Exercise capacity of a contemporary cohort of children with hypoplastic left heart syndrome after staged palliation

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Abstract

Objective: Outcome of staged palliation for hypoplastic left heart syndrome has improved over the past decades. However, only little is known about the exercise capacity of children with palliated hypoplastic left heart syndrome where a systemic right ventricle supports the systemic circulation. The aim of the study was to assess exercise capacity in a contemporary cohort of children with hypoplastic left heart syndrome palliated in a single centre according to a uniform surgical strategy. Methods: Standardised cardiopulmonary exercise testing on a treadmill was performed in 46 consecutive hypoplastic left heart patients (median age: 6.0 (4.1–11.4) years). All but one patient reached the anaerobic threshold. Exercise data were compared to normal values obtained with a similar exercise protocol in a large cohort of paediatric volunteers. Results: Oxygen uptake at anaerobic threshold (26.9 ± 6.0 ml kg⁻¹ min⁻¹; 74.5 ± 18.2% of predicted) and maximal oxygen uptake (31.0 ± 6.8 ml kg⁻¹ min⁻¹; 60.8 ± 15.0% of predicted) were significantly reduced compared with controls (P < 0.0001 for both). The limitation in exercise capacity was due to an impaired rise in heart rate (158 ± 23 bpm; 79.7 ± 11.5% of predicted; P < 0.0001) and oxygen pulse (4.5 ± 1.6 ml per beat; 85.5 ± 22.0% of predicted; P < 0.0001). Furthermore, respiration during exercise was inefficient with an elevated respiratory rate and reduced maximal tidal volume and minute ventilation at maximal exercise. Conclusions: The exercise capacity of children with hypoplastic left heart syndrome is markedly reduced. Limitations in heart rate increase and stroke volume augmentation are the major contributors to this. An abnormal ventilatory response to exercise also adds to their limitation in exercise tolerance. However, the degree of physical disability does not justify discouraging these patients from school and leisure sports.

Keywords: Hypoplastic left heart syndrome; Exercise testing; Aerobic capacity; Total cavo-pulmonary connection

1. Introduction

Since the staged surgical palliation of patients with hypoplastic left heart syndrome (HLHS) has become an established therapeutic approach with survival rates that continuously increased over the last decades [1,2], attention has turned towards further improvement of long-term outcome and quality of life. However, only little is known about the degree of any physical disability in palliated paediatric HLHS patients [3,4]. Nevertheless, this information seems essential to individualise the level of surveillance and to guide on recommendations for physical activity in these patients.

The aim of this study was to assess exercise capacity in a contemporary cohort of patients after the staged palliation of HLHS. We paid particular attention to potential clinical, anatomical and physiological factors that might limit exercise performance.

2. Patients and methods

All children enrolled in the study underwent a modified Norwood operation between February 1996 and March 2003 at the Children’s Heart Center of the University Hospital of Schleswig-Holstein, Campus Kiel, Germany. In this period, a Norwood procedure was performed on 107 HLHS patients of whom 73 survived to undergo the subsequent operation, a superior cavo-pulmonary anastomosis (hemi-Fontan technique) [5]. As nine patients died after this second procedure, the Fontan completion consisting of a total cavo-pulmonary connection (TCPC) with a fenestrated lateral tunnel [6] was performed on 64 patients, of whom two died postoperatively.
Therefore, a total of 62 patients from this period were potential candidates for exercise testing. A treadmill cardiopulmonary exercise test was intended in 53 of these patients since they attended our outpatient department for routine clinical follow-up in the period from March 2005 to July 2007. As seven children or their parents refused to undergo exercise testing or were found not to be able to cooperate appropriately, exercise data only on 46 children could be analysed. All patients except one reached the anaerobic threshold (AT), and this patient was excluded from further analysis. Full exercise data of the remaining 45 patients were compared to normal values obtained in a large cohort of paediatric volunteers studied with the similar exercise protocol [7].

All surgeries were performed at the Children’s Heart Center of the University Hospital of Schleswig-Holstein. The diagnosis of HLHS was defined as normal segmental anatomy with mitral valve atresia or stenosis, aortic valve atresia or stenosis or a combination of both, and a left ventricle too small to support the systemic circulation. Informed consent was obtained from all parents.

