Long-term cardiopulmonary exercise capacity after modified Fontan operation

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Abstract

Objective: Early circuit separation enhances the long-term success of Fontan haemodynamics. To test this hypothesis, we analysed the postoperative cardiopulmonary capacity in children and adults. Patients: Spiroergometry was performed at least twice in 43 patients with a median age of 14 (range: 7—43) years, with a median time interval of 4.6 (1.1—10.4) years between early and late testing. Twenty-eight patients had been operated on in childhood and 15 as adults. The exercise capacity (median age of 14 (range: 7—43) years, with a median time interval of 4.6 (1.1—10.4) years between early and late testing. Twenty-eight patients went twenty-eight patients between children and adults. Results: The VO max in children early postoperatively was better than in adults (median 27.9 vs 22.9, p = 0.032). Both VO max (median 30.1 ml min \(^{-1}\) kg \(^{-1}\) vs 16.9 ml min \(^{-1}\) kg \(^{-1}\), \(p < 0.001\)), and W max (median 2.2 W kg \(^{-1}\) vs 1.4 W kg \(^{-1}\), \(p < 0.001\)) were significantly better in children late after surgery. In the patient group as a whole, there was a significant decrease of VO max between early and later testing (median 26.5 l min \(^{-1}\) kg \(^{-1}\) vs 20.7 l min \(^{-1}\) kg \(^{-1}\), \(p < 0.001\)). Conclusions: Fontan palliation in early childhood results in better cardiopulmonary capacity during long-term follow-up. Regular surveillance of the physical capacity by spiroergometry is indispensable for the supervision of patients with Fontan haemodynamics.

1. Introduction

The Fontan operation in patients with single ventricle physiology was introduced with the aim of achieving better physical capacity if clinical signs of cardiac failure occur [1]. After a successful Fontan operation performed in strictly selected patients, their physical capacity is most often improved. However, Fontan et al. stated in 1990, 20 years after the introduction of the revolutionary surgical therapy, that the encouraging initial early postoperative results should be critically re-evaluated because of the long-term morbidity [2]. This led to stricter selection criteria and operative techniques that are being further developed to achieve better early and late postoperative results [3,4]. Thus, modern surgical methods such as the creation of a lateral tunnel and more recently the extracardiac Fontan operation are now being used to achieve optimal haemodynamics and flow within the Fontan pathway. Further, one of the most important factors for improving outcome may be the age at operation. It is postulated that early separation of the blood circuit preserves ventricular function due to avoidance of long-term cyanosis and volume overload of the single ventricle. Therefore, the optimal age for Fontan operation is now accepted to be approximately 2—4 years [5,6].

The signs of gradually developing heart failure are often silent and do not correlate with the subjectively good physical condition, partly because these patients are well adapted to their restricted capacity, and little has been published about the long-term results with regard to exercise capacity [7,8]. Specifically, the results of clinical exercise testing of grown-up patients who have undergone the Fontan operation are frequently lacking. Follow-up methods such as magnetic resonance imaging (MRI) measurements are expensive for repeated short-term examinations and tissue Doppler monitoring requires special equipment and qualifications and is still not standardised for this patient population. Even if we have magnetic resonance imaging and tissue Doppler data, there is no data to suggest that these modalities will replace exercise testing for evaluating the patient’s performance. We probably need all of these to provide sufficient information about the patient’s condition.

However, as spiroergometric monitoring is a relatively simple procedure that may be performed at regular intervals...
to objectively measure the patient’s physical condition in general terms; it may be the method of choice for reliable and clinically relevant follow-up of these patients in the long term. Thus, we analysed our data regarding the long-term postoperative cardiopulmonary exercise capacity in children and adults after the Fontan operation.

