International Journal of Cardiology 290 (2019) 86–92

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Differences in cerebral and muscle oxygenation patterns during exercise in children with univentricular heart after Fontan operation compared to healthy peers☆

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ARTICLE INFO

Article history:
Received 5 October 2018
Received in revised form 2 April 2019
Accepted 17 May 2019
Available online 18 May 2019

Keywords:
Univentricular heart
Fontan operation
Near infrared spectroscopy
Exercise test
Children
Muscle oxygenation

ABSTRACT

Background: We assess whether the lower exercise tolerance in children with univentricular heart (UVH) after Fontan operation is associated with altered peripheral muscular and cerebral tissue oxygenation.
Methods: 18 children with UVH and 20 healthy subjects performed an incremental ramp exercise test. Changes in the cerebral and muscular pattern of oxygenated (O_2Hb) and deoxygenated hemoglobin (HHb) and local tissue oxygenation (TOI) were analyzed by means of Near Infrared Spectroscopy (NIRS). Correlations between arterial saturation during exercise and tissue oxygenation were evaluated.
Results: In UVH, maximal oxygen consumption (VO_2peak/kg, 28.9 ± 7.9 vs. 46.3 ± 11.9 ml/min/kg, $P < 0.001$), heart rate (HRpeak, 168 ± 13 vs. 193 ± 12 bpm, $P < 0.001$) and load (Ppeak, 73 ± 19 vs. 133 ± 68 W, $P < 0.001$) were lower, VE/VCO_2 slope was higher (34.5 ± 5.9 vs. 27.1 ± 3.9, $P < 0.001$). A faster and steeper course up to the same level of HHb and absent increase in O_2Hb was seen at cerebral level in UVH; tissue oxygenation index (TOI) demonstrated a steady decrease from the start of exercise. At the muscular level, HHb curve has a similar pattern compared to controls, with an early cessation. O_2Hb has a similar pattern, but with early discontinuation at a higher O_2Hb-level. Muscular TOI has the same course throughout exercise, starting from a lower level. Lower arterial saturation and higher age correlated with lower VO_2peak; higher amplitude of muscular TOI and lower amplitude cerebral TOI correlated with higher VO_2peak.
Conclusion: Children after Fontan procedure have different oxygenation mechanisms at muscular and cerebral level. This reflects a different balance between O_2 supply to O_2 demand which might contribute to the reduced exercise tolerance in this patient population.

1. Introduction

The Fontan circulation has become the strategy of choice for surgical treatment in children with univentricular heart (UVH) [1]. Exercise performance in this patient group however remains impaired in children [2] as well as in adults [3]. Inadequate preload reserve has been proposed as one of the main limiting factors of exercise performance in children with UVH [4]. Other factors, e.g. ventricular dysfunction, residual atrioventricular or arterial valvar insufficiency and residual arch obstruction might lead to further diminished exercise performance. Cardiopulmonary exercise testing (CPET) can be safely performed in patients after Fontan operation [5]. Interventions to augment cardiac preload and to maintain or strengthen lean muscle mass may help to improve exercise capacity, thus slowing down the progressive decline of exercise performance over years [6]. The follow-up of peak oxygen

Abbreviations: %predPPeak, load at peak exercise, expressed as % of normal; % predVO$_2$peak, oxygen consumption at peak exercise, expressed as % of normal; CPET, cardiopulmonary exercise test; EF, ejection fraction; GET, gas exchange threshold; HHb, deoxygenated hemoglobin; HR, heart rate; NIRS, near infrared spectroscopy; O_2Hb, oxygenated hemoglobin; OUES, oxygen uptake efficiency slope; QO_2, oxygen supply; RERpeak, respiratory exchange ratio at peak exercise; SaO_2, arterial saturation; TOI, tissue oxygenation index; UVH, univentricular heart; VCO_2, CO_2 delivery; VE, minute volume; VO_2, oxygen consumption; VO_2peak, maximal oxygen consumption at peak exercise.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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https://doi.org/10.1016/j.ijcard.2019.05.040
0167-5273/

consumption has proven to have a predictive value and might lead to risk stratification in this patient group [5]. Cardiac output in a Fontan patient is decreased at rest (70% of normal) and approximately half that of normal during exercise, with normal or supranormal oxygen utilization [4].

