at the third minute of the test, AT, 150 beats/min, and peak exercise. The central dot is the sample mean. The bottom and top edges of the box are the sample 25th and 75th percentiles.](image1)

![Figure 3. Relation between peak $V_{O}_2$ (mL/min/kg) and age (months) at surgery in patients.](image2)

![Figure 4. Oxygen pulse (mL/beat) in normal subjects and patients. Data (mean±SEM) were obtained at the third minute of exercise, AT, 150 beats/min, and peak exercise. Two asterisks indicate $p<0.001$.](image3)
was absent in normal subjects. However, peak \( \text{VO}_2 \) decrease \((-27\%)\) is only partially explained by chronotropic alteration \((-12\%)\) after atrial repair. This chronotropic limitation may not be specific to atrial repair but might be a common denominator to all intracardiac repair, as the cardiopulmonary bypass procedure has been associated with surgical fibroelastosis that could directly or indirectly disrupt the integrity of the sinus node.\(^ {14} \)

The other cause suggested for limited capacity after venous switch operation is an inadaptation of the right ventricle in the systemic position. Several echocardiographic, angiographic, and especially isotopic exercise studies have shown ventricular hypokinesia and a decrease in stroke volume.\(^ {19–23} \) Although right ventricle dilatation may be a compensatory mechanism for chronotropic insufficiency,\(^ 6 \) CO\(_2\) rebreathing and isotopic measurements of cardiac flow showed a decrease in stroke volume during exercise testing under constant maximal load.\(^ {9} \) In our study, oxygen pulse, an indirect indicator of the stroke volume, was decreased at the end of testing \((7.4\pm2.9 \text{ vs } 10.7\pm4.2 \text{ mL/beat}; p<0.001)\) and at submaximal loads.

In normal children and adolescents, oxygen pulse correlates better than peak \( \text{VO}_2 \) with morphometric parameters, particularly body surface.\(^ {25} \) In our patients and control subjects, these correlations were excellent but with different coefficients.

Although our study unfortunately confirms that children treated with the Senning technique have a long-term functional limitation close to that in children operated on a few years earlier with the Mustard operation, it does show for the first time an inverse relationship between age and peak \( \text{VO}_2 \). We observed no significant relationship between age at surgery and maximal heart rate or \( \text{O}_2 \) pulse at peak effort. Unlike previous series in which no association was noted between time since intervention and exercise capacity, it seems that the earlier the children are operated on with the Senning technique, the better their ultimate effort capacity.

Our patients were all operated on by the same surgeon, and were operated on as quickly as possible when functional tolerance was poor (persistent cyanosis despite an efficient atrioseptostomy of Rashkind-Miller). It may be that submitting the right ventricle early to conditions of systemic load leads to better long-term tolerance, with exercise capacities similar to those in patients operated on with an arterial switch technique.\(^ {26} \)

The ventilatory adaptation of our patients during exercise testing was also quite different from that of normal patients and is reminiscent of the modifications described in cardiac insufficiency.\(^ {27,28} \) There is, in fact, an excess ventilatory response as measured by the respiratory frequency (or overall ventilation) compared to the production of \( \text{CO}_2 \).\(^ {29} \) Such anomalies have also been described more recently after Fontan procedures and repair of tetralogy of Fallot.\(^ {30} \)

However, we found no correlation between respiratory equivalents for \( \text{CO}_2 \) measured at the end of exercise and peak \( \text{VO}_2 \) in patients or control subjects, contrary to a previous report.\(^ {24} \) The relationship \( \text{VT-RR} \), which is all the more disturbed as the limitation of effort capacity increases, was also abnormal in our patients. This disturbance is associated more with a decrease in \( \text{VT} \) at the end of effort than with an acceleration in respiratory frequency. However, the mechanisms involved in this abnormal ventilatory response are not well understood. Unfortunately our patients did not have additional respi-
monary function tests (including vital capacity, pulmonary diffusing properties, lung distensibility, etc) and our study cannot elucidate this discussion. But as in patients with cardiac insufficiency, the relationship between ventilation and CO₂ production was not linear in our patients, so there is growing support for another stimulus being involved, particularly a muscular ergoreflex.27 This could explain the benefits of physical training observed in recent years in patients with cardiac insufficiency,31 and also in children operated on by venous switch operation.32

Our study in a large series of patients mainly operated on with the Senning technique and with a long follow-up confirms that atrial repair is associated with a limitation in maximal aerobic capacity with an early anaerobic AT. Although patients may be asymptomatic, they have an inadapted ventilatory response to exercise. Chronotropic insufficiency and especially the already documented relative inadaptation of the right ventricle to exercise should make clinicians vigilant about the long-term outcome of these patients. However, it would seem that interventions performed earlier with the Senning technique lead to better long-term exercise capacity, thus reopening the debate concerning the respective advantages of the arterial36-33 with venous switch operation.

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