2. Methods

2.1. Patients

Forty-three patients with a median age of 14 (range: 7–43) years underwent repeated testing (at least twice) of their physical capacity by spiroergometry. The median time interval between early and late testing was 4.6 (1.1–10.4) years. The total postoperative follow-up was 3.1 (0.7–5.2 years) for early and 7.2 (5.9–14.1) years for late testing. Twenty-eight patients had been operated on in childhood and 15 as adults. The number of previous operations was 42 in children and 11 in adults (Table 1). The median age in children at the time of Fontan surgery was 4.9 (range: 1.3–15) years and in adults 22 (range: 16–37) years. Twenty-one patients received an extracardiac conduit and, in 22 patients, an intra-atrial tunnel was created. Thirty-four patients had systemic left ventricle and nine had systemic right ventricle. There were no differences between children and adults regarding gender, left or right systemic ventricle and modification of Fontan operation (Table 1). The majority of patients (n = 32) remained in sinus rhythm peripherically and during follow-up. Five patients had a third-degree atrioventricular block with normal sinus node activity and six had sinus node dysfunction. All 11 were treated by pacemaker implantation. Two patients had ectopic atrial rhythm with normal heart rate (HR) variability since the onset of pacemaker implantation. All patients underwent regular follow-up with echocardiography and timed exercise testing in our outpatient department.

2.2. Cardiopulmonary testing

Exercise testing was performed using the cycle spiroergometer Jaeger Oxycon with non-steady-state step-loading profile using the Johnson protocol: after a 2-min warm-up period at 20 W, the workload was continuously increased in 16-W steps of 1 min each. All patients worked to exhaustion. Continuous 12-channel echocardiogram (ECG) monitoring was performed during exercise and for 2 min in the recovery period. For children, the minimal height for inclusion in the study was 125 cm. The physical exercise capacity, measured by watt per kg of body weight (Wmax), and cardiopulmonary capacity, measured by maximal oxygen uptake in millilitre per kg of body weight per minute (VO2max), were quantitatively determined and calculated as percentages of the normal values for a healthy aged-matched population (coeval) with respect to gender. The first test that was available for the follow-up was performed in the period 1–5 years (median 3 years) postoperatively at a median age of 11 years (range: 4–38 years). The second test was performed in the time period of 6–14 years (median 7 years) postoperatively at a median age of 13.5 (range: 7–44) years. The median time period between the first and the second exercise test was 3.9 (range: 2.1–11) years. In patients who underwent more than one exercise test early or late postoperatively during a short time period, the maximal exercise capacity was included in the study.

To investigate the differences in cardiopulmonary capacity between small children (<13 years old), adolescents (13–18 years) and adults early and later postoperatively, the early and late postoperative data of these three groups were compared.

3. Statistical analysis

Variables are given as medians and ranges. The comparison between the early and later postoperative cardiopulmonary testing in the total group was performed using the non-parametric Wilcoxon signed-rank test. For the comparison of the categorical data Fisher’s exact test was used. For the group variation analysis between children and adults, the Mann–Whitney test was used. Linear regression was used for the analysis of the cardiopulmonary capacity and HR dependency. The analysis was processed using SPSS for Windows, version 12.0 (SPSS Inc., Chicago, IL, USA). A p value ≤0.05 was considered significant.

4. Results

4.1. Cardiopulmonary capacity (VO2max) early and late postoperatively

The mean VO2max early postoperatively was slightly better in children (median 27.9 (14.3–44.4) ml min−1 kg−1 = 62% (31–98%) of norm) in comparison to adults (median 22.9 (13.9–37.4) = 53.5% (24–81%), p = 0.032) and significantly better late postoperatively (median 30.1 (14.8–39.2) ml min−1 kg−1 = 64.9% (32–87%) vs median 16.9 (10.7–27.9) ml min−1 kg−1 = 39% (29–62%), p < 0.001), p = 0.012; Fig. 1A and B). All patients, both children and adults, showed a significant reduction of VO2max between the early and late postoperative testing (26.5 (13.9–44) vs 20.7 (10.3–39), p < 0.001; Fig. 2).

The comparison of cardiopulmonary capacity in small children (<13 years), adolescents (13–18 years) and adults early and later postoperatively showed that the adults suffered a significant loss in capacity, whereas adolescents lost slightly and small children maintained stable or slightly improved median level with reduction of the maximal capacity (Fig. 3).

<table>
<thead>
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<th>Table 1 Preoperative and intra-operative data in children and adults.</th>
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<td><strong>Data</strong></td>
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<td>Gender (m/w, n)</td>
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<tr>
<td>LV/RV systemic morphology (n)</td>
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<td>Previous BCPS (n)</td>
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<td>Aorto-pulmonary shunt</td>
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<td>Lateral tunnel/extracardiac Fontan (n)</td>
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BCPS: bidirectional cavopulmonary shunt; LV: left ventricle; and RV: right ventricle.
4.2. Exercise capacity (W\textsubscript{max}) early and late postoperatively

The exercise capacity also showed a tendency to be better in children early postoperatively (median 2.2 (0.8–3.4) W kg\textsuperscript{-1} vs 1.8 (0.4–3.4) W kg\textsuperscript{-1}, p = n.s.). In the total patient group, we observed a trend towards a decrease in the exercise capacity of 2.1 (0.8–3.5) versus 1.8 (0.4–3.4) W kg\textsuperscript{-1}, p = n.s.

