Cardiology in the Young

cambridge.org/cty

Appropriate heart rate during exercise in Fontan patients

Eva R. Hedlund, Liselott Söderström and Bo Lundell

Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden

Original Article

Cite this article: Hedlund ER, Söderström L, and Lundell B (2020) Appropriate heart rate during exercise in Fontan patients. *Cardiology in the Young* **30**: 674–680. doi: 10.1017/S1047951120000761

Received: 16 December 2019
Revised: 26 February 2020
Accepted: 13 March 2020
First published online: 17 April 2020

Keywords:
Heart rate; exercise; oxygen consumption; oxygen pulse; Fontan patients

Author for correspondence:
E. R. Hedlund, MD, PhD, Karolinska University Hospital, Astrid Lindgren Children's Hospital Solna, Barnhjärtcentrum, Eugeniavägen 23, C8:34, S-171 76 Stockholm, Sweden.
Tel: +46-707421285; Fax: +46-8-51777778;
E-mail: eva.rylander-hedlund@sll.se

Abstract

Objective: To evaluate heart rate against workload and oxygen consumption during exercise in Fontan patients. *Method:* Fontan patients (n = 27) and healthy controls (n = 25) underwent cardiopulmonary exercise testing with linear increase of load. Heart rate and oxygen uptake were measured during tests. Heart rate recovery was recorded for 10 minutes. *Results:* Heart rate at midpoint (140 ± 14 versus 153 ± 11, $p < 0.001$) and at maximal effort (171 ± 14 versus 191 ± 10 beats per minute, $p < 0.001$) of test was lower for patients than controls. Heart rate recovery was similar between groups. Heart rate in relation to workload was higher for patients than controls both at midpoint and maximal effort. Heart rate in relation to oxygen uptake was similar between groups throughout test. Oxygen pulse, an indirect surrogate measure of stroke volume, was reduced at maximal effort in patients compared to controls (6.6 ± 1.1 versus 7.5 ± 1.4 ml·beat^{-1}·m^{-2}, $p < 0.05$) and increased significantly less from midpoint to maximal effort for patients than controls ($p < 0.05$). *Conclusions:* Heart rate is increased in relation to workload in Fontan patients compared with controls. At higher loads, Fontan patients seem to have reduced heart rate and smaller increase in oxygen pulse, which may be explained by inability to further increase stroke volume and cardiac output. Reduced ability to increase or maintain stroke volume at higher heart rates may be an important limiting factor for maximal cardiac output, oxygen uptake, and physical performance.

Stepwise surgery to a Fontan circulation[1,2] in infants and children with univentricular heart defects has improved survival since the early 1970s. Today at least 80–90% of infants with these severe heart malformations are expected to reach adult life.[3,4] Children and adolescents with Fontan circulation have been extensively studied regarding physical capacity and measures of quality of life. Many studies have shown a reduced maximal physical capacity[5–7] and reduced quality of life[8–11] in Fontan patients compared to healthy patients. Physical capacity is an important factor for perceived health-related quality of life in these patients.[12] In healthy patients, cardiac output increases 4–6 times during a maximal effort exercise test. During low-intensity exercise, both stroke volume and heart rate contribute to increased cardiac output, whereas at higher intensity and loads, heart rate becomes the main determinant of further elevation of cardiac output. Near maximal effort also increased oxygen extraction in muscles contributes to maximal physical performance.[13,14] Almost all studies of physical capacity and performance in young Fontan patients have shown a reduced maximal heart rate, and many have suggested this to be a limiting factor for physical performance and tolerance.[15–17] Repeated heart surgery early in life has been suggested to injure the heart's autonomous nervous system and impair sinoatrial response to exercise.[18] A recent report with measurements of stroke volume during exercise in a small number of adult Fontan patients suggests that the main limiting factor for cardiac output and maximal exercise capacity is impaired diastolic filling and stroke volume by the ventricle rather than heart rate.[19] Gewillig and others have in several publications[15,20–23] suggested that a limited increase in heart rate during exercise in Fontan patients may be an autonomous protective measure against a fall in cardiac output rather than a limiting factor of cardiac output per se.

We have previously published studies of quality of life,[24] physical capacity and effects of endurance training,[25] and lung function[26] in a cohort of young Fontan patients compared with a matched group of healthy children and adolescents. For detailed information about our Fontan cohort, control group, and methods used, we refer to those publications. The present study was made to evaluate the relationship between heart rate and level of physical effort (workload) and oxygen uptake during exercise. The hypothesis being that heart rate response to exercise in Fontan patients may be adequate in relation to the level of work exercised.

Material

Children with Fontan circulation born between 1990 and 2005 in the Stockholm region, N = 53, were considered for participation. Exclusion of 16 patients was made after hospital chart review. Exclusion criteria were neurodevelopmental disorder (n = 5), heart transplant (n = 2), acute myocarditis (n = 1), under investigation for further surgery (n = 1), muscle weakness

© The Author(s), 2020. Published by Cambridge University Press.