The relationship between O_2 supply and O_2 utilization at the level of the microcirculation can be assessed using near infrared spectroscopy (NIRS). Changes in oxygenated (O_2Hb), deoxygenated hemoglobin (HHb) and tissue oxygenation index (TOI) can reflect an inadequate matching between O_2 supply and O_2 demand. A specific sigmoid response in the locomotor muscles (femoral) during exercise has been described in adults [7,8] and in healthy children [9]. Also, studies comparing younger adult subjects to older subjects demonstrate a poorer matching of O_2 supply to O_2 demand in the latter group [10]. More recent studies also focus on cerebral perfusion and the possible relationship with exercise tolerance. Cerebral O_2Hb increases from low to high intensities, where a breakpoint occurs around 80% of maximal exercise. After this breakpoint, there is a slow decrease towards maximal exercise. HHb in contrast has a breakpoint at high intensities followed by a second more pronounced increase [9,11]. The breakpoints in both muscle HHb and O_2Hb have also been linked to whole-body exercise intensity thresholds (maximal lactate steady state, critical power and respiratory compensation point) [12–14].

What happens to cerebral and muscular local tissue oxygenation during exercise in Fontan patients, remains poorly investigated. One study by Roa et al. [15] investigated the regional oxygen saturation in 5 Fontan patients compared to healthy controls. They concluded that the reduced cerebral blood flow probably leads to reduced exercise intolerance. One other study [16] investigated the effect of Fontan fenestration closure on regional oxygen saturation during exercise. No difference however was found in blood flow distribution or regional oxygen saturation after fenestration closure. The impact of local muscular and cerebral changes on exercise performance and overall functioning however might be underestimated. Goldberg et al. stated that, besides central cardiovascular factors, peripheral muscular factors might also play a substantial role in the exercise limitation in Fontan patients [6]. Different local mechanisms of oxygenation/deoxygenation might lead to early exercise abundance.

The purpose of the present study was twofold: First, cardiorespiratory capacity levels in a population of Fontan patients were assessed by means of CPET and compared to healthy controls. Second, regional oxygenation responses (TOI, O_2Hb, HHb) to the incremental exercise were investigated and compared to healthy subjects in order to study whether exercise tolerance might be limited by different mechanisms in Fontan patients. We presume that exercise tolerance in Fontan patients might be limited by different distributive and local mechanisms at the level of the brains and muscles.

2. Methods

2.1. Participants

18 children with Fontan circulation (14 boys, 4 girls) and twenty healthy children (9 boys, 11 girls) volunteered to take part. The age and anthropometric characteristics of the two groups are presented in Table 1. The groups did not differ significantly for these characteristics. Mean age at Fontan completion was 3.1 ± 0.7 years, mean age at test was 11.8 ± 3.0 years.

All patients were in stable follow-up, with normal blood pressures at rest. Five patients had hypoplastic left heart, 13 patients hypoplastic right heart. 17 patients had good ventricular function (EF > 50%), one patient had mildly impaired ventricular function. Mean arterial saturations (SaO_2) at rest were 93.4 ± 4.1%. Further characteristics are given in Table 1. This study was performed conform the guidelines of the Declaration of Helsinki and was approved by the ethical committee of the Ghent University Hospital (Ghent, Belgium). Written informed consent was obtained from both parents. For children older than 12 years, assent from the children was also obtained.

