Oxygen uptake versus exercise intensity: a new concept in assessing cardiovascular exercise function in patients with congenital heart disease

T Reybrouck, L Mertens, S Brusselle, M Weymans, B Eyskens, J Defoor, M Gewillig

Abstract

Objective—To assess the relation between exercise intensity and oxygen uptake during graded exercise in paediatric patients who underwent surgical repair of congenital heart disease, and to compare it with conventional measures of aerobic exercise function.

Design—Cross sectional study. Exercise testing was performed on a treadmill and gas exchange was measured on a breath by breath basis.

Patients—29 patients who underwent an atrial switch operation for transposition of the great arteries (TGA) (mean (SD) age at testing 10.3 (2.5) years) and 30 patients who underwent total repair of tetralogy of Fallot (TF) (age 12.1 (3.3) years) performed graded exercise testing. Exercise responses were compared with data obtained in 24 normal controls (age 11.4 (2.6) years).

Results—The slope of oxygen uptake versus exercise intensity averaged 1.50 (0.64) ml O₂/min²/kg in the patients with TGA and 1.68 (0.75) ml O₂/min²/kg after TF repair, both lower (p < 0.005) than in normal controls (2.42 (0.68) ml O₂/min²/kg). The lower slope of oxygen uptake was correlated with a subnormal value for ventilatory anaerobic threshold, which averaged 78.0 (13.3)% of normal in TGA and 85.1 (10.6)% in TF. This was associated with a steeper slope (p = 0.001) of carbon dioxide output versus oxygen uptake above the ventilatory anaerobic threshold in TGA (1.26 (0.20)) and TF (1.20 (0.18)) compared with the normal controls (1.05 (0.13)), and also a steeper slope of ventilation versus carbon dioxide in TGA (47.0 (15.4)) and TF (41.5 (13.7)) than in the controls (30.3 (8.5)).

Conclusions—Calculation of the steepness of the slope of oxygen uptake versus exercise intensity is a valid measure of oxygen flow to the exercising tissues, which may be limited in congenital heart disease.

Methods

SUBJECTS
Exercise tests were performed in three groups of subjects (two patient groups and one normal control group).
The first group consisted of 29 patients (19 boys and 10 girls), who underwent cardipulmonary exercise testing 9.9 years after an atrial switch operation for transposition of the great arteries (TGA). The Senning operation was performed in 27 subjects and the Mustard procedure in two. Age at surgery varied from 1 to 19 months, mean (SD) 5.4 (4.8) months, and age at exercise testing varied from 5.7 to 14.7 years, mean 10.3 (2.5) years. All these patients were in sinus rhythm at the time of exercise testing. Echocardiographic evaluation at that time showed patent venous pathways in all but one patient.

A second group of 30 patients (18 boys and 12 girls) was studied 8.3 (4.4) years after total surgical repair of tetralogy of Fallot (TF). Age at surgery varied from 0.75 to 11.5 years (mean 3.7 (2.8) years), and age at exercise testing varied from 5.5 to 16.7 years (mean 12.1 (3.3) years).

The values for the slope of oxygen uptake versus exercise intensity in the two patient groups were compared with a third group of 24 normal controls of comparable age (7.2 to 17.7 years, mean 11.4 (2.6) years). These normal controls were children and adolescents who were referred to our paediatric cardiology outpatient clinic for a heart murmur (or functional complaints), and in whom a definite diagnosis of a functional heart murmur in a morphologically and functionally normal heart was made. The diagnosis was based on clinical findings, ECG, and echocardiography.

All patients with TF repair and atrial switch operation for TGA were asymptomatic at the time of exercise testing. On the ECG, right bundle branch block was found in all patients. On the ECG, and echocardiography. The diagnosis was based on clinical findings, ECG, and echocardiography.