4.3. Peak HR early and late postoperatively

Median HR at peak (HR\textsubscript{max}) was 136 (101–153) min\textsuperscript{-1} in children and 112 (84–151) min\textsuperscript{-1} in adults and showed mostly HR increase during exercise early postoperatively. Further, at later testing we observed an increase of the HR\textsubscript{max} in the majority of patients (median 151 (87–200) min\textsuperscript{-1} in children and 119 (84–184) min\textsuperscript{-1} in adults). There were no differences in the HR\textsubscript{max} between early and late postoperative measurement at peak of exercise (p = n.s.) in the whole group.

Compared with the norm of HR\textsubscript{max} for healthy population, patients showed inadequate HR\textsubscript{max} (in median <5% of the norm according to age and gender), both children and adults, and both early and late postoperatively [9,10]. The complete data of the HR at exercise are given in Table 2. We observed a statistical correlation between the HR\textsubscript{max} and VO\textsubscript{2max} at the early testing (p = 0.049). At the late postoperative testing, this correlation became much more significant (p < 0.001, R = 0.71; Fig. 5).

The HR\textsubscript{max} in patients with pacemaker was significantly lower, as it was in patients with intact sinus node, both early postoperatively (median 133 beats min\textsuperscript{-1} vs 150 beats min\textsuperscript{-1}, p = 0.012) and late postoperatively (median 95 beats min\textsuperscript{-1} vs 146 beats min\textsuperscript{-1}, p < 0.001).

The cardiopulmonary capacity in patients treated by pacemaker implantation was lower, as those with intact sinus node, but the difference did not reach statistical significance early (VO\textsubscript{2max} in median 31.6 ml min\textsuperscript{-1} kg\textsuperscript{-1} vs 29.7 ml min\textsuperscript{-1} kg\textsuperscript{-1}, p = 0.7, n.s.) or late postoperatively (VO\textsubscript{2max} 22.0 ml min\textsuperscript{-1} kg\textsuperscript{-1} vs 17.7 ml min\textsuperscript{-1} kg\textsuperscript{-1}, p = 0.4, n.s.).

One patient with complete AV block (treated by permanent pacemaker) and sick sinus syndrome showed significantly decreased cardiopulmonary exercise capacity during late postoperative testing 11 years after Fontan operation at the age of 17, with significantly altered chronotropic competence between 80 and 88 beats min\textsuperscript{-1}. After maximal sensor activation in dual chamber rate adaptive pacemaker (DDDR) mode, the HR\textsubscript{max} increased to 103 min\textsuperscript{-1} and the VO\textsubscript{2max} increased from 17 ml min\textsuperscript{-1} kg\textsuperscript{-1}. 

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Fig. 1. Cardiopulmonary capacity (VO\textsubscript{2max}) early and late postoperatively in children and adults. The box-plot diagram shows the early (A) and late (B) postoperative cardiopulmonary capacity (VO\textsubscript{2max}) in the comparison between children and adults. The differences are clear, especially late postoperatively, where they are statistically highly significant.

Fig. 2. Cardiopulmonary capacity early and late postoperatively in the total group. The box-plot diagram shows significant decrease in cardiopulmonary capacity (VO\textsubscript{2max}) in the total group between early and late postoperative measurements.

Fig. 3. The box-plot diagram shows the early (A) and late (B) postoperative cardiopulmonary capacity (VO\textsubscript{2max}) in the comparison between children, adolescents and adults.

Fig. 4. Cardiopulmonary capacity early and late postoperatively in children and adults. The box-plot diagram shows the early (A) and late (B) postoperative cardiopulmonary capacity (VO\textsubscript{2max}) in the comparison between children and adults. The differences are clear, especially late postoperatively, where they are statistically highly significant.
(39% of norm) to 19.7 ml min⁻¹ kg⁻¹ (43% of norm), but remained significantly lower, as early postoperatively at the age of 11 years (25.3 ml min⁻¹ kg⁻¹, 56% of norm).