2.2. Experimental procedure

An incremental exercise test was performed on an electromagnetically braked cycle ergometer (Ergoline Ergoselect 100K, Bitz, Germany). Following a 3-min warm-up at unloaded cycling, the work rate increased in a linear and continuous way (i.e. ramp exercise). The ramp slope (i.e., the increase in work rate per minute) was individualized and determined by dividing the individual body weight by 4 and rounding off to the closest natural number (0 W + (body weight / 4) W·min^{-1}). Participants were asked to maintain a pedal rate of 60 rounds per minute (rpm) and the test was terminated when they reached their self-determined point of full exhaustion or were unable to maintain the required pedal rate despite strong verbal encouragement. This protocol has been validated at our center and results in an exercise time around 8–12 min with normal values in healthy children as described by Wasserman et al. [17].

Table 1
Anthropometric and univentricular characteristics and exercise tolerance parameters for UVH compared to healthy controls.

	Fontan	Controls	P-value
Age (years)	11.8 ± 2.8	11.3 ± 2.9	P = 0.759
Gender (boys/girls)	14/4	14/4	
Weight (kg)	39.5 ± 11.5	39.1 ± 13.8	P = 0.811
Height (m)	1.48 ± 0.15	1.48 ± 0.19	P = 0.742
Puberty status (median) (boys/girls)	Stage 2/stage 3	Stage 2/stage 2	
Age at surgery (years)	3.1 ± 0.7 years		
Age since Fontan (years)	8.7 ± 3.3 years		
Type of surgery	Lateral tunnel 12/18 Extra-cardiac 6/18		
Fenestration (yes/no)	13/5		
Ventricular dominance (RV/LV)	13/5		
Arterial saturation rest (%)	93.4 ± 4.1	>95	
Arterial saturation max (%)	90.8 ± 4.3	>95	
HR rest (bpm)	97.1 ± 10.8	90.9 ± 11.25	P = 0.115
VO_2 rest (ml·min^{-1})	317.1 ± 369.9	369.9 ± 144.2	P = 0.236
Ppeak (W)	73 ± 19	133 ± 68	P < 0.001*
Ppeak/kg (W·kg^{-1})	1.89 ± 0.35	3.24 ± 0.60	P < 0.001*
% PredPpeak (%)	60.8 ± 11.1	99.8 ± 18.0	P < 0.001*
VO_2peak (ml·min^{-1})	1091 ± 309	1795 ± 791	P < 0.001*
VO_2peak/kg (ml·min^{-1}·kg^{-1})	28.9 ± 7.9	46.3 ± 11.9	P < 0.001*
% PredVO_2peak (%)	68.3 ± 20.2	114.0 ± 17.1	P < 0.001*
HRpeak (bts·min^{-1})	168 ± 13	193 ± 12	P < 0.001*
RERpeak	1.01 ± 0.08	1.09 ± 0.08	P = 0.021*
VO_2 at GET (ml·min^{-1})	648.1 ± 173.6	863.9 ± 306.8	P = 0.015*
GET% (ml·min^{-1}·kg^{-1})	60.5 ± 11.24	46.3 ± 8.6	P < 0.001*
Load at GET(W)	33.4 ± 11.7	44.5 ± 25.12	P = 0.103
HR at GET (bpm)	123.5 ± 13.7	120.6 ± 12.8	P = 0.532
VEmax (ml·min^{-1})	41.2 ± 10.1	64.4 ± 26.7	P = 0.002*
Oxygen pulse (ml/kg/beat)	6.48 ± 1.82	9.26 ± 3.96	P = 0.01*
VE/VCO_2 slope	34.5 ± 5.9	27.1 ± 3.9	P < 0.001*
OUES	1331.3 ± 385.8	1987.5 ± 696.9	P = 0.004*

HR: heart rate; bpm: beats per minute; VO_2peak: oxygen consumption at peak exercise; Ppeak: load at peak exercise; RER: respiratory exchange ratio; GET: gas exchange threshold; VEmax: maximal minute ventilation; Oxygen pulse: VO_2peak/HR; VE/VCO_2 slope: minute ventilation per CO_2-exchange; OUES: oxygen uptake efficiency slope.
* Statistically significant P < 0.05.