Exercise testing procedure

The methods for exercise testing have been fully described previously. Briefly, exercise testing was performed on a treadmill, and the speed was set at 4.8 km/h for children less than 6 years of age and at 5.6 km/h for children six years of age or older. This study was intended to assess exercise performance using submaximal exercise. The inclination of the treadmill was increased by 2% every minute until the submaximal target heart rate of 170 beats/min was reached. A target heart rate of 170 beats/min was chosen, because this is a conventional limit in cardiovascular exercise testing that has often been used in the past; it corresponds to the highest heart rate of submaximal steady state work and has been shown to correlate with maximum oxygen uptake.

Gas exchange was measured on a breath by breath basis by a computerised system using a mass spectrometer (Marquette MGA 1100; Milwaukee, USA). The adequacy of the oxygen transport system was assessed by calculating the steepness of the slope of oxygen uptake versus exercise intensity during the graded treadmill exercise, using linear regression analysis. In this analysis, exercise intensity was estimated from exercise time (expressed in minutes or fractions of minutes), as all patients performed the same standardised graded exercise test. Therefore the slope of the regression of oxygen uptake (determined as ml O2/min/kg) versus exercise intensity (time in minutes) is expressed as ml O2/min2/kg. This regression was calculated on all breaths, averaged every 10 seconds, using the moving average principle, in order to reduce the variability and disturbing effect of noise. The data of the first 60 seconds of exercise were omitted because it is known that the breathing pattern is very irregular at the onset of exercise. A typical example is shown in fig 1.

To account for the influence of body weight, which determines the size of the work incre-
ments on a treadmill, an estimate of the external work for a fixed inclination (10%) was calculated using standard equations. Cardiorespiratory exercise function was further assessed by determining the ventilatory anaerobic threshold. This was defined using the V slope method and calculated from a computer algorithm. Data for ventilatory anaerobic threshold were expressed in ml/min/kg. As the values for ventilatory anaerobic threshold are to a large extent influenced by age and sex in children of varying age, the results from the patients were also expressed as a percentage of the normal mean value obtained in healthy children of comparable age and sex, extracted from a large pool of 237 normal children.

The oxygen uptake versus exercise intensity slope was also compared with two other recently developed indices used for assessing cardiorespiratory exercise performance. First, we determined the steepness of the slope of carbon dioxide output versus oxygen uptake above the ventilatory anaerobic threshold; this slope was calculated between the ventilatory anaerobic threshold and the exercise intensity at which a heart rate of 170 beats/min was reached (slope 2). Second, we assessed the slope of ventilation versus carbon dioxide output for all exercise levels, excluding the first minute because of hyperventilation. This was used as an index of ventilatory efficiency. The respiratory gas exchange ratio (R) was calculated as the ratio of carbon dioxide output to oxygen uptake.

**Statistical Analysis**

Differences between the mean values were calculated by univariate analysis of variance. Post hoc analysis of differences between the subgroups was performed by the Bonferroni method. For regression analysis, a linear regression technique was applied, and for correlation analysis we used the Pearson correlation. Reproducibility was determined by calculating the coefficient of repeatability according to Bland and Altman; this was defined as two times the standard deviation of the differences. In addition, the coefficient of variation was defined as 100 times the standard deviation of differences divided by the mean, and the percentage difference was calculated as 100 times the absolute difference between two tests divided by the mean value of both measurements. Significance levels were set at p < 0.05.

**Results**

**Determining the Slope of Oxygen Uptake Versus Exercise Intensity and Related Variables**

We were able to calculate the slope of oxygen uptake versus exercise intensity in all subjects. A target heart rate of 170 beats/min was reached in all the normal controls. In two of the patients with TF repair a target heart rate of 170 beats/min could not be reached because of exhaustion. In these patients, maximum heart rates were 150 and 153 beats/min. In three patients with TGA it was also not possible to achieve the target heart rate of 170 beats/min, because of exhaustion and dyspnoea in two and the development of second degree atrioventricular block in one. In these patients the maximum heart rates were 150 and 167 beats/min in the first two and 138 beats/min in the patient with atrioventricular block. In these subjects, the slope of oxygen uptake versus exercise intensity was calculated using the maximum exercise heart rate achieved.