2.1 Exercise protocol

Exercise testing was conducted on a computer-directed motor-driven treadmill as described by Dubow et al. [7]. All tests were performed between March 2005 and June 2008.

After a 90-s warm-up phase on a flat treadmill with a speed of 2.0 km h$^{-1}$, speed and inclination were increased every 90 s by 0.5 km h$^{-1}$ and 3%, respectively. Maximal incline was 21%. Testing was terminated at volitional exhaustion or for the following circumstances: maximal heart rate of 220 beats per minute minus years of age, lack of ventilatory reserve, respiratory exchange rate higher than 1.15, plateau in oxygen consumption, personal discomfort or significant cardiac arrhythmia.

The AT was calculated by the V-slope method [8]. A lung function test was performed before exercise testing either by body plethysmography ($n=21$) or spirometry ($n=22$). Two children refused to take part in lung function testing. Pulmonary restriction was defined as reduced inspiratory vital capacity (IVC) on spirometry or reduced total lung capacity (TLC) and reduced IVC on body plethysmography. Patients breathed through a mask connected to a flowmeter. Ventilation and gas exchange were measured breath by breath (ZAN 600 Ergo test, ZAN Messgeräte GmbH, Oberthulba, Germany). Heart rate and rhythm were monitored with a 12-lead electrocardiography (ECG).

Heart rate (HR), oxygen pulse ($O_2$ pulse), respiratory rate (RR), tidal volume (TV), minute ventilation (MV), oxygen uptake ($V_O_2$), carbon dioxide production ($V_CO_2$), respiratory exchange ratio (RER) and the ventilatory equivalents for oxygen and carbon dioxide were recorded in real time and displayed on a monitor during exercise testing. Blood pressure (BP) was measured manually on the right arm at least thrice: at rest, at anaerobic threshold and at maximal workload.

2.2 Clinical data

Functional status was graded according to the New York Heart Association (NYHA) score. As part of routine follow-up, all patients received Holter monitoring to detect rhythm abnormalities such as intermittent heart block or sinus node dysfunction. Sinus node dysfunction was defined as sinus bradycardia (children aged 2–6 years: HR <60 per min; children aged 6–12 years: HR <45 per min), severe sinus arrhythmia, junctional escape rhythm >20 min, sinus pause >1.82 s or atrial tachyarrhythmia [9].

To delineate any potential effect of the size of the hypoplastic left ventricle on exercise capacity, the patients were allocated to distinct groups according to left ventricular size. One group consisted of those with marked left ventricular hypoplasia resulting from the combination of mitral and aortic atresia (MA/AA). The other group consisted of patients with all other variants of HLHS with less-severe left ventricular hypoplasia (mitral atresia/aortic stenosis (MA/AS), mitral stenosis/aortic atresia (MS/AA) and mitral stenosis/aortic stenosis (MS/AS)). The size of the left ventricle and the underlying anatomy were defined on the basis of trans-thoracic echocardiography.

Group comparisons were also made between patients older and younger than the median age of 6 years ($n=22$ and $n=23$), respectively, male and female gender, patients with and without any medication and those with and without a closed fenestration in the lateral tunnel.

2.3 Statistical analysis

Data are expressed as mean ± standard deviation (SD) or median and range as appropriate. Comparisons between subgroups were made with unpaired Student’s t-test after testing for normality with the Kolmogorov–Smirnov method (number of tests: 36). Exercise data and the expected normal values were compared using a Student’s t-test for one mean (number of tests: 10). Univariate and multiple linear regression analyses were used to assess associations between exercise variables and clinical and echocardiographic parameters. For statistical analyses, the NYHA functional class was considered a continuous variable. For all analyses, a P-value <0.05 was considered statistically significant. Calculations were performed with MedCalc® for Windows statistical software, version 9.5.2.0 (MedCalc® Software, Mariakerke, Belgium).

3 Results

3.1 Patients

Baseline characteristics including age, sex, anatomy, surgical data, data on heart rhythm and medication are outlined in Table 1.