5. Discussion

Our findings showed that oxygen consumption and exercise capacity progressively decreased in all patients who had undergone Fontan operation, both as children and as adults, whether operated upon early or late. This underlines the palliative character of the surgical treatment and that neither normal exercise capacity nor stable cardiac situation during long-term follow-up can be achieved. The Fontan haemodynamics tends unavoidably towards failure in the long term.

Nevertheless, patients operated on in early childhood showed clearly better long-term exercise capacity. The reason for this is the early circuit separation with removal of cyanosis and volume unloading of the single ventricle, which may preserve better physical capacity, although the Fontan operation remains only a palliative procedure.

The attempt to provide a better quality of life and life expectancy in patients with single ventricle by definitive circuit separation is nowadays performed at an early age using gentle surgical techniques and in accordance with strict selection criteria [8,11]. Despite this strategy, the morbidity in this patient population is significantly higher and the life expectancy of 30—40 years is clearly shorter compared with the normal, healthy population. The cause of mortality is mostly progressive heart failure [12—14].

Iserin et al. wrote in 1997 that, despite correction with Fontan-type surgery, the exercise tolerance and symptoms of univentricular patients remained similar to those of patients who were cyanotic [15]. Contrariwise, Driscoll et al. comparing the results of graded exercise found that values for total work performed, duration of exercise and maximal oxygen uptake increased significantly, and exercise tolerance and the cardiorespiratory responses to exercise improved after the Fontan operation [7].

The restrictive character of diastolic dysfunction, however, may be irreversible despite volume unloading of the stiff and hypertrophied myocardium, aggravated by use of

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the cardiopulmonary bypass, especially in patients operated on as older children and as adults [16]. This correlates with the clinical findings of the different work groups that noted significantly reduced cardiovascular capacity, tested by spiroergometry, late after Fontan operation in comparison to age-matched control patients, especially in older patients [17].

Mahle et al. published findings in 1999 that children who underwent volume unloading before 2 years of age showed significantly better aerobic capacity than older children do (2–10 years). In our series, we did not conclude that a strict age limitation of less than 2 years for the Fontan operation is necessary to achieve better postoperative physical capacity but we entirely agree that early circuit separation preserves the functional status of the patients for longer. Our results in no way confirmed those of Nir et al., who described unchanged exercise tolerance for more than 13 years after Fontan operation [18]. Gentles et al. analysed a large series of 500 patients after Fontan operation and noted that poor functional state (class III or IV) was associated with longer duration of follow-up [4].

Spiroergometric testing of the cardiopulmonary capacity with ascertainment of the maximal oxygen uptake helps to objectify the exercise limitations, as a first sign of suboptimal Fontan, before clinical failure occurs. In contrast to the results of Mahle et al. we noted that cardiopulmonary capacity decreases in all age groups as time progresses. Some of our patients, operated upon in childhood, had reached adolescence by the time of later testing. It is notable (Fig. 4) that the cardiopulmonary capacity decreased during the follow-up. However, if we compare the cardiopulmonary capacity between small children (<13 years), adolescents (13–18) and adults early and later postoperatively, we see that the adults lost capacity significantly, whereas adolescents lost slightly and small children maintained a stable or slightly improved median level with reduction of the maximal capacity. According to these findings, we would speculate that the curve of the postoperative capacity does not decline monotonically but shows a slight improvement in small children early postoperatively and shows only a slight decline in adolescents. Therefore, the timing of surgery is important, to give small children the possibility of this capacity improvement. More previous operations, especially previous bidirectional cavopulmonary shunts, were performed in children. Correctly and timely planned circuit separation may play a role in the optimal postoperative course. Nowadays, no patients may be accepted for the circuit separation reach adolescence without Fontan surgery, so that it is not possible to compare coevals operated upon and not operated upon. Furthermore, we observed that the cardiopulmonary capacity in young children remains stable at least during childhood. Nevertheless, the improved physical capacity in children during mid-term follow-up will probably not remain on this level when they reach adulthood. Providing better quality of life realises the main goal of the circuit separation, although the Fontan surgery remains palliative.