The oxygen uptake at a heart rate of 170 beats/min averaged 29.9 (7.7) ml/min/kg in the patients with TGA and 30.4 (6.3) ml/min/kg in the patients with TF repair, versus 36.5 (5.3) ml/min/kg in the normal controls (p < 0.001; patients v controls). The relation between heart rate and oxygen uptake in both the patient groups and the normal controls is shown in fig 2. The lowest value for oxygen uptake at a heart rate of 170 beats/min was reached in patients with TGA. For a further assessment of the relative exercise intensity performed at a heart rate of 170 beats/min, we determined the R value at that heart rate, and also the level of exercise (per cent inclination of the treadmill) at which an R value of 1.0 was achieved. R at a heart rate 170 beats/min averaged 0.97 (0.08) in the patients with TGA, 0.96 (0.07) in the patients with TF repair, and 0.90 (0.07) in the normal controls (p < 0.005; patients v controls). The exercise level at which R reached 1.0 averaged 7.2 (2.7)% in the patients with TGA, which was less (p < 0.001) than the values obtained in the patients with TF repair (12.2 (3.1)% and in the normal controls (12.9 (3.9)%).

The ventilatory anaerobic threshold could not be determined in 13 of the 59 patients (22%) (six in the TGA group and seven in the TF group). This was a prerequisite for subsequent analysis of the slopes of carbon dioxide output versus oxygen uptake above the ventilatory anaerobic threshold. In the normal controls we were able to determine the ventilatory anaerobic threshold in all cases.

A reproducibility study was performed in 10 normal subjects. These performed two exercise tests, separated by a minimum of 24 hours. The coefficient of repeatability was 0.33 ml O₂/min/kg. The coefficient of variation was 3.6% and the percentage difference amounted to 5.5 (4.4)%.

![Figure 2](http://heart.bmj.com/)

**Figure 2** Relation between oxygen uptake and heart rate during graded exercise in patients with transposition of the great arteries and atrial switch (solid circles) and patients with repair of tetralogy of Fallot (solid squares), compared with normal controls (open circles). The data points represent mean values for the different patient groups.
The lowest value for the slope of oxygen uptake versus exercise intensity was found in patients with TGA, but the difference between TGA and TF was not significant. The decreased oxygen uptake slope was associated with significantly lower values for the ventilatory anaerobic threshold, expressed as per cent of the normal mean value obtained in children or adolescents of the same age and sex. In patients after total repair for TF, it averaged 85.1 (10.6)% of normal, and in patients with TGA, 78.0 (13.3)% (table 1).

To account for the influence of differences in body weight on the magnitude of the work rate increments during graded treadmill exercise, an estimate of the external work rate was calculated for a standard inclination and speed of the treadmill (10% elevation; speed 5.6 km/h). In the normal subjects external work averaged 57.2 (16.4) W, in the patients with TGA it averaged 51.8 (17.1) W, and in the patients with TF repair, 64 (24.5) W. No significant difference was found between the three groups (p > 0.05).

Above the ventilatory anaerobic threshold, a disproportionate rise in carbon dioxide output against oxygen uptake was found. The steepness of the slope of carbon dioxide versus oxygen uptake was significantly greater in both the patient groups than in the normal controls. The highest value was found in the patients with TGA (table 1). Moreover, in both patient groups, the slope of ventilation versus carbon dioxide output was also greater (p = 0.001) than in the normal controls (41.5 (13.7) in TF repair and 47.0 (15.4) in TGA, v 30.3 (8.5) in the controls).

**CLINICAL APPLICATION OF THE SLOPE OF OXYGEN UPTAKE VERSUS EXERCISE INTENSITY**

To assess the clinical applications of this concept, we correlated the results of the slope of oxygen uptake against exercise intensity with the clinical outcome after surgery in both patient groups. In 10 of the patients with TF repair, a subnormal value was found (< 1.8; that is, below the lower limit of the 95% confidence interval of 1.8 to 3.04, determined from the data obtained in the 24 normal controls).

