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Research Article

Exercise Tolerance in Children with Simple Congenitally Corrected Transposition of the Great Arteries: A Comparative Study

Abstract

Background: The aim of our study was to investigate the exercise capacity of children with congenitally corrected transposition of the great arteries without significant associated heart defects (l-TGA) in comparison with children with the classical type of TGA (d-TGA) and a healthy control group.

Methods: Seven children with isolated l-TGA (11.2 ± 3,2 years), 17 children after a Senning operation (13.4 ± 1,6 years), 26 children with an arterial switch operation (11.0 ± 2,3 years) and 34 healthy controls (12.0 ± 2,9 years) performed a maximal graded cardiopulmonary exercise test on a treadmill, during which oxygen uptake (VO_2) and heart rate (HR) were registered.

Results: Significant differences were present between groups for peak VO_2 ($p<0,001$) and peak HR ($p<0,001$). Compared to the control group, l-TGA patients had a significantly lower peak VO_2 (35.4 ± 10.5 $mL.min^{-1}.kg^{-1}$ vs 45.3 ± 8.65 $mL.min^{-1}.kg^{-1}$) and peak HR (161 ± 47 beats. min^{-1} vs 193 ± 9 beats. min^{-1}). Between the arterial switch group and the control group, no significant differences were found, nor between the l-TGA group and the Senning group.

Conclusions: Children with simple l-TGA and children who underwent a Senning procedure for d-TGA have similar exercise capacity, which is significantly lower when compared to arterial switch patients and healthy controls. The underlying mechanism for the impaired exercise capacity seems to be rather HR-related in children with l-TGA, whereas in children with Senning operation reduced right ventricular function and therefore reduced increase in stroke volume with exercise is more present.

Introduction

Congenitally corrected transposition of the great arteries (l-TGA), also called levi-transposition of the great arteries is a very uncommon type of transposition of the great arteries (TGA) which is characterized by the presence of atrioventricular discordance with ventriculoarterial discordance [1]. It is especially rare when no concomitant heart defects are present (simple l-TGA). In this condition, the blood is normally oxygenated, so no immediately identifiable symptoms are detectable and the anomaly is often not diagnosed or recognised in early life. However, in the patients' third or fourth decade, problems such as arrhythmia's and tricuspid valve regurgitation may arise [1]. In addition, the right ventricle may eventually become hypertrophic and dysfunctional due to increased pressure and further contribute to the development of symptoms such as dyspnoea or fatigue [1]. These symptoms typically arise at first during exercise.

In this light, cardiopulmonary exercise testing might be a sensitive tool to detect the first signs of a reduced cardiac function as objectivised by an impaired exercise capacity.

Only few studies, in adults or a mixed age group, were performed in patients with l-TGA and reported reduced exercise capacities [2-6]. Based on these studies, it seems that the reduction in exercise capacity is present, even when the patients are asymptomatic. The role of right ventricular dysfunction was put forward as an important cause for the reduced exercise tolerance [2-5].

Indeed, in adults with a systemic right ventricle such as patients with Mustard or Senning operation for TGA, reduced

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exercise capacities are present and a relation with right ventricular function exists [7,8]. Winter et al. documented the exercise tolerance of a group of adult patients with a systemic right ventricle and also reported reduced exercise capacities [9]. They however did not investigate patient groups separately even though they admit the fact that patients with l-TGA are different from those with an atrial switch operation. Giardini et al. reported similar exercise capacities in adults with l-TGA when compared to adults who underwent the Senning operation for d-TGA [5].

Patients after an atrial switch operation are known to have diminished exercise capacities already during childhood [10,11], whereas patients after an arterial switch operation [12,13], show mildly diminished to normal exercise capacities. In patients with l-TGA, complications such as right ventricular dysfunction usually only arise during adulthood. Whether the impaired exercise capacity is already present during childhood in this population, is not known. To the best of our knowledge, the exercise capacity in children with l-TGA without other heart defects has never been investigated and compared to children with d-TGA and an atrial or arterial switch operation.