3.2 Cardiopulmonary exercise testing

3.2.1 Work load assessment

Running time and running distance were significantly reduced compared to reference values ($P < 0.0001$) (Table 2 and Fig. 1)
3.2.2. Cardiac assessment

Maximal HR and maximal systolic BP were significantly reduced in comparison to healthy controls (Fig. 1). Maximal HR and maximal systolic BP were not different between patients younger and older than 6 years (159/16/22 bpm vs 157/16/24 bpm and 138/16/37 mmHg vs 147/16/29 mmHg, respectively; P = NS for both). No differences were also found between the group of patients with severe hypoplasia of the left ventricle and the remainder of patients with less hypoplastic left ventricles (maximal HR: 161/16/22 bpm vs 155/16/24 bpm; maximal systolic BP: 143/16/35 mmHg vs 142/16/30 mmHg; P = NS for both) or between patients with a closed or patent fenestration (maximal HR: 159/16/25 bpm vs 156/16/18 bpm; maximal systolic BP: 143/16/32 mmHg vs 142/16/36 mmHg; P = NS for both).

There was a trend towards reduced systolic BP in patients treated with an angiotensin-converting enzyme (ACE) inhibitor (134/16/35 mmHg vs 154/16/26 mmHg, P = 0.054).

The maximal O₂ pulse was significantly reduced in the entire patient cohort compared with controls (Fig. 1). Maximal O₂ pulse, however, was higher in older patients compared to the younger subgroup (5.2 ± 1.9 ml per beat vs 3.8 ± 0.9 ml per beat, P = 0.003) and in those with a closed
fenestration compared to those with a patent fenestration (4.9 ± 1.7 ml per beat vs 3.7 ± 1.1 ml per beat, P = 0.019). Although, even in those with a closed fenestration, maximal O2 pulse was significantly lower than in healthy subjects (89.2 ± 23.9% of predicted, P = 0.021). No significant difference was also found between the groups of patients with marked hypoplasia of the left ventricle and those with a less hypoplastic left ventricle (4.8 ± 1.8 ml per beat vs 4.3 ± 1.4 ml per beat, P = NS). Maximal HR, maximal systolic BP and maximal O2 pulse were not different between males and females nor were these variables related to NYHA functional class on linear regression analyses (r = −0.17, r = 0.09, r = 0.04, respectively; P = NS for all).

During exercise, most patients showed a typical pattern of HR and O2 pulse with a continuous rise in HR during exercise but an early plateau of O2 pulse. An example is shown in Fig. 2.

3.2.3. Pulmonary assessment

Maximal TV and MV were significantly reduced in the HLHS group whereas maximal RR was significantly elevated (Fig. 1). Maximal TV and MV were significantly higher in children older than 6 years compared to those younger (TV: 0.64 ± 0.2 l vs 0.49 ± 0.1 l, P = 0.0067; MV: 31.3 ± 9.2 l min⁻¹ vs 23.6 ± 5.6 l min⁻¹, P = 0.0013). No difference was found between these groups for maximal RR.

Maximal TV and MV were higher in patients with a closed tunnel fenestration compared to those with a patent fenestration (TV: 0.60 ± 0.19 l vs 0.49 ± 0.13 l, P = 0.038; MV: 29.1 ± 8.8 l min⁻¹ vs 24.4 ± 7.1 l min⁻¹, P = 0.018) and maximal RR was lower (55.3 ± 8.9 l min⁻¹ vs 62.9 ± 9.5 l min⁻¹, P = 0.012).

Maximal TV, MV and RR were not related to the NYHA functional class on linear regression analysis (r = 0.15, r = 0.05, r = 0.04, P = NS for all) nor were they related to O2 saturation at rest (r = 0.12, r = 0.10, r = −0.26, P = NS for all).

Maximal RR was inversely related to O2 saturation at maximal effort (r = −0.40, P = 0.05) whereas maximal TV and MV were not (r = −0.11 and r = 0.06, P = NS for both).