2.3. Experimental measures

During the exercise tests, VO_2 was measured continuously on a breath-by-breath basis by means of a computerized O_2-CO_2 analyzer-flowmeter combination (Jaeger Oxycon Pro, Germany). Twelve-lead ECG (Marquette, GE Healthcare, USA) was recorded, blood pressure was measured every 3 min during the exercise phase and every 2 min during the recovery phase with an integrated blood pressure monitor (SunTech Tango) that uses 3D K-Sound Analysis. Arterial saturation was monitored continuously throughout the test (Nellcor™ N65P-1, Medtronic, USA).

Muscle and cerebral oxygenation (O_2Hb and HHb) were measured by means of near infrared spectroscopy technology (NIRO-200NX, Hamamatsu Photonics K.K., Hamamatsu, Japan). This system consists of an emission probe emitting near-infrared light at three wavelengths (735, 810 and 850 nm) and a photon detector which measures the intensity of incident and transmitted light at a frequency of 2 Hz. For measurements of oxygenation, the probe was positioned longitudinally over the distal section of the left M. Vastus Lateralis and adhered to the skin. For measurements of cerebral oxygenation, the probe was placed over the left pre-frontal lobe, approximately 3 cm from the midline and just above the supra-orbital ridge [18,19]. This device measures tissue oxygenation index (TOI) as a reflection of mixed arterio-venous O_2 saturation (in %) at the location of the probe. Additionally, relative changes to baseline values in the concentration of O_2Hb and

HHb (in μmol) are recorded. Baseline cycling at 0 W was used as baseline values for O_2Hb and HHb and were set to 0 μmol.

2.4. Data analysis

2.4.1. Pulmonary gas exchange

The breath-by-breath data from the gas exchange responses were filtered upon exportation based on the following criteria: tidal volume < 0.2 and >10 l·min^{-1}; fraction of expired CO_2 < 1 and >10% [12]. The VO_2peak was calculated as the highest 30s average VO_2 throughout the test. Since a supramaximal test was not performed in the current study to validate the determination of VO_2max [20,21] and since a levelling-off in VO_2 is often not reached in children [22], the term VO_2peak will be used throughout to avoid erroneous conclusions on maximal effort. The peak work rate (Ppeak) was determined as the work rate attained at the termination of the exercise phase. The VO_2peak and Ppeak were expressed relative to the predicted values (%predVO_2peak, %predPpeak), based on age and anthropometric values, obtained from the metabolic measurement system. The GET was determined using the criteria of a disproportionate increase in carbon dioxide production (VCO_2) to VO_2 [23], a first departure from the linear increase in minute ventilation (VE) and an increase in VE/VO_2 with no increase in VE/VCO_2. The peak Respiratory Exchange Ratio (RERpeak) was determined as the highest 30s RER throughout the test, the peak heart rate (HRpeak) as the highest value obtained throughout the test.

2.4.2. Cerebral and muscle oxygenation

The changes in the concentration of cerebral and muscle O_2Hb and HHb from baseline values (i.e. baseline cycling at 0 W) and TOI of each individual were expressed as a function of work rate by calculating the mean O_2Hb and HHb and TOI at each 10 W intervals (i.e., at 10 W, 20 W, 30 W, etc.). The values at these work rates were calculated as the average of the corresponding TOI, O_2Hb and HHb values 10s prior and 10s following this absolute work rate. Additionally, the amplitude of the O_2Hb, HHb and TOI response was determined by calculating the difference between the value at Ppeak and baseline cycling.