CAMBRIDGE UNIVERSITY PRESS

Table 1. Characteristics

	Patients	Controls	p
Number (N)	27	25	
Female/male (N)	13/14	12/13	0.84
Age (years)	14.4 ± 3.1	13.6 ± 3.5	0.34
Height (m)	1.54 ± 0.14	1.58 ± 0.16	0.40
Weight (kg)	44.3 ± 11.9	49.1 ± 16.0	0.22
Body mass index (kg/m^2)	18.3 ± 2.2	19.2 ± 3.3	0.22

Values are presented as mean ± 1SD.

Table 2. Results from cardiopulmonary exercise testing

	Patients	Controls	p
Test duration (minutes)	7.2 ± 1.9	8.2 ± 1.8	<0.05
Start			
Workload (watt)	30.0 ± 8.8	37.2 ± 9.4	<0.01
Workload/kg (watt/kg)	0.68 ± 0.11	0.79 ± 0.15	<0.01
Oxygen uptake (l/min)	0.31 ± 0.12	0.31 ± 0.13	0.97
Oxygen uptake/kg (ml/min/kg)	7.1 ± 4.0	6.4 ± 3.3	0.52
At midpoint of test – mid			
Workload (watt)	66.4 ± 21.1	92.2 ± 33.4	<0.01
Workload/kg (watt/kg)	1.49 ± 0.21	1.90 ± 0.39	<0.001
Oxygen uptake (l/min)	1.11 ± 0.27	1.40 ± 0.39	<0.01
Oxygen uptake/kg (ml/min/kg)	24.7 ± 3.9	28.8 ± 5.1	<0.01
At maximal effort			
Workload (watt)	102.6 ± 34.7	146.3 ± 58.5	<0.01
Workload/kg (watt/kg)	2.31 ± 0.41	2.99 ± 0.67	<0.001
Oxygen uptake (l/min)	1.57 ± 0.45	2.11 ± 0.70	<0.01
Oxygen uptake/kg (ml/min/kg)	35.2 ± 5.1	43.7 ± 8.4	<0.001
Respiratory exchange ratio	1.06 ± 0.08	1.11 ± 0.08	<0.05

Values are presented as mean ± SD.

(n = 1), moved to other geographical region (n = 2), short stature below 125 cm (n = 1), and pacemaker treatment due to sinus node dysfunction (n = 3). Ten patients declined participation for non-medical reasons. Each patient and their parents were asked to suggest a healthy peer of the same age and gender to serve as a healthy control. Nine patients could not suggest a healthy peer, so eight healthy unrelated matched control patients were also recruited from families and friends of hospital staff.[24,25] A matched control group for comparisons was considered important, in order to avoid comparisons with old reference material, since studies have shown a decline in physical activity and exercise performance in the general population over time.[27,28]

Thus, the study groups comprised 27 patients with Fontan circulation and 25 healthy control patients. Gender, age, height, weight, or body mass index did not differ between patients and controls (see Table 1). Fontan circulation was completed at median age 2.4 (1.1–6.4) years. Eighteen patients had an intra-atrial tunnel and nine patients had an extracardiac conduit. No fenestrations were present. All patients were on anticoagulation treatment with either aspirin or warfarin. Enalapril or captopril was prescribed for 19 patients. No patient was treated with betablockers.

Methods

Cardiopulmonary exercise testing

All patients performed symptom-limited exercise tests using a stationary, calibrated upright cycle ergometer (Monark Ergomedic 839E; Monark Exercise AB, Vansbro, Sweden) with a continuous increase in load, connected to a testing system (GE CASE Exercise testing system; Davis Medical Electronics Inc., Vista, California, United States of America). Start and increment of load during the test were chosen individually based on previous exercise tests and self-reported physical capacity and activity, in order for each individual to reach maximal exhaustion within approximately 10 minutes. Echocardiography was made on all individuals prior to the test in order to detect signs of thrombosis or significant valvular incompetence. The children were instructed to maintain a constant pedalling rate of 60 rpm and were actively encouraged throughout the test to continue to maximal exhaustion. Standard 12-lead electrocardiogram, blood pressure, and pulse oximetry were monitored before, during, and for 10 minutes after the test. Blood pressure was measured with cuff and radial artery Doppler signals during the test.

Breath-by-breath analyses of metabolic variables (V-max Encore; Viasys HealthCare Inc., Yorba Linda, California, United States of America), including oxygen uptake and respiratory parameters, were performed continuously throughout the test using a mouthpiece and a nose clip. The mass flow metre was calibrated with a fixed volume and the gas analyser with two reference gases prior to every test. Data were recorded as epochs by averaging every 20 seconds throughout each test and corrected for each individual's weight in kilogram.

Heart rate was continuously recorded during exercise and for 10 minutes recovery time after maximal effort. Heart rate, load, and oxygen uptake were analysed at start (rest), at midpoint of exercise test as a measure of submaximal effort (mid) and at maximal effort (max). Also, heart rate in relation to load and oxygen uptake, respectively, was analysed. Heart rate reserve was analysed as the difference between maximal and resting heart rate. Chronotropic index was calculated as (peak heart rate – resting heart rate)/(220 – age – resting heart rate).[29,30] Heart rate was also recorded during recovery at 2, 4, and 10 minutes after maximal effort. Oxygen pulse was calculated by dividing oxygen uptake by heart rate and has been shown to be a surrogate estimate of stroke volume during maximal exercise in healthy adolescents.[31]

Statistical analyses

The statistical analyses between the groups were performed using t-tests and chi-square tests as appropriate. Statistical significance was set at $p < 0.05$. The statistical programme used was Statistica 12 (StatSoft Inc, Tulsa, OK, United States of America).