The aim of this study was therefore to investigate the exercise performance and cardiovascular response during graded exercise of children with simple l-TGA in comparison with children operated for d-TGA by the atrial or arterial switch procedures and with a control group of healthy children.

Methodology

Study design and patient selection

This study was a single-centre retrospective investigation of the exercise capacity of children with different types of TGA in comparison with each other and with healthy controls.

All patients with simple l-TGA were selected from a database of exercise tests performed at the department of paediatric cardiology at the University Hospital of Leuven, Belgium. Furthermore, all patients with Senning operation and with arterial switch operation for d-TGA were selected. Only patients who were asymptomatic at the moment of testing were included in this study. The control group consisted of a random sample of healthy children of comparable age who were referred to the paediatric cardiology unit for exercise testing but in whom a diagnosis of a morphologically and functionally normal heart was made. Children mentally or physically unable to perform an exercise test until exhaustion were excluded. Other exclusion criteria were obesity (>95% CI), additional congenital heart defects or other medical conditions such as muscular or endocrine disease, and age below 7 and above 16 years old.

All patients and parents gave informed consent prior to participation. The study was approved by the local medical ethics committee.

Cardiopulmonary exercise testing (CPET)

Prior to exercise testing, height (cm) and weight (kg) were assessed using a wall-mounted stadiometer and a digital scale with children barefoot and wearing light clothes. Both patients and controls performed a graded maximal CPET on a treadmill, of which the speed was set at 5.6 km/h. Inclination of the treadmill was increased by 2% every minute until exhaustion (as defined by shortness of breath and/or fatigue in the legs) or until symptoms arose. The children were verbally encouraged to perform a true maximal effort. Support from the handrails in order to maintain balance was not allowed. During the test, the heart rhythm was continuously monitored by the ECG monitor (Max Personal Exercise Testing, Marquette, WI) and a 12-lead electrocardiogram was recorded at one-minute intervals. Oxygen uptake (VO_2) and carbon dioxide output (VCO_2) were measured on a breath-by-breath basis by a computerized system with fast-responding electronic gas analysers (MedGraphics Ultima CPX, Medical Graphics Corporation, St Paul, MN). Inspiratory and expiratory flow was measured with a Pitot flow meter (VMM-110; Alpha Technologies, Akron, OH). The system was calibrated before each exercise test with a test gas of known composition.

Peak exercise performance was assessed by means of the peak oxygen uptake (peak VO_2), defined as the highest value for VO_2 calculated over a 60 second time window. After the exercise test, the ventilatory anaerobic threshold (VAT) was determined by using the V-slope method and expressed as the VO_2 at that point of graded exercise [14]. Peak oxygen pulse was calculated by dividing peak VO_2 by peak heart rate. Peak exercise values were compared with reference values for healthy children of the same age and gender and expressed as a percentage of predicted [14].

Echocardiography

Routine transthoracic echocardiography was performed in all patients by experienced echocardiographers using standardized views either on an Accuson 128 or Interspec apparatus. Quantitative grading as normal (grade 1), mild (grade 2), moderate (grade 3) and severe dysfunction (grade 4) was performed to asses systemic ventricular function.

Similar quantitative evaluation was used to assess systemic ventricular dilatation as no, mild, moderate or severe dilatation on a scale from 1 to 4. Systemic ventricular hypertrophy was scored as 1 if present and as 0 when no hypertrophy was present.

Statistical analysis

SAS® statistical software, version 9.3 for windows (SAS Institute Inc, Cary, NC, USA), was used for the analyses. QQ-plots and histograms supported the assumption of normally distributed data of all parameters, except for peak heart rate. Data were reported as numbers and percentage, mean and standard deviation or as median and range.