Of the 43 children, 21 (48.9%) showed pulmonal restriction on lung function testing. IVC in the study group was 1.02 ± 0.36 l (70 ± 14.9% of predicted). All pulmonary function parameters were not different between restrictive and non-restrictive patients (maximal RR: 56.9 ± 7.9 l min⁻¹ vs 59.1 ± 11.4 l min⁻¹; maximal TV: 0.57 ± 0.22 l min⁻¹ vs 0.55 ± 0.14 l min⁻¹; maximal MV: 27.3 ± 10.7 l min⁻¹ vs 27.4 ± 6.2 l min⁻¹; P = NS for all).

3.2.4. Metabolic assessment

VO2 AT and maximal VO2 were significantly reduced in our cohort of patients with HLHS compared to healthy controls (Fig. 1). Absolute values of these parameters are shown in Table 2.

Maximal VO2 was significantly higher and VO2 AT tended to be higher in children with a closed fenestration compared to those where the fenestration was still patent (maximal VO2: 32.6 ± 6.6 ml kg⁻¹ min⁻¹ vs 28.1 ± 6.6 ml kg⁻¹ min⁻¹, P = 0.038; VO2 AT: 28.1 ± 5.9 ml kg⁻¹ min⁻¹ vs 24.5 ± 5.9 ml kg⁻¹ min⁻¹, P = 0.061). We found no differences regarding the measures of O2 uptake between subgroups when dividing our patient cohort according to age, sex, use of any cardiac medication, left ventricular size or presence of pulmonary restriction. Furthermore, VO2 AT and maximal VO2 did not correlate significantly with the NYHA function class or oxygen saturation at rest or at maximal effort on linear regression analysis (VO2 AT and maximal VO2 vs NYHA functional class: r = −0.13 and P = NS for both; VO2 AT and maximal VO2 vs oxygen saturation at rest: r = 0.27 and P = 0.078 for both; VO2 AT and maximal VO2 vs oxygen saturation at maximal effort: r = 0.19 and r = 0.19, P = NS for both).

Maximal VO2 correlated significantly with maximal MV (r = 0.60, P < 0.0001) and TV (r = 0.56, P = 0.0001) and was inversely related to maximal RR (r = −0.35, P = 0.017).

Normalised VO2 AT expressed as percentage of predicted was significantly higher than maximal VO2 percentage of predicted (74.5 ± 18.2% vs 60.8 ± 15.1%, P = 0.0002) (Fig. 1). On univariate linear regression analysis O2 pulse correlated significantly with maximal VO2 (r = 0.48, P = 0.0008). On bivariate regression analysis the combination of maximal O2 pulse and maximal HR added accuracy to the prediction of maximal VO2 (multiple correlation coefficient r = 0.62, P < 0.001).

3.3. ECG analysis

During exercise, a total of five children (11.1%) showed pathological ECG changes. These were significant ST segment changes (n = 2), first-degree AV block (n = 2) and intermittent complete AV block (n = 1).

4. Discussion

To our knowledge, this is the largest study on exercise capacity of children early after the three-stage surgical palliation of HLHS. It shows that exercise capacity in these patients is markedly reduced and that this limitation is mainly related to a blunted increase in HR and stroke volume during exercise. An abnormal respiratory response to exercise with an impaired increase in TV and MV and an inappropriate increase in RR adds to this limitation.

In contrast to the earlier studies, which reported on exercise data of smaller groups, we were able to analyse a homogeneous group of HLHS patients who were treated...
according to a uniform strategy in a single centre [3,4]. Furthermore, this study is the first to compare exercise data in young children with HLHS with normal values obtained from a large cohort of healthy children [7].

In our cohort, aerobic capacity was found to be significantly reduced mainly due to a limited increase in HR and $O_2$ pulse, the latter being a surrogate marker of stroke volume [10]. The inability to increase HR appropriately during exercise (i.e., chronotropic incompetence) has previously been described not only for children with palliated HLHS but also for patients with other univentricular hearts after a Fontan-type procedure [3,4,11,12]. Chronotropic incompetence is probably resulting from sinus node dysfunction that has been described to be a non-specific sequelae of any Fontan-type procedure independent of the underlying ventricular anatomy resulting from surgical damage to the sinus node or its arterial supply [3,11,12]. Sinus node dysfunction has been found in one-third of our patients. Drugs with a negative chronotropic effect may further reduce HR in these patients. However, as only five of 45 patients in our cohort received a β-blocker, this effect is certainly not dominant in our study.