In the normal subjects no significant correlation was found between the slope of oxygen uptake versus exercise intensity and age (r = 0.093, p = 0.66).

**Table 1**  
Slopes of oxygen uptake versus exercise intensity, carbon dioxide output versus oxygen uptake, and ventilation versus carbon dioxide together with anaerobic threshold in patients with congenital heart disease and normal controls

<table>
<thead>
<tr>
<th>Group</th>
<th>Slope VO₂ v exercise intensity (ml/min/kg)</th>
<th>Ventilatory anaerobic threshold (ml/min/kg)</th>
<th>Ventilatory anaerobic threshold (% normal)</th>
<th>Slope VO₂ v V̇O₂</th>
<th>Slope V̇E v V̇O₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal controls (n=24)</td>
<td>2.42 (0.68)</td>
<td>29.0 (3.1)</td>
<td>-</td>
<td>1.05 (0.13)</td>
<td>30.3 (8.5)</td>
</tr>
<tr>
<td>TF (n=30)</td>
<td>1.68 (0.75)*</td>
<td>24.9 (3.6)*</td>
<td>85.1 (10.6)*</td>
<td>1.20 (0.18)*</td>
<td>41.5 (13.7)*</td>
</tr>
<tr>
<td>TGA (n=29)</td>
<td>1.50 (0.64)*</td>
<td>22.6 (4.7)*</td>
<td>78.0 (13.3)*</td>
<td>1.26 (0.20)*</td>
<td>47.0 (15.4)*</td>
</tr>
</tbody>
</table>

Data are means (SD).

*p < 0.005, normal controls v patients (TF and TGA).

Slope VO₂, slope of oxygen uptake from oxygen uptake at ventilatory anaerobic threshold until oxygen uptake at heart rate of 170 beats/min; slope V̇E v V̇O₂, slope of ventilation v carbon dioxide output during graded exercise; TF, tetralogy of Fallot after repair; TGA, transposition of the great arteries after atrial switch operation; V̇O₂, carbon dioxide output; VO₂, oxygen uptake. Ventilatory anaerobic threshold (% of normal) is expressed as a percentage of the mean value obtained in normal children and adolescents of same age and sex.
In the 10 patients after TF repair who had a subnormal value for the slope, seven had moderate to severe pulmonary regurgitation assessed by echocardiographic examination, two had right ventricular dysfunction, and one had an absent left pulmonary artery. In the 20 TF patients with a normal value for this slope (> 1.8), only three had a moderate degree of pulmonary regurgitation, while the rest had only trivial regurgitation during echocardiography or on clinical examination.

In all the patients with the atrial switch operation for TGA, we found a dilated and hypococontractile right ventricle during echocardiographic examination, as is usually observed in such patients. Subnormal values for the slope of oxygen uptake versus exercise intensity were found in 17 patients with residual haemodynamic defects such as subvalvar pulmonary stenosis, moderate to severe tricuspid regurgitation, and cardiomegaly on chest X ray. In the other 12 patients with a normal slope of oxygen uptake versus exercise intensity (> 1.8), no significant residual haemodynamic lesions were observed.