Results

All patients and controls had sinus rhythm during the cardiopulmonary exercise tests and tolerated maximal exercise tests well, without any significant arrhythmias. Test duration to maximal exhaustion was shorter for patients than controls (7.2 ± 1.9 minutes versus 8.2 ± 1.8 minutes, $p < 0.05$). Oxygen saturation at rest was lower for patients than controls (94 ± 3% versus 98 ± 1%, $p < 0.001$). Oxygen saturation at maximal effort was also lower for patients than controls (91 ± 4% versus 98 ± 1%, $p < 0.001$). Respiratory exchange ratio at maximal effort was lower for patients than controls (see Table 2).

https://doi.org/10.1017/S1047951120000761 Published online by Cambridge University Press

Table 3. Heart rate reactions during cardiopulmonary exercise testing

	Patients	Controls	p
HR rest (bpm)	82.1 ± 16.1	81.5 ± 12.1	0.88
HR mid of exercise testing (bpm)	140.4 ± 13.9	153.2 ± 11.0	<0.001
HR max (bpm)	171.4 ± 14.2	191.2 ± 10.1	<0.001
HR reserve (HR max − HR rest) (bpm)	89.3 ± 22.7	109.7 ± 12.3	<0.001
HR recovery after 2 min			
Absolute (bpm)	107.8 ± 18.1	112.2 ± 16.4	p = 0.34
Relative (percentage of max)	63.2 ± 11.7	58.7 ± 7.9	p = 0.11
HR recovery after 4 min			
Absolute (bpm)	93.4 ± 13.1	103.7 ± 13.3	p < 0.01
Relative (percentage of max)	54.7 ± 8.7	54.2 ± 6.3	p = 0.82
HR recovery after 10 min			
Absolute (bpm)	89.7 ± 12.8	99.2 ± 13.0	p < 0.05
Relative (percentage of max)	52.5 ± 7.7	51.8 ± 5.5	p = 0.71
HR/W/kg mid of test (bpm)	95.9 ± 16.8	84.0 ± 17.9	p < 0.05
HR/W/kg max (bpm)	76.3 ± 13.6	67.1 ± 14.3	p < 0.05
HR/VO_2/kg rest (bpm)	13.8 ± 6.7	15.1 ± 7.1	p = 0.54
HR/VO_2/kg mid of test (bpm)	5.7 ± 1.0	5.5 ± 1.1	p = 0.45
HR/VO_2/kg max (bpm)	4.9 ± 0.7	4.5 ± 0.9	p = 0.07
ΔHR/(ΔVO_2/kg) rest-max (bpm)	3.3 ± 1.0	3.2 ± 0.8	p = 0.60

bpm = beats per minute; HR = heart rate; W = Watt.

Load at start was set lower for patients than controls (0.68 ± 0.11 watts·kg^{-1} versus 0.79 ± 0.15 watts·kg^{-1}, p < 0.01). Increase of load during the tests was similar between patients and controls (0.24 ± 0.07 watts·min^{-1}·kg^{-1} versus 0.27 ± 0.06 watts·min^{-1}·kg^{-1}, p = 0.06). Load at midpoint of exercise test (mid) and at maximal effort was lower for patients than controls (Table 2).

Oxygen uptake corrected for body weight was similar between patients and controls at start of exercise tests (7.1 ± 4.0 ml·min^{-1}·kg^{-1} versus 6.4 ± 3.3 ml·min^{-1}·kg^{-1}, p = 0.52). At midpoint (mid) of exercise test, oxygen uptake was lower for patients than controls (24.7 ± 3.9 ml·min^{-1}·kg^{-1} versus 28.8 ± 5.1 ml·min^{-1}·kg^{-1}, p <0.01). At maximal effort corrected, oxygen uptake was also lower for patients than controls (35.2 ± 5.1 ml·min^{-1}·kg^{-1} versus 43.7 ± 8.4 ml·min^{-1}·kg^{-1}, p <0.001) (Table 2). Maximal oxygen uptake was closely correlated with maximal workload for both patients and controls (see Fig 1).

Heart rate at rest, midpoint, maximal effort, and during recovery time after the test are presented in Table 3. Heart rate at rest was similar between patients and controls. Heart rate at midpoint of the test and maximal effort was lower for patients than controls. Also, heart rate reserve was lower for patients than controls. Heart rate at 2 minutes after maximal effort was similar between patients and controls. Heart rate in absolute values was lower at 4 and 10 minutes after maximal effort for patients than controls. However, when heart rate was analysed in relation to maximal heart rate (relative, %), the two groups had similar heart rate recovery (Table 3, Fig 2).

Furthermore, heart rate in relation to workload was higher for patients than controls at mid and maximal effort. The patients seemed to have a lower increase in heart rate at higher load and later in the exercise test compared with the healthy controls (Table 3, Fig 3).