The ability to increase $O_2$ pulse was significantly reduced in HLHS patients, a finding that has also been reported for patients with other forms of univentricular hearts after a Fontan operation [13,14]. As expected, maximal $O_2$ pulse was significantly higher in children with a closed fenestration compared with those with a patent fenestration as they had a higher oxygen saturation reflecting less right-to-left shunting during exercise. Nevertheless, the peak $O_2$ pulse was also markedly reduced in this subgroup compared with controls so that a limitation in stroke volume augmentation can be assumed in all palliated HLHS patients. As a subpulmonary ventricle is missing in a Fontan-type circulation, the ability to increase pulmonary blood flow and ventricular filling during exercise is limited — a mechanism that could well explain the inability of these patients to increase $O_2$ pulse or stroke volume during exercise [15,16]. Whether or not the ability to increase stroke volume is different between Fontan patients with a morphological left or right ventricle has not been answered yet. Further comparative studies are warranted to answer that question.

It has been speculated that a large, non-contractile left ventricle impairs right ventricular function in HLHS patients. Often these left ventricles show distinct endocardial fibroelastosis without contraction and hence may become a burden for the systemic right ventricle [17]. In our preliminary experience, an inverse correlation between left ventricular mass and right ventricular systolic function, both assessed with cardiovascular magnetic resonance imaging, was found [18]. However, we could not find any difference between our subgroup of patients with extremely hypoplastic left ventricles and the remainder with regard to their ability to increase $O_2$ pulse.

Maximal TV and MV were significantly diminished in children with HLHS compared with normal values. This may relate to the restrictive pattern of lung function, which was found in almost 50% of our patients. This finding has been reported before for Fontan patients other than HLHS and has been attributed to surgery-related changes in vital capacity [19–21].

Maximal RR was significantly elevated in comparison to controls and correlated significantly with the degree of cyanosis during exercise. This abnormal ventilatory response to exercise has been explained by a ventilation–perfusion mismatch present in Fontan patients or by the persistence of right-to-left shunting when the fenestration is still patent [21,22]. Even though the exact mechanism why Fontan patients and especially cyanotic Fontan patients ventilate excessively during exercise remains uncertain, this phenomenon seems related to their limitation in exercise capacity. Taking the slope of the relationship between minute ventilation and carbon dioxide production during exercise as a measure of the inefficiency of ventilation, a relationship between such an abnormal response to exercise and cyanosis has been described for cyanotic congenital heart disease as well [23].

Although reduced compared to healthy controls, maximal $VO_2$ was higher in our study compared to other studies on Fontan patients with HLHS [3,4] and other types of cardiac morphology [12,24]. However, our study population consisted of patients who were considerably younger than those reported on in other studies [3,24]. This difference might be relevant in this respect as an age-related decrease in $VO_2$ has been reported in paediatric HLHS patients [3].

In our clinical practice, we encourage the parents to allow their children normal daily activities including school and leisure sports, and it could be demonstrated that maximal $VO_2$ significantly improves in children with congenital heart disease after a cardiac rehabilitation programme [25]. Therefore, it could be alternatively speculated that an effect of regular exercise is reflected in the data presented here.

The parameter of submaximal exercise performance, $O_2$ AT percentage of predicted, was significantly higher than maximal $VO_2$ percentage of predicted. The latter is normally used to estimate aerobic capacity in patients. We therefore regard submaximal measures of exercise performance superior when studying young children in whom motivation and compliance might be an issue.

4.1. Study limitations

Although we report on the largest homogeneous group of children after surgical palliation of HLHS, the patient numbers are not big enough to clearly delineate potential differences in exercise capacity in subgroups.

Lung function testing with body plethysmography must be regarded superior to spirometry but was available in only 21 of 45 children. However, the limitations in lung function could consistently be demonstrated in our patient group.

4.2. Conclusion

Exercise capacity of children with HLHS is markedly reduced. Limitations in HR increase and stroke volume augmentation are the major contributors to this. An abnormal ventilatory response to exercise also adds to the limitation in exercise tolerance in this patient group. However, the degree of physical disability does not justify discouraging these patients to participate in school and leisure sports.
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