Discussion
The major finding in this study was the smaller increase of the oxygen uptake versus exercise intensity relation with increasing inclination of the treadmill in the patients with surgically treated congenital heart disease compared with normal controls. This was associated with a subnormal value for the ventilatory anaerobic threshold and a significantly steeper value for the slope of carbon dioxide output against oxygen uptake above the anaerobic threshold. In addition, the slope of ventilation versus carbon dioxide output was higher in both patient groups compared with the normal controls. This is in agreement with previous studies in patients with congenital heart disease, as well as in other studies in patients with ischaemic heart disease, where significantly lower values for the slope of oxygen uptake against work rate were found, and a steeper value of the slope of carbon dioxide output versus oxygen uptake. Moreover, in patients with chronic heart failure, and more specifically after TF repair or after the Mustard operation for TGA, an increase in the slope of ventilation against carbon dioxide output has been reported; this has been attributed to maldistribution of pulmonary blood flow, with increased physiological dead space ventilation. In our present study on patients with congenital heart disease, as well as in other studies in patients with ischaemic heart disease, the reduced slope of oxygen uptake is also associated with a steeper slope of carbon dioxide output versus oxygen uptake, which is thought to reflect the buffering of lactic acid by bicarbonate. The excessive ventilatory response to carbon dioxide has been ascribed to the use of the respiratory cycle as an auxiliary pump in patients with decreased ventricular function, to improve venous return and consequently pulmonary blood flow. The reduced slope of oxygen uptake versus exercise intensity, together with the inefficient ventilatory response to carbon dioxide, can be considered as factors limiting exercise capacity as they reflect impaired oxygen delivery to the exercising tissues and wasted ventilation.

In previous studies on children and adolescents with congenital heart disease, aerobic exercise performance has often been assessed by determining maximum oxygen uptake or anaerobic threshold. However, both measures can be criticised, especially in the paediatric age group. Determination of maximum oxygen uptake is dependent on motivation, which can be low in children, while calculation of the anaerobic threshold is influenced by several factors that increase the variance of the result, including differences in the exercise protocol, the method used for threshold determination, and interobserver differences. We studied the clinical value of the slope of oxygen uptake versus exercise intensity in two groups of patients known to have reduced aerobic exercise performance. Subnormal values have been reported for maximum oxygen uptake and ventilatory anaerobic threshold in patients with TGA and atrial switch and in patients with TF repair. In addition, a reduction in oxygen uptake in relation to exercise intensity has also been found in exercise studies examining the kinetics of gas exchange. For example, in children with total repair of TF and in those with an atrial switch operation for TGA, a slowed rate of oxygen uptake was observed during a constant level of exercise. This may explain the lower value for the slope of oxygen uptake versus exercise intensity that we found in both patient groups in the present study. It also confirms the subnormal value of these determinants of aerobic exercise function, and suggests impaired oxygen delivery to the exercising tissues.

In patients with TGA and atrial switch operation, the reduced oxygen delivery to the exercising tissues has been attributed to a lower, and inappropriate, right (systemic) ventricular ejection fraction and a subnormal cardiac output during moderate exercise, caused by relative obstruction to flow. In patients who have had total repair of TF, the lower value of the slope of oxygen uptake versus exercise intensity—together with a steeper value of the slope of carbon dioxide output versus oxygen uptake above the ventilatory anaerobic threshold, and an increased slope of ventilation versus carbon dioxide output—results from haemodynamic dysfunction. This may be caused by pulmonary valve incompetence, an impaired ejection fraction, or impaired chronotropic exercise response, resulting in a subnormal cardiac output during submaximal and maximal exercise. In our present study the lowest values for the slope of oxygen uptake against exercise intensity were found in the patients with residual haemodynamic defects, such as severe pulmonary regurgitation after TF repair and subvalvar pulmonary stenosis after atrial switch operation in TGA.
In most previous studies investigating oxygen uptake during exercise in patients with cardiovascular disease, the slope of oxygen uptake versus work rate on a bicycle ergometer was calculated. In the present study we used graded treadmill exercise and assessed the relation between oxygen uptake and exercise time during a one minute incremental exercise test (reflecting exercise intensity). Although external work can be difficult to quantify during treadmill exercise owing to differences in walking pattern, a rough estimate can be made by using standard equations. As body mass may influence the work rate increment during graded treadmill exercise, it could be hypothesised that differences in body mass between different groups may have influenced the rate of increase in external work performed during the exercise. We calculated the difference in work rate for a given inclination (10%) and standard speed (5.6 km/h) in the three different groups. This showed that the magnitude of the difference in work rate between patients with TGA and normal controls (9.6%) was much smaller than the difference in the slope of oxygen uptake against exercise (38%). Furthermore, as oxygen uptake was normalised for body weight, this factor was cancelled out. Therefore a lower body mass in patients with TGA cannot explain the lower slope of oxygen uptake against exercise intensity.

