Impaired chronotropic response to exercise in children with repaired cyanotic congenital heart disease

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Objective — Conventionally the heart rate response to exercise has been considered as a useful parameter for the assessment of exercise performance. However, in patients with surgical repair of congenital heart defects sino-atrial dysfunction has been observed after cardiac surgery. The purpose of this study was to assess whether the heart rate response to exercise can be used in the assessment of exercise performance.

Methods — Fifty-three patients with surgical repair of congenital heart disease underwent exercise testing. The patients were 19 children with repair of tetralogy of Fallot (TOF), 17 patients with arterial switch operation for transposition of the great arteries and 17 patients with a Fontan circulation for functional univentricular heart. The patients were compared to age-matched control subjects. Exercise capacity was assessed by determination of the maximal oxygen uptake. To account for the effect of age and gender on heart rate response, values in the patients were compared to age-matched control subjects of the same age and gender and were expressed as a Z-score of the normal value.

Results — In the 3 groups of patients a lower than normal heart rate response was observed during submaximal and maximal exercise, varying from -1.7 to -4.6 standard deviation scores. This was not associated with normal values for exercise capacity in patients with TOF or Fontan circulation, as should be expected.

Conclusion — In patients with surgical repair of congenital heart disease, the use of heart rate response in the assessment of cardiovascular exercise performance may be seriously misleading and should be complemented with measurements of gas exchange.

Keywords: *Chronotropic incompentence – exercise testing – heart rate response.*

Due to improved surgical repair of congenital heart diseases, a large number of patients reach adolescence and adulthood. However, in many patients sino-atrial dysfunction has been described as an acquired problem after cardiac surgery[1]. When assessing the cardiorespiratory exercise performance capacity, a considerable number of exercise test procedures rely on the heart rate response during exercise or on the relative exercise intensity, expressed as a percentage of the maximal heart rate[2].

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The purpose of the present study was to analyse whether the heart rate response during submaximal and maximal exercise can be used in various pathologies for the assessment of exercise intensity and exercise performance.

Patients and methods

Patients

The exercise response was studied in a total sample of 53 patients after surgical repair of cyanotic congenital heart disease. This was a retrospective analysis of data obtained during exercise testing in patients with congenital heart disease. At a routine outpatient visit,

Table 1. – *Anthropometrical and clinical variables*

	N	Age exercise testing (years)	Weight (kg)	Height (cm)	Age surgery (years)
TOF – PO	19	12.3 ± 2.9	45.1 ± 13.6	155 ± 16	2.36 ± 1.84
TGA switch	17	8.3 ± 2.5	26.3 ± 9.6	131 ± 12	0.03 ± 0.03
Fontan operation	17	11.2 ± 2.9	35.9 ± 12	143 ± 17	3.84 ± 1.30

Values represent mean and standard deviation of the sample. TOF – PO = postoperative tetralogy of Fallot; TGA switch = transposition of great arteries, arterial switch operation; N = number of patients, kg = kilogram, cm = centimeter.

the patients were clinically assessed and underwent also electrocardiographic and echocardiographic examinations. The patients were referred by the paediatric cardiologists for assessment of exercise performance and also for evaluation of the heart rhythm during exercise. The data were obtained sequentially. The total group of 53 patients was divided into 3 subgroups. The first group consisted of 19 patients after total repair of tetralogy of Fallot (TOF). The mean age at surgery was 2.4 ± 1.8 years. The second group consisted of 17 patients after an arterial switch operation for transposition of the great arteries (TGA). During the neonatal period a Rashkind manoeuvre was performed in all patients. Age at surgery (switch operation) was 0.3 ± 0.3 months. The third group consisted of 17 patients after a Fontan operation for functional univentricular heart. Anthropomethrical data are presented in table 1. The patients with arterial switch operation were significantly younger ($P < 0.01$) than the other patient groups, but comparisons were made with age-matched control subjects. None of the patients was taking medications which could influence heart rate. All patient groups were compared to normal values obtained in a group of 257 healthy children, who were studied at the same laboratory with the same exercise protocol[3].