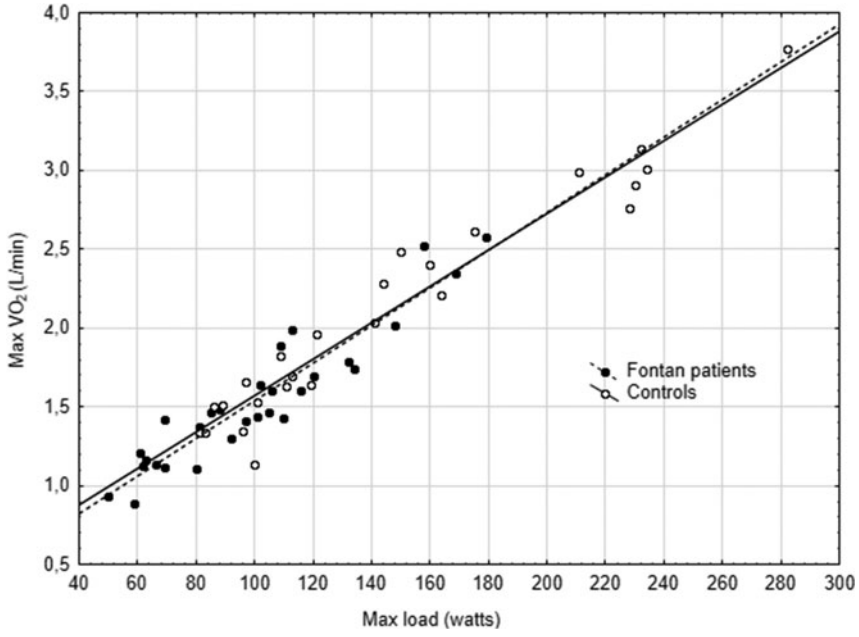


Figure 1. Maximal oxygen uptake, VO_2, (litre·min^{-1}) versus maximal workload (watts) for Fontan patients (y = 0.30 + 0.01*x; r = 0.95; p < 0.001) and controls (y = 0.42 + 0.012*x; r = 0.97; p < 0.001).

https://doi.org/10.1017/S1047951120000761 Published online by Cambridge University Press

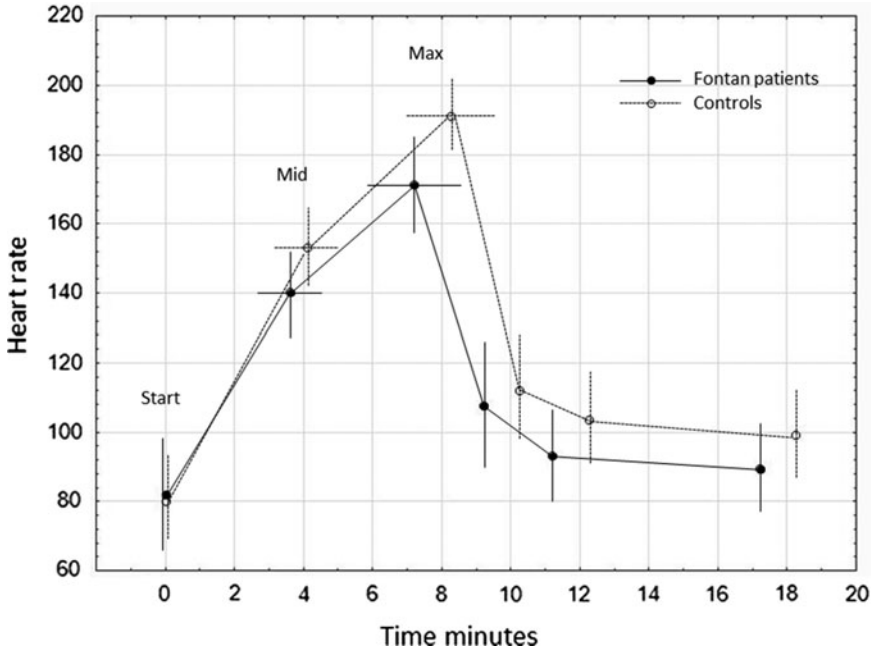


Figure 2. Heart rate (beats per minute) at start, midpoint (mid), maximal effort, and during recovery at 2, 4, and 10 minutes after the test for Fontan patients and controls. Mean ± 1SD.

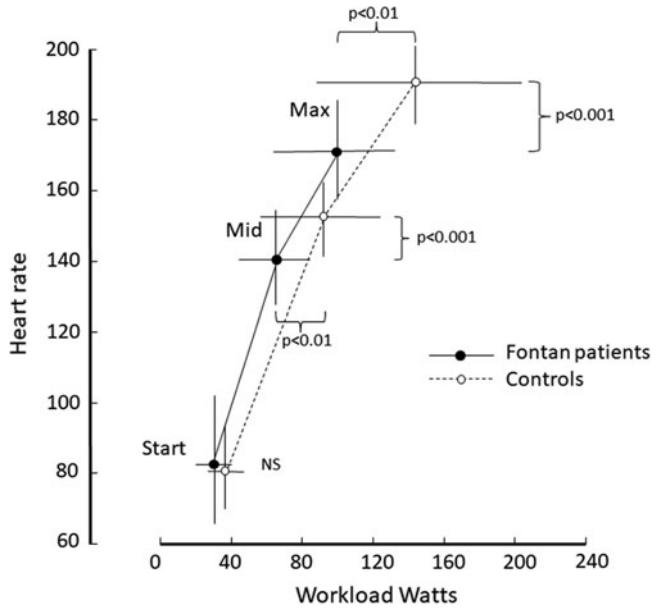


Figure 3. Heart rate versus workload (watts) at start, midpoint (mid), and maximal effort for Fontan patients and controls. Mean ± 1SD. p-Values denote comparisons between groups.