In patients with congenital heart disease, one should take into account that the slope of oxygen uptake versus work rate is dependent on the exercise protocol. In a comparison between a one minute incremental exercise protocol and a four minute (steady state) graded exercise protocol in a large series of 540 patients with congenital heart disease, Wessel reported significantly higher values for the slope of oxygen uptake versus work rate in the four minute test than in the one minute test. Therefore each laboratory should determine its own appropriate normal standards for comparing clinical values.

**Study Limitations**

We assessed the results of this new index of cardiovascular exercise function in congenital heart disease in relation to the clinical outcome after surgical correction. Direct measurements of cardiac function using intracardiac pressures and determination of myocardial contractility by analysis of dP/dt were not available, neither were measurements of cardiac output or blood pressure response during exercise. However, on the basis of echocardiography and clinical examination we were able to show that the lowest values for the slope of oxygen uptake versus exercise intensity occurred in patients with the most severe pulmonary regurgitation after TF repair, and in patients with significant residual subvalvar pulmonary stenosis or cardiomegaly in TGA.

Despite these limitations, this new index appears useful as it can discriminate between patients with more severe haemodynamic sequelae and those with more trivial haemodynamic lesions.

**Conclusions**

Our study shows that the determination of the slope of oxygen uptake versus exercise intensity is a reproducible, valid, and comprehensive index of cardiorespiratory exercise function. It provides information on oxygen flow to the exercising tissues, which may be a limiting factor in exercise performance in patients with congenital heart disease. Determination of this slope is particularly useful in patients with congenital heart disease, as a subnormal value is associated with important residual haemodynamic defects both after TF repair and after the atrial switch operation for TGA.

**Remarks**

This study was supported in part by grants from the National Fund for Research in Pediatric Cardiology and the National Fund for Medical Research (3.020.94). We gratefully acknowledge the help of D Schepers MS, during the statistical analysis of the data.

Visualising fatty deposits in familial arrhythmogenic right ventricular cardiomyopathy by magnetic resonance imaging

This 70 year old man had familial arrhythmogenic right ventricular cardiomyopathy (ARVC) with recurrent ventricular tachycardia since the age of 41. The diagnosis of ARVC was made on the basis of recurrent, refractory ventricular tachycardia, echocardiographic findings, a positive family history, and the detection on magnetic resonance imaging (MRI) of fatty deposits in the right ventricle. Transoesophageal echocardiography (top) showed a dilated right ventricle and focal thinning of the right ventricular wall apicoseptally and apicoposteriorly with two localised bulges in the right ventricular wall (arrows) (RV, right ventricle; LV, left ventricle). MRI (bottom) showed an almost akinetic thin wall of the right ventricle with fatty deposits, confirming the diagnosis of familial ARVC. Fatty deposits are seen in the atrioventricular groove (1); the right ventricular free wall is completely replaced by fatty tissue (2), which also extends to the apex and part of the lateral wall of the left ventricle (3); pericardium is seen at the base of the left and right ventricles (4); slow flow artefacts are particularly predominant in the right atrium (5).

MRI is a non-invasive method for detecting isolated fatty deposits in the myocardium of the right ventricle. The abnormalities shown by MRI are generally the starting point for the observed ventricular tachycardias. The differential diagnosis has to take account of Uhl’s anomaly, which also involves localised involvement of the right ventricle. In contrast with ARVC, wall areas in Uhl’s anomaly are characterised by a complete absence of myocardial cells. In such wall sections the endothelium and epithelium are in direct apposition.
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