Exercise testing procedure

A graded submaximal and maximal exercise test was performed on a treadmill. The speed was set at 5.6 km/h and the inclination was increased by 2% every minute until exhaustion -despite moderate encouragement-, severe leg fatigue or symptoms such as dyspnoea or arrhythmias occurred. Heart rate and respiratory gas exchange measurements were recorded during submaximal and maximal exercise. Gas exchange was measured on a breath-by-breath basis by a computerised system using a mass spectrometer (Marquette MGA 1100; Milwaukee, USA). Inspired and expired volume of air was measured with a flow turbine (VMM 110, Alpha Technologies, CA, USA). The concentrations of inspired and expired O_2, CO_2 and N_2 were continuously measured by the mass spectrometer. Gas concentrations were sampled at 50 Hz. The system was calibrated before each exercise test with test gas of known composition. Heart rhythm was continuously monitored during exercise and a twelve-lead electrocardiogram was recorded every minute.

Exercise performance was assessed by determination of the peak oxygen uptake ($\dot{V}O_2$ peak), or symptom-limited oxygen uptake (VO_2 SL). The values for $\dot{V}O_2$ peak were expressed as ml/min/kg or as a percentage of the normal mean value for age and gender.

Since in children and adolescents the heart rate response during graded exercise is to a large extent determined by age and gender, the values in the patients were compared to age- and gender-matched normal values, extracted from a large pool of 257 normal children[3]. Exercise tests were performed at the occasion of a medical examination at school. To account for the effect of age and gender, the values for the heart rate response in the patients were expressed during submaximal exercise as a standard deviation score (Z-score) of the normal mean value for age and gender. This was calculated as: (heart rate patients - heart rate normal)/standard deviation of heart rate in normal subjects. Chronotropic incompetence was defined as the inability to increase heart rate to more than 80% of the age-predicted normal value (220 - age (years) [4]. Furthermore, chronotropic incompetence was also assessed by using a Z-score < 2 SD under the normal mean value for heart rate at maximal exercise of the age-matched control group.

Patients and/or parents gave informed consent after the nature of the testing procedure was fully explained. The study was approved by the local medical ethics committee.

Statistical analysis

Statistical calculations were performed by SPSS software (version 15.0). The data are presented as the mean and standard deviation of the sample. For comparisons between groups a one-way analysis of variance was used and for comparison of the heart rate response during different levels of exercise an analysis of variance (ANOVA) with repeated measurements. The level of statistical significance was set at $P < 0.05$.

Table 2. – *Cardiorespiratory variables at maximal exercise*

	$\dot{V}O_2$ peak (ml/min/kg)	$\dot{V}O_2$ peak (%nl)	HR max (bpm)	HR max (%nl)	R
TOF	35.9 ± 9.0	78.1 ± 14.9	173.4 ± 16.9	83.7 ± 8.3	1.04 ± 0.06
TGA switch	47.1 ± 7.7	101.7 ± 19.4	186.0 ± 7.6	88.1 ± 3.8	1.03 ± 0.06
Fontan operation	34.4 ± 9.5	74.8 ± 18.8	167.4 ± 19.8	80.5 ± 9.6	1.01 ± 0.08

Values represent mean and standard deviation of the sample. $\dot{V}O_2$ peak: peak value for oxygen uptake; HR max: maximal value for heart rate; R = respiratory exchange ratio; TOF, tetralogy of Fallot; TGA, transposition of great arteries; bpm = beats per minute.

Results

Submaximal exercise

The values for heart rate response during exercise were expressed as a standard deviation score of the normal mean value obtained in control subjects of the same age and gender (figure 1). The Z-score varied from -1.7 to -4.6. At all exercise levels, during graded submaximal exercise the heart rate response was significantly reduced in the 3 patient groups (TOF, TGA and Fontan circulation), compared to normal control subjects ($P < 0.001$ for all groups). The lowest values were found in children after total repair of TOF and patients with a Fontan circulation. In both normal children and children with congenital heart disease, the variability of heart rate was highest at the lowest levels of exercise, therefore the lower heart rate in patients with congenital heart disease, expressed as a Z-zcore, showed a decrease with increasing intensity of exercise.