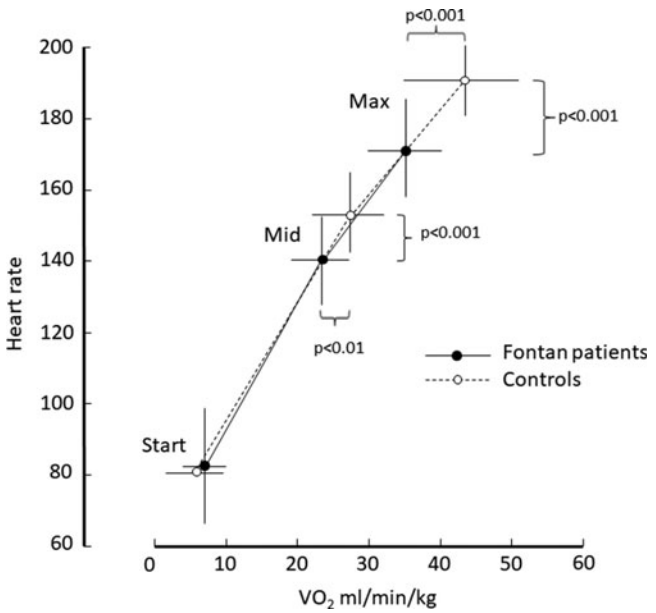


Figure 4. Heart rate versus oxygen uptake, VO_2 ($ml \cdot min^{-1} \cdot kg^{-1}$), at start, midpoint (mid), and maximal effort for Fontan patients and controls. Mean ± 1SD. p-Values denote comparisons between groups.

Also, heart rate in relation to oxygen uptake at start, midpoint, and maximal effort was similar for patients and controls (Table 3, Fig 4). Delta values for heart rate (ΔHR) in relation to delta values for oxygen uptake (ΔVO_2) between rest and maximal effort were similar for patients and controls (Table 3).

Chronotropic index was lower for patients than controls (0.72 ± 0.13 versus 0.88 ± 0.08, $p < 0.001$).

We found that oxygen pulse at start and midpoint of test was similar between patients and controls (data not shown). Oxygen pulse at maximal effort seemed to be smaller in our patients than in controls (9.3 ± 2.8 versus 11.0 ± 3.6 $ml \cdot beat^{-1}$, $p = 0.05$). When correcting oxygen pulse for body surface area, oxygen pulse was significantly smaller for patients than controls (6.6 ± 1.1 versus 7.5 ± 1.4 $ml \cdot beat^{-1} \cdot m^{-2}$, $p < 0.05$). Oxygen pulse increased significantly less from midpoint of exercise test to maximal effort for patients than controls (0.83 ± 0.66 versus 1.24 ± 0.69 $ml \cdot beat^{-1}$, $p < 0.05$) (Fig 5).

Discussion

In agreement with most similar studies, we found maximal heart rate to be reduced in our Fontan patients. However, in relation to workload exercised, heart rate was increased compared to healthy controls. Furthermore, increase in oxygen pulse seemed to level off

https://doi.org/10.1017/S1047951120000761 Published online by Cambridge University Press

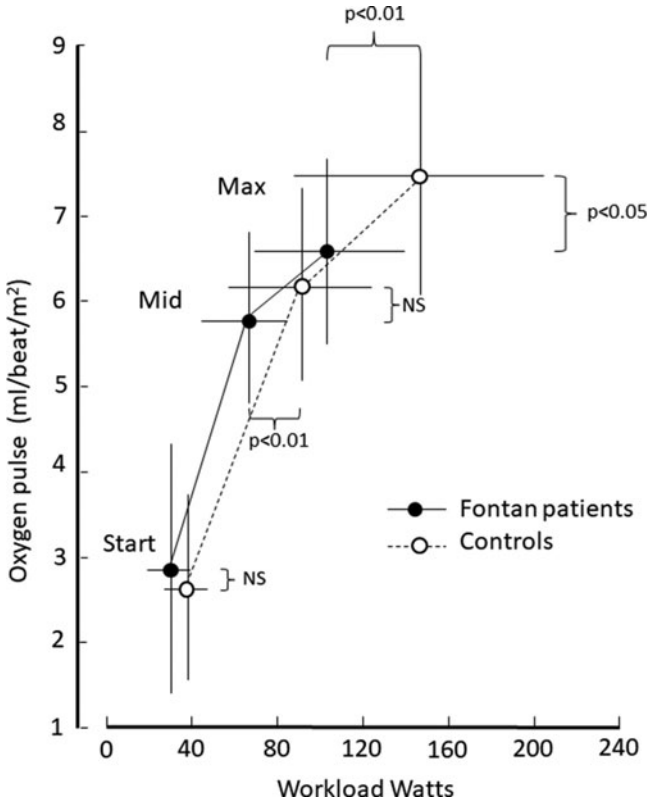


Figure 5. Oxygen pulse (ml·beat^{-1}·m^{-2}) versus workload (watts) at start, midpoint (mid), and maximal effort for Fontan patients and controls. Mean ± 1SD. p-Values denote comparisons between groups.

at higher load and heart rate more than in controls. The reduced maximal heart rate may be an appropriate response to maintain stroke volume and cardiac output in the Fontan circulation.