Analysis of covariance and post hoc Scheffé's comparison of means between more than two groups were performed with age as covariate. Kruskal–Wallis analysis of variance and Wilcoxon signed rank tests with correction for multiple testing were used for non-normally distributed data. All statistical tests were 2-sided at a significance level of ≤0.05.

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Results

Patients

The first study group consisted of 7 patients (2 male, 5 female), who were born with a simple l-TGA. The second study group consisted of 17 (14 male, 3 female) patients who were born with d-TGA and underwent an atrial switch operation by the technique of Senning. The third study group consisted of 26 patients (16 male, 10 female) who underwent an arterial switch operation for d-TGA. Thirty four (20 male and 14 female) healthy children of comparable age were included in the control group.

Demographic characteristics of the study groups are reported in table 1. No significant differences were found between sex, weight and height between the four groups. Children with Senning operation were significantly older compared to the three other groups ($p<0.05$).

Exercise measurements

Exercise parameters of the four groups are summarized in table 2. There were significant differences between groups for peak VO_2 ($p<0,0001$) and peak heart rate ($p<0,001$) (Figures 1,2). Peak VO_2 was significantly lower when compared to the control group for children with l-TGA and for children after a Senning procedure. The two former groups showed also a significant difference with the children who underwent an arterial switch operation (see Figure 1). Differences in peak heart rate between groups are shown in figure 2.

Table 1: General characteristics of the included patients.

	l-TGA	Senning	Art. switch	Control	p
Number of patients	7	17	26	34	
Sex					0.18
male	2 (29)	14 (82)	16 (61)	20 (59)	
female	5 (71)	3 (18)	10 (39)	14 (41)	
Age at operation (years)	-	0.44 ± 0.29	0.13 ± 0.21	-	0.0002
Age at exercise test (years)	11.2 ± 3.18	13.4 ± 1.60	11.0 ± 2.31	11,5 ± 2,93	0.028
Height (cm)	141.6 ± 17.12	159 ± 13.7	146 ± 14.1	147 ± 14.6	0.01
Weight (kg)	35.6 ± 13.6	43.5 ± 14.2	36.8 ± 11.8	39.4 ± 12.6	0.34

All variables are expressed as means ± standard deviation or number (percentage).

Heart rate could only be increased to a median value of 182 (average 161, range 92 – 207) beats per minute in the patients with l-TGA, which was significantly lower than normal. This result was driven by clear chronotropic limitation in 2 patients. Those two patients presented respectively with a 2nd and 3rd degree AV block at rest.

No significant differences between groups could be found for peak oxygen pulse and oxygen uptake at VAT.

Systemic ventricular function and morphology

Information regarding function and morphology of the systemic ventricle is provided in table 3. Only one of the l-TGA patients showed normal right ventricular morphology, in all others, right ventricular hypertrophy and moderate (or severe in one patient) right ventricular dilatation was present. Only one patient with l-TGA had mild right ventricular dysfunction. Mild to moderate right ventricular dysfunction, right ventricular hypertrophy and mild to moderate right ventricular dilatation was present in all patients with Senning operation. Patients with arterial switch operation and subjects from the control group all had normal left ventricular contractility and showed normal left ventricular morphology.

Discussion

Our study demonstrates that children with a simple l-TGA have a reduced exercise capacity. Peak VO_2 from this patient group is similar to that from children with a Senning operation and significantly lower when compared to patients who underwent the arterial switch operation and to healthy controls.

A subnormal peak VO_2 in a small group of children with simple l-TGA was revealed, despite the fact that they had no associated heart defects, that all but one child had a normal right ventricular function and that all children were asymptomatic. Moreover we could not document a difference with the exercise capacity in children with Senning operation for d-TGA. These results are in agreement with results from previous studies about this patient group. Previously, these significant lower values were supposed to be due to the presence of systemic right ventricular dysfunction [2,3,15]. Our data can however not support this assumption.