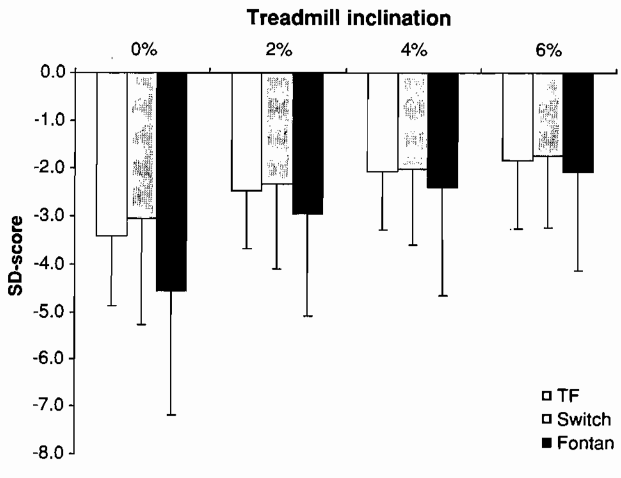

Fig. 1. – Differences in heart rate response between patients and normal control subjects, expressed as standard deviation score (SDS), for different levels of exercise on a treadmill. Data are expressed as mean and standard deviation of the mean.

Maximal exercise

The maximal inclination on the treadmill was 13.6 ± 5.5% for TOF, 15.1 ± 2.9% for TGA and arterial switch, 11.2 ± 4.5% for patients with Fontan operation and 15.2 ± 4.2% for normal control subjects of a comparable age ($P = 0.028$). Patients with a Fontan operation were significantly different from normal control subjects.

At maximal exercise, heart rate was significantly lower in a considerate number of patients with surgical repair of cyanotic congenital heart disease (TOF, Fontan), compared to normal subjects. Chronotropic incompentence was found in 21% of the patients with TOF repair and in 33% of the patients with Fontan operation. All patients with arterial switch operation were able to reach at least 80% of the predicted maximal heart rate value. If we recalculate the data and use a Z-score of -2 SD as cutoff point for chronotropic incompentence, 8/19 (42%) of patients with TOF repair had a Z-score of > -2 SD of the normal mean for age. In the patients with a Fontan operation 10/12 (83%) were below 2 SD below the normal mean value and for arterial switch operation for TGA, 3/17 (17%) of the patients.

The values for respiratory gas exchange ratio (R) exceeded 1.0 and were not significantly different between the different groups, indicating that the patients performed a maximal exercise test. In 7 patients R values below 1.0 at maximal exercise were found, because the exercise test was symptom-limited by dyspnoea in 2 patients and early onset of fatigue in 5 other patients (table 2).

Association of chronotropic incompetence and maximal exercise performance

In 2 groups of patients with surgical repair of cyanotic congenital heart disease a subnormal value for peak oxygen uptake was found (Fontan: 74.8 ± 18.8; % of normal, 95% CL = 64 - 86% and TOF: 78.1 ± 14.9% of normal; 95% CL = 71 - 85%). In the patients with arterial switch the lower value for heart rate was associated with a normal value for peak $\dot{V}O_2$ (101.7 ± 19.4% of normal; 95% CL = 95 - 109).

Discussion

In normal individuals a lower than normal heart rate response during exercise correlates with good or excellent exercise performance, while a high value for heart rate is typical for a deconditioned individual[5].

In the present study, for the 3 groups of patients with surgical repair of cyanotic congenital heart disease (TOF, TGA switch and Fontan circulation), the heart rate response during submaximal exercise was attenuated. This study analyses whether a relationship exists between the heart rate response and aerobic fitness in these patients.

The heart rate response during exercise is determined by several factors such as (i) the condition of the sinus node, (ii) modulation of the autonomic nervous and (iii) the venous return. The sinus node can be dysfunctional due to primary sinus node malformation or, after surgery, because of sinus node damage. The modulation of the heart rate is dependent on an adequate adrenergic response during exercise. In congenital heart disease surgical intervention can lead to partial denervation because of disruption of adrenergic nerve fibres during surgical intervention near the sinus node[6]. During long-term follow-up a considerable number of patients develop atrial arrhythmias and some need a pacemaker[7]. In patients after a Fontan operation with total cavopulmonary connection (TCPC), the cardiac output is decreased compared to normal subjects. The circulatory pattern is changed. In these patients the venous blood is directed from the legs to the lungs without submitting the atrium to a sudden change of venous return. This lower heart rate response and longer diastolic filling time during exercise may be advantageous in patients with Fontan operation. Otherwise the tachycardia would lead to a low stroke volume and decreased coronary perfusion. In 2 patient groups in the present study (TOF and Fontan), the subnormal value for heart rate during submaximal exercise was associated with a suboptimal or impaired aerobic exercise performance capacity. Therefore the heart rate response during graded exercise cannot be considered as a reliable index of cardiovascular fitness, or relative exercise intensity in patients with surgical repair for congenital heart disease. During maximal exercise, the lower than normal value for maximal heart rate indicates a decreased chronotropic reserve capacity, which may be a limiting factor of exercise performance and $\dot{V}O_2$ peak value in these patient groups.