The growing number of patients with a complex heart malformation and palliation with a Fontan circulation face limitations in daily life and have a high risk for cardiovascular complications. Many studies have reported a reduced quality of life.[8–11] It has been shown,[12] and there is a general consensus that reduced exercise capacity and tolerance is one major factor for reduced self-perceived health-related quality of life, especially in children and adolescents. Exercise capacity and tolerance have been reported to be reduced in most age groups of Fontan patients and long-lasting fatigue after exercise is a common complaint. Peak oxygen consumption and maximal work load are usually reported to be 60–70% of normal when corrected for age and weight.[5–7] Furthermore, a low maximal heart rate is invariably recorded during exercise testing in Fontan patients.

Chronotropic incompetence is broadly defined as the inability to increase heart rate commensurate with increased physical activity or demand and often mentioned as a limiting factor for physical capacity in Fontan patients.[19,32] The question is if limited maximal heart rate is a primary sinoatrial dysfunction or a secondary effect of the Fontan haemodynamics. In our study, chronotropic index was lower for patients than controls. Chronotropic incompetence can be defined as failure to achieve a chronotropic index of 0.8 or higher, but these data are derived from studies on healthy adults.[30] In a large cohort of children and adolescents with CHD, chronotropic index was lowest for patients with single-ventricle haemodynamics, but an index below 0.8 was a frequent finding even also in the control group. Thus, this index may not be a useful measure of chronotropic incompetence in children.[18]

Maximal physical capacity is determined by many variables already in healthy patients. Heart rate and stroke volume are indirectly both dependent of parasympathetic/sympathetic balance, catecholamine surge, venous return and atrial filling, systemic vascular resistance and blood pressure, and many other variables. In the Fontan circulation, the absence of a pumping subpulmonary ventricle with venous pooling of blood and limited atrial filling makes regulation of cardiac output even more complex especially during exercise. We focused our study on the relationship between heart rate and exercise capacity measured as load and oxygen uptake.

Our Fontan patients also had significantly lower maximal work load (77%), maximal oxygen uptake (81%), and maximal heart rate (90%) compared with the matched healthy control group. These numbers are somewhat higher than previously reported and may be explained by our selection of patients and controls. The 10 Fontan patients who choose not to participate may represent a subgroup with less physical capacity so that the study group represents a positive selection of Fontan patients. Furthermore, healthy control patients among peers of the Fontan patients may have resulted in selection of patients less active in sports and exercise than in the general population. Since we also made studies of quality of life and effects of training, we believe it was important to use control patients from similar socioeconomic background. It has also been reported that maximal physical capacity and oxygen uptake are falling in the general population and that children and adolescents live a more sedentary life than previously.[27,28] We therefore believed that it was important to use a contemporary healthy control group rather than population-based statistics and old reference material for comparison. The maximal oxygen uptake in our Fontan patients (35.2 ± 5.1 ml·min^{-1}·kg^{-1}) also suggests that they represent a group of physically capable Fontan patients although with a reduced quality of life which we have previously reported.[24]

Both the Fontan patients and the control patients showed a similar and close to linear relationship between maximal oxygen uptake and maximal load (Fig 1). This is expected and a good measure of the exercise testing procedure used. It also suggests that the muscular metabolic characteristics were similar in the two groups.

Heart rate during exercise was lower in the Fontan patients, both at midpoint and maximal effort as expected (Fig 2). The difference in heart rate during recovery is probably only reflecting the different preceding maximal heart rates. We did not follow heart rate recovery after 10 minutes, so we cannot say when this difference ceases.

When heart rate was related to workload for the two groups (Fig 3), an interesting observation was made. There were significant differences in heart rates and workloads between the two groups both at midpoint and at maximal effort (Table 2). The Fontan patients had a significantly increased heart rate response in relation to workload at midpoint and maximal effort compared to the controls. Both groups were exposed to a continuous and linear increase in load during the test, however, with different starting loads. Both groups also showed similar linear heart rate response to oxygen uptake corrected to weight (Fig 4). The increased or similar heart rate in relation to workload and oxygen uptake could suggest that heart rate during exercise in Fontan patients is adequate for the exercise performed. But, it is also likely that Fontan patients have a different heart rate in relation to workload at lower levels

https://doi.org/10.1017/S1047951120000761 Published online by Cambridge University Press

of work compared with higher levels of work, compared with healthy controls. We choose midpoint in time of exercise test for our measurements so we can only speculate when this shift in heart rate response occurs. It has been suggested that Fontan patients perform better at submaximal exercise level and that training should be designed accordingly.[33] In a recent publication by Claessen et al,[19] they reported Fontan patients with higher increase in heart rate relative to workload than in a control group. However, their control group was not matched regarding age or gender, and the exercise test was only submaximal with heart rates of 144–155 beats per minute, more corresponding to our midpoint values.