Different problems should be discussed with regard to the decreased oxygen consumption capacity. Ventilation–perfusion mismatch in the lung, residual right-to-left shunting (fenestration, veno-venous collaterals and leak), restrictive thoracic excursions because of the small vital capacity after repeated surgery or cardiomegaly with restriction of the lung volume and so on, cause progressive hypoxia during exercise. This leads to accelerated ventilation and therefore to secondary hypcapnia and may be responsible for insufficient ventilation during exercise, low oxygen saturation and therefore limited cardiopulmonary exercise capacity [19].

The other important factor that may limit exercise capacity is deterioration of the normal heart rhythm. Adult patients with single ventricle frequently suffer from supraventricular tachyarrhythmia, especially after intra-atrial or periatrial surgery because of sinus node damage and chronotropic incompetence, resulting in an inadequate HR increase and aggravating the limited exercise capacity [11,20,21].

The HR data at peak of exercise in Fontan patients in our series, in both children and adults, were clearly lower than in healthy coevals [9,10]. This might restrict the cardiopulmonary capacity in comparison to that of the normal population. We found a high statistical correlation between the VO2max and the HR at peak of exercise by the second (p = 0.001, R = 0.71) testing. As discussed previously by Ohuchi et al., the Fontan circulation per se, aside from possible surgical damage, leads to impaired cardiac autonomic nervous activity, which may reduce the physical capacity of the patients [19].

During our current follow-up of maximally 14 years, we have observed no statistically significant differences in HR at peak in the entire patient population while younger patients show a trend to better chronotropic competence by the later testing. This might be an additional factor for decrease of the cardiopulmonary capacity during the follow-up. We did not observe a correlation in the limitation of cardiopulmonary exercise tolerance in patients with stable sinus rhythm (n = 33) and those without (n = 11). One patient with sick sinus syndrome showed a significant decrease in exercise capacity because of inadequate chronotropic competence, but the capacity improved after his pacemaker function was optimised. Therefore, assuming correct pacemaker treatment, the HR per se was not the limiting factor for cardiopulmonary capacity in our study during the follow-up. Long-term study of the total patient group may reveal the pathological mechanisms of the impairment of the HR. We would speculate that early treatment by pacemaker implantation in patients with sinus node dysfunction and junction rhythm is necessary after Fontan operation to enable normal chronotropic competence and, therefore, satisfactory exercise capacity. Mavroudis et al. describe aggressive Fontan conversion accompanied by additional arrhythmia surgery with significant improvement of the NYHA class from III–IV to II [20]. This could be an option in some selected patients; nevertheless, identification of the patient who needs any kind of therapy, either non-invasive or invasive, before critical heart failure occurs is paramount.

We assume that accurate monitoring and close surveillance of the cardiopulmonary capacity in patients with subjective apparently ‘normal’ conditions can help the timely begin of prophylactic medical treatment and timely acceptance for heart transplantation, which is important for better outcome of transplantation in failing Fontan patients [22]. During postoperative monitoring in our outpatient clinic, we frequently observed discrepancies between the subjective clinical assessment of the Fontan patients...
regarding their cardiovascular limitations and objectively acquired data. Using ergospirometry, we were able to create the individual cardiopulmonary capacity curve for each patient as an objective follow-up parameter.

5.1. Limitations of the study

The main limitations of the current study are the retrospective design and therefore the lack of standardised testing intervals.

5.2. Limitation of the oxygen uptake

Pulmonary testing was not performed routinely. Therefore, we were unable to show the impact of lung function on the exercise and oxygen consumption capacity in the total patient group. Although the ventilatory measurements were not performed immediately before the exercise testing, clinical examination did not reveal any abnormalities such as bronchial obstruction or severe thoracic skeletal deformations except in one adult patient with significant scoliosis.

5.3. Limitations of the exercise capacity testing

Inadequate psychological motivation for reaching the maximal capacity and deficient physical training additionally affects the results of the different age groups.

6. Conclusions

Patients operated upon in early childhood show better cardiopulmonary capacity during long-term follow-up. Regular surveillance of the physical capacity by spirometry is indispensable for the supervision and medical support of Fontan haemodynamics and accurate timing of treatment decisions such as change of medication, re-operation or thoracic organ transplantation.

Further randomised prospective studies are required to investigate the long-term benefits of Fontan-type procedures in these patients in terms of exercise tolerance, symptoms and prognosis.

In summary, we would emphasise that not only the comparison of the impaired physical capacity in patients after Fontan operation to that of the healthy population, but also serial longitudinal and objectively quantified testing is necessary in these patients to optimise the follow-up.

Acknowledgement

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References