In two of the included patients with simple l-TGA, the heart rate could not be increased appropriately during exercise due to

Table 2: Comparison of exercise tersting variables between study groups.

	l-TGA	Senning	Art. switch	Control	p
Peak VO_2 (mL/min/kg)	35,4 ± 10,5[a,b]	37,0 ± 7,52[a,b]	45,2 ± 5,95	45,1 ± 8,67	0.0004
Peak VO_2 (%)	79 ± 20[a]	73 ± 12[a,b]	95 ± 12	95 ± 15	<0,0001
Peak heart rate (beats/min)	182 (92 - 207)[a,b]	186 (138 - 194)[a]	191 (147 - 202)	196 (170 - 209)	0.001
Peak heart rate (%)	86 (44 - 100)[a,b]	90 (67 - 94)	90 (71 - 97)	93 (82 - 100)	0.006
Peak oxygen pulse (ml/beat)	8,26 ± 3,90	8,78 ± 2,64	8,92 ± 3,83	8,94 ± 2,67	0.96
VO2 at VAT (ml/min/kg)	26,8 ± 7,25	26,4 ± 5,63	30,1 ± 4,41	29,6 ± 4,87	0.14
VO2 at VAT (%)	93 ± 15	85 ± 14	96 ± 12	96 ± 11	0.059

All variables are expressed as means ± standard deviation or median (range), Art.= Arterial, VO2= oxygen uptake. VAT= ventilatory aerobic threshold, a=significantly different from Control group ($p<0.05$), b=significantly different from Arterial switch group ($p<0.05$), c.

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conduction abnormalities. Low exercise capacity in this group is therefore driven by the very small increase in heart rate of these two subjects. Conduction abnormalities are common in l-TGA and the presence of clear chronotropic incompetence in 2 out of 7 patients is therefore not surprising [16]. Underlying reasons for chronotropic incompetence might furthermore consist of dilatation and hypertrophy of the systemic ventricle since in normal hearts [17].

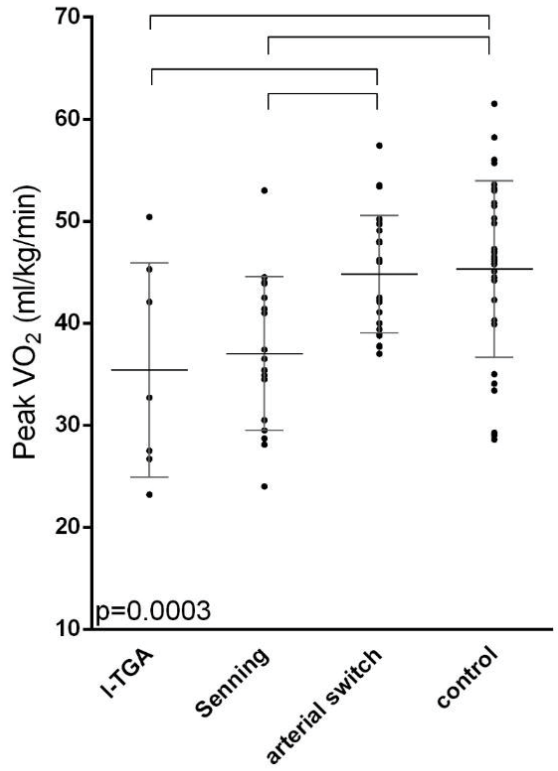

Figure 1:

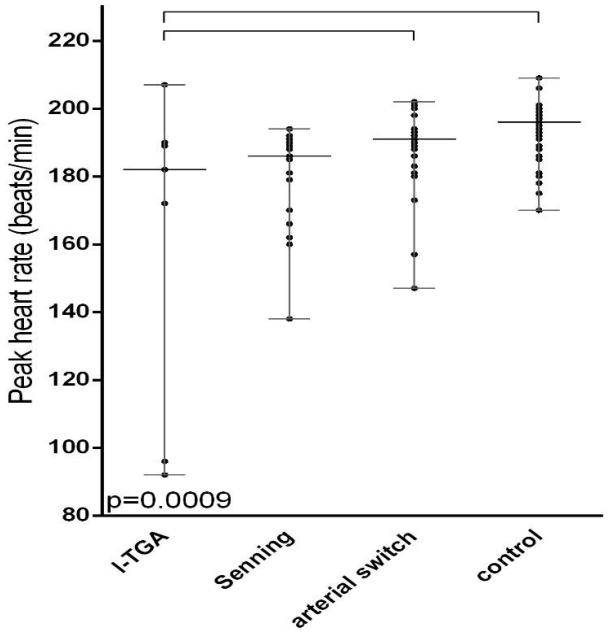

Figure 2:

Table 3: Qualitative echocardiographic assessment of systemic ventricular function.

	l-TGA	Senning	Art. switch	Control	p
SV dysfunction	1 (1 - 2)[c]	2 (1 - 3)[a,b]	1	1	<0,0001
SV dilatation	3 (1 - 4) [a,b]	3 (2 - 3) [a,b]	1	1	<0,0001
SV hypertrophy	1 (0 - 1) [a,b]	1 [a,b]	0	0	<0,0001

SV=systemic ventricle; data are presented as median (range), if no range is mentioned, all patients showed the same result. SV dysfunction: none (grade 1), mild (grade 2), moderate (grade 3), severe (grade 4). SV dilatation: none (grade 1), mild (grade 2), moderate (grade 3), severe (grade 4). SV hypertrophy: no hypertrophy (score 0), hypertrophy (score 1), a=significantly different from Control group ($p<0.05$), b=significantly different from Arterial switch group ($p<0.05$), c=significantly different from Senning group $p<0.05$).

The underlying mechanism for the impaired exercise capacity thus seems to be rather related to chronotropic incompetence in children with l-TGA, whereas children with Senning operation show reduced right ventricular function and consequently reduced increase in stroke volume with exercise while heart rate increase is only mildly subnormal.

The exercise tolerance in the studied group of patients with D-TGA and arterial switch operation was normal and significantly higher than the exercise tolerance of the group with a Senning operation, which was as expected and in line with former studies [12,13]. The non-significant difference between the control group and the children in the arterial switch group is in line with previous reports and can be interpreted as an evidence of the efficiency of the arterial switch procedure [11-13].

Our findings demonstrate that additional attention is necessary regarding follow-up of children with a simple l-TGA especially when it comes to sport participation. Because exercise testing was safe, these children should be encouraged to be fully active during daily life. Exercise or sport activities can be adopted by avoiding isometric or long lasting exercise. The ESC guidelines state that these children may participate in physical activities including low to moderate dynamic or static sports [18]. Nevertheless, physical activity uptake in children with CHD is generally reduced, which has partly been attributed to overprotective parents [19]. Rehabilitation programs might be useful for increasing uptake of physical activity aimed at improving exercise tolerance and motor function in children with CHD, which might at the same time increase the childrens' confidence in their physical capacity and decrease anxiety and concerns of both the patients and their parents.

Limitations

Simple l-TGA is rare and hardly diagnosed before symptoms occur. We could only include 7 children with this condition in our study, due to which statistical power was low. More studies with a larger group of children with simple l-TGA are necessary to allow for generalizations to be made as well as to allow for the investigation of differences between boys and girls.

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Conclusion

Children with simple l-TGA and children who underwent a Senning procedure for d-TGA have similar exercise capacity which is significantly lower when compared to arterial switch patients and healthy controls. The underlying mechanism for the impaired exercise capacity seems to be rather heart rate related in children with l-TGA, whereas in children with Senning operation reduced right ventricular function and consequently reduced increase in stroke volume with exercise seems to mainly determine the subnormal exercise capacity.

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