The limited maximal heart rate in Fontan patients has been attributed to sinoatrial injury from repeated heart surgery and disconnection of the caval veins. Resulting chronotropic incompetence has been suggested.[18] Heart rate variability has also been reported to be reduced in Fontan patients and depending on surgical techniques.[34] There were no differences in heart rate at rest, response during exercise, or recovery between our small subgroups of Fontan patients with intra-atrial and extracardiac systemic-to-pulmonary venous connections.

If sinoatrial function and heart rate are adequate to workload, there may be another explanation for the lower maximal heart rate. Stroke volume and cardiac output measured non-invasively were reported many years ago to increase less during exercise in Fontan patients compared with controls.[35] Recently, cardiac MRI has been used to measure stroke volume and cardiac output during exercise in Fontan patients.[19] An early reduction in stroke volume and a cardiac output plateau at submaximal heart rates were found. We had no direct measurements of central haemodynamics, but our calculation of oxygen pulse at maximal effort supports the concept of impaired stroke volume in the Fontan patients. It seems as our patients have a smaller oxygen pulse and cannot increase oxygen pulse at higher workloads as the healthy controls (Fig 5). Oxygen pulse has been shown to be a valid predictor of stroke volume during exercise in healthy non-athlete adolescents. Healthy adolescents have been shown to have an oxygen pulse of 13.3 ± 2.5 ml·beat^{-1} for males and 11.0 ± 1.7 ml·beat^{-1} for females,[31] corresponding well with our results. It was also shown by Hebert et al[15] that stroke volume index decreased significantly for Fontan patients near the end of exercise testing close to maximal effort. Hebert et al[15] also concluded that the low stroke volume index was the most important limiting factor for exercise capacity in these patients and the chronotropic response had a smaller impact. Impaired venous return and diastolic filling of the single ventricle at higher heart rates are likely to be secondary to the limited increase in pulmonary perfusion, in spite of systemic venous congestion, without a pumping subpulmonary ventricle.

Limitations

The patients who joined the study may represent a group of more physically active patients with better heart–lung function than those who declined participation. The peers selected by the Fontan patients may be less interested in sports and less physically capable than the average population. With these assumptions of a high-performance selection of Fontan patients and a low-performance selection of controls, the differences observed between Fontan patients and controls may have been underestimated.

Fontan patients have been reported less willing to perform exercise to maximal exhaustion. This is also supported by lower respiratory exchange ratio recorded in our patient group. However, we recorded higher maximal heart rate, loads, and oxygen uptake than in most previous studies and this we believe were indeed signs of near-absolute maximal efforts also in the Fontan group.

Midpoint of exercise was chosen as a measure of submaximal effort. Differences in heart rate and oxygen uptake response do of course not occur at midpoint but are more likely to be continuous and more gradual changes during exercise. More studies with continuous recording of heart rate, oxygen uptake, and, if possible, direct measurements of stroke volume are needed.

Conclusions

In summary, we have found an increased heart rate in relation to workload in young Fontan patients compared with healthy matched controls. At higher efforts, the Fontan patients have a limited ability to further increase heart rate which may be a protective autonomic measure to sustain maximal cardiac output and physical capacity. Impaired diastolic filling and stroke volume at higher heart rates may be an important limiting factor for maximal cardiac output, oxygen uptake, and physical performance in Fontan patients.

Acknowledgements. None.

Financial support. This research was financed by The Swedish Order of Freemasons, The Mayflower Charity Foundation for Children, The Samariten Foundation for Paediatric Research, Sällskapet Barnavård, and The Swedish Heart-Lung Foundation.

Conflicts of interests. None.

Ethical standards. The study was approved by the Ethical Review Board at Karolinska Institutet (DNR 2010/84-31/4), Stockholm.

References

1. Fontan F Baudet E. Surgical repair of tricuspid atresia. Thorax 1971; 26: 240–248.
2. Kanakis MA, Petropoulos AC, Mitropoulos FA. Fontan operation. Hellenic J Cardiol 2009; 50: 133–141.
3. d'Udekem Y, Iyengar AJ, Galati JC et al. Redefining expectations of long-term survival after the Fontan procedure: twenty-five years of follow-up from the entire population of Australia and New Zealand. Circulation 2014; 130: S32–S38.
4. Kverneland LS, Kramer P, Ovroutski S. Five decades of the Fontan operation: a systematic review of international reports on outcomes after univentricular palliation. Congenit Heart Dis 2018; 13: 181–193.
5. Hock J, Reiner B, Neidenbach RC et al. Functional outcome in contemporary children with total cavopulmonary connection - Health-related physical fitness, exercise capacity and health-related quality of life. Int J Cardiol 2018; 255: 50–54.
6. Jenkins PC, Chinnock RE, Jenkins KJ et al. Decreased exercise performance with age in children with hypoplastic left heart syndrome. J Pediatr 2008; 152: 507–512.
7. Muller J, Christov F, Schreiber C, Hess J, Hager A. Exercise capacity, quality of life, and daily activity in the long-term follow-up of patients with univentricular heart and total cavopulmonary connection. Eur Heart J 2009; 30: 2915–2920.
8. Dulfer K, Bossers SS, Utens EM et al. Does functional health status predict health-related quality of life in children after Fontan operation? Cardiol Young 2016; 26: 459–468.
9. Holbein CE, Fogleman ND, Hommel K et al. A multinational observational investigation of illness perceptions and quality of life among patients with a Fontan circulation. Congenit Heart Dis 2018; 13: 392–400.