Exercise performance was assessed by determination of peak oxygen uptake, as this reflects the integrative function of the maximal cardiac output and the muscle tissue oxygen extraction (arteriovenous O_2 difference). One of the main determinants of peak $\dot{V}O_2$ is the ability to accelerate heart rate during exercise. In normal well-trained individuals a lower heart rate response is accompanied by a longer diastolic filling time and higher stroke volume. However, in patients with TOF, the lower than normal values for exercise capacity have been shown to correlate with low values for right ventricular ejection fraction and stroke volume (MRI)[8,9] and prolonged values for stroke volume recovery after maximal exercise (MRI)[10]. In patients with Fontan circulation for functional univentricular heart the situation is different. In the majority of the patients cardiac output is not determined by the heart but by the transpulmonary flow controlled by pulmonary vascular resistance[7].

To measure a true maximal oxygen uptake value, a plateau or levelling off should be found for oxygen uptake vs. increasing exercise intensity[11]. A levelling of for $\dot{V}O_2$ has only been found in about 50% of the children, due to the lower anaerobic capacity of children compared to adults. Therefore other auxiliary criteria are used to ascertain whether a true $\dot{V}O_2$ max has been reached, such as a respiratory gas exchange ratio ($\dot{V}CO_2$/ $\dot{V}O_2$), exceeding 1.0, or a heart rate which is close to the predicted value for that age. In the present series R values exceeded 1.0 in all groups of patients. This indicates that the patients performed a true maximal effort. The heart rate cannot be used as a criterion variable in these patients because of the chronotropic impairment.

Peak oxygen uptake was decreased in patients with TOF repair, which can be ascribed to the residual haemodynamic defects, such as pulmonary valve incompetence and residual valve stenosis[9]. Also the efficiency of gas exchange is impaired[12,13]. In patients with tetralogy of Fallot and residual pulmonary artery stenosis successful balloon angioplasty resulted in an improvement of peak $\dot{V}O_2$[14]. On the other hand, in patients with an arterial switch operation for TGA normal or near normal values for aerobic exercise capacity were found, which is in agreement with other studies[15,16]. Although the functional status of patients with a univentricular heart is dramatically improved after a Fontan operation, numerous studies have shown reduced values for maximal or submaximal aerobic exercise capacity in these patients during formal exercise testing[13,17].

Limitations of the study

This study was as single-centre study without selection bias, which represents the clinical condition of the patients randomly assessed on a routine clinical basis. Data were collected in children varying in age from 7 to 16 years (11 years on average). It is not known if the same response is also found in young adults. In earlier studies in adolescents of 15 years of age on average, Perrault et al.[18] could also demonstrate a blunted heart rate response during submaximal and maximal exercise in patients with TOF repair.

The present study reports data in 3 types of cardiac surgery but has also been described in other types of congenital heart disease, such as VSD or ASD[18].

However, it is difficult to present data on all types of congenital heart disease. Therefore we chose to focus on 3 types of severe cyanotic congenital heart disease after surgery. It is not known if we can extrapolate these data to all patient groups. However, it seems prudent in the assessment of patients with congenital heart disease, not to rely on the heart rate response during exercise but to study also respiratory gas exchange.

In conclusion, an impaired chronotropic response during submaximal exercise has been found in a considerable number of patients after surgical repair for cyanotic congenital heart disease (TOF, Fontan). The use of the heart rate response in the estimation of exercise intensity or assessment of exercise performance can be seriously misleading. Gas exchange measurements should be recommended.

Conflict of interest: none declared.

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