https://doi.org/10.1017/S1047951120000761 Published online by Cambridge University Press

10. Knowles RL, Day T, Wade A et al. Patient-reported quality of life outcomes for children with serious congenital heart defects. Arch Dis Child 2014; 99: 413–419.
11. Uzark K, Zak V, Shrader P et al. Assessment of quality of life in young patients with single ventricle after the Fontan operation. J Pediatr 2016; 170: 166–172 e161.
12. Atz AM, Zak V, Mahony L et al. Longitudinal outcomes of patients with single ventricle after the Fontan procedure. J Am Coll Cardiol 2017; 69: 2735–2744.
13. Astrand PO, Rodahl K. Textbook of Work Physiology. McGraw Hill, New York 1970.
14. Higginbotham MB, Morris KG, Williams RS et al. Regulation of stroke volume during submaximal and maximal upright exercise in normal man. Circ Res 1986; 58: 281–291.
15. Hebert A, Jensen AS, Mikkelsen UR et al. Hemodynamic causes of exercise intolerance in Fontan patients. Int J Cardiol 2014; 175: 478–483.
16. Legendre A, Guillot A, Ladouceur M, Bonnet D. Usefulness of stroke volume monitoring during upright ramp incremental cycle exercise in young patients with Fontan circulation. Int J Cardiol 2017; 227: 625–630.
17. Smas-Suska M, Dluzniewska N, Werynski P et al. What determines the quality of life of adult patients after Fontan procedure? Cardiol J 2018; 25: 72–80.
18. von Scheidt F, Meier S, Kramer J et al. Heart rate response during treadmill exercise test in children and adolescents with congenital heart disease. Front Pediatr 2019; 7: 65.
19. Claessen G, La Gerche A, Van De Bruaene A et al. Heart rate reserve in Fontan patients: chronotropic incompetence or hemodynamic limitation? J Am Heart Assoc 2019; 8: e012008.
20. Gewillig M, Brown SC. The Fontan circulation after 45 years: update in physiology. Heart 2016; 102: 1081–1086.
21. Gewillig M, Brown SC, Eyskens B et al. The Fontan circulation: who controls cardiac output? Interact Cardiovasc Thorac Surg 2010; 10: 428–433.
22. Gewillig M, Brown SC, Heying R et al. Volume load paradox while preparing for the Fontan: not too much for the ventricle, not too little for the lungs. Interact Cardiovasc Thorac Surg 2010; 10: 262–265.
23. La Gerche A, Gewillig M. What limits cardiac performance during exercise in normal subjects and in healthy Fontan patients? Int J Pediatr 2010; 2010.
24. Hedlund ER, Lundell B, Villard L, Sjoberg G. Reduced physical exercise and health-related quality of life after Fontan palliation. Acta Paediatr 2016; 105: 1322–1328.
25. Hedlund ER, Lundell B, Soderstrom L, Sjoberg G. Can endurance training improve physical capacity and quality of life in young Fontan patients? Cardiol Young 2018; 28: 438–446.
26. Hedlund ER, Ljungberg H, Soderstrom L, Lundell B, Sjoberg G. Impaired lung function in children and adolescents with Fontan circulation may improve after endurance training. Cardiol Young 2018; 28: 1115–1122.
27. Ortega FB, Konstabel K, Pasquali E et al. Objectively measured physical activity and sedentary time during childhood, adolescence and young adulthood: a cohort study. PLoS One 2013; 8: e60871.
28. Raustorp A, Pagels P, Froberg A, Boldemann C. Physical activity decreased by a quarter in the 11- to 12-year-old Swedish boys between 2000 and 2013 but was stable in girls: a smartphone effect? Acta Paediatr 2015; 104: 808–814.
29. Paridon SM, Mitchell PD, Colan SD et al. A cross-sectional study of exercise performance during the first 2 decades of life after the Fontan operation. J Am Coll Cardiol 2008; 52: 99–107.
30. Wilkoff BL, Miller RE. Exercise testing for chronotropic assessment. Cardiol Clin 1992; 10: 705–717.
31. Unnithan V, Rowland TW. Use of Oxygen pulse in predicting Doppler-derived maximal stroke volume in adolescents. Pediatr Exerc Sci 2015; 27: 412–418.
32. Brubaker PH, Kitzman DW. Chronotropic incompetence: causes, consequences, and management. Circulation 2011; 123: 1010–1020.
33. Banks L, McCrindle BW, Russell JL, Longmuir PE. Enhanced physiology for submaximal exercise in children after the fontan procedure. Med Sci Sports Exerc 2013; 45: 615–621.
34. Dahlqvist JA, Karlsson M, Wiklund U et al. Heart rate variability in children with Fontan circulation: lateral tunnel and extracardiac conduit. Pediatr Cardiol 2012; 33: 307–315.
35. Gewillig MH, Lundstrom UR, Bull C, Wyse RK, Deanfield JE. Exercise responses in patients with congenital heart disease after Fontan repair: patterns and determinants of performance. J Am Coll Cardiol 1990; 15: 1424–1432.

https://doi.org/10.1017/S1047951120000761 Published online by Cambridge University Press