2.5. Statistical analysis

The statistical analysis was performed in SPSS 21.0 (IBM Corp., Armonk, USA). The data were normally distributed, and therefore the data are presented as mean values ± SD and parametric statistical analyses were performed. The parameters quantifying exercise tolerance (Ppeak, VO_2peak, GET, VE/VCO_2 slope, OUES) were compared between the Fontan patients and healthy controls by means of Independent Samples *t*-tests. The cerebral and muscle O_2Hb and HHb, and TOI responses at each work rate (10 W, 20 W, 30 W, etc.) and also at Ppeak were compared between the Fontan patients and healthy controls by means of Independent Sample *T*-Tests. Pearson correlation was calculated between NIRS-variables, SaO_2 and parameters quantifying cardiorespiratory capacity (VO_2peak, GET). Statistical significance was set at $P < 0.05$.

3. Results

3.1. Exercise tolerance

In Table 1 the parameters quantifying exercise tolerance, obtained from the incremental ramp exercise, are presented. Fontan patients and controls did not differ with regards to age, length, and weight and maturation stage. Heart rate and oxygen consumption at rest were equal in both groups. The parameters quantifying cardiorespiratory capacity (Ppeak, VO_2peak, GET, VE/VCO_2, OUES) were significantly ($P < 0.05$) lower in Fontan patients compared to healthy controls, when expressed in absolute values, relative to body weight and relative to the predicted values for age, gender, height and weight. Also, HRpeak and RERpeak were significantly lower in Fontan patients. VO_2 at GET and load at GET were lower, but HR at GET was not different compared to healthy peers.

3.2. Cerebral and muscular oxygenation

In Figs. 1 and 2 respectively, the patterns of cerebral and the muscular O_2Hb and HHb, as well as TOI are presented as a function of work rate. Cerebral TOI did not differ between Fontan patients and controls from unloaded cycling to 30 W ($P > 0.05$). However, from 40 to 70 W and at Ppeak cerebral TOI was significantly ($P < 0.05$) lower in Fontan patients (60.9 ± 3.6% at Ppeak) compared to controls (72.2 ± 4.1% at Ppeak). Whereas in healthy controls cerebral O_2Hb increased as work rate increased, the pattern of cerebral O_2Hb remained stable in Fontan patients. Therefore, the cerebral O_2Hb values at 40–70 W and at Ppeak were significantly ($P < 0.05$) higher in controls (6.06 ± 2.1 μmol at Ppeak) compared to Fontan patients (−0.34 ± 1.22 μmol). On the other hand, cerebral HHb increased more progressively in Fontan patients compared to controls, resulting in significantly higher cerebral HHb at 40–70 W. However, cerebral HHb was similar in both groups ($P = 0.482$) at Ppeak (3.35 ± 2.10 μmol vs. 3.59 ± 2.39 μmol in patients and controls, respectively).

Muscle TOI was significantly lower in Fontan patients throughout the test, i.e. from baseline cycling to 70 W ($P < 0.05$). However, muscle TOI was significantly ($P = 0.039$) lower at Ppeak in controls (56.0 ± 3.9%) compared to Fontan patients (59.5 ± 2.1%). Muscle O_2Hb and HHb responses did not differ between the groups at the different work rates, but in controls muscle O_2Hb was significantly ($P < 0.01$) lower at Ppeak (−3.44 ± 1.89 μmol vs. −6.60 ± 3.51 μmol in patients and controls, respectively), whereas muscle HHb was significantly higher ($P < 0.01$) (3.57 ± 1.22 μmol vs. 5.07 ± 2.10 μmol in patients and controls, respectively).

3.3. Determinants of cardiorespiratory capacity

The VO_2peak and %predVO_2peak in the Fontan patients was significantly correlated ($r = 0.49$, $P = 0.04$ for VO_2peak and $r = 0.47$, $P = 0.04$ for predVO_2peak) with arterial saturation at rest (Fig. 3), indicating that patients with a lower arterial saturation have a lower cardiorespiratory capacity level. Also, the age of the Fontan patients was significantly correlated to VO_2peak ($r = -0.57$, $P = 0.01$), %predVO_2peak ($r = -0.55$, $P = 0.02$), and GET ($r = -0.61$, $P = 0.02$) indicating that VO_2peak and GET is higher in younger patients. Finally, VO_2peak and predVO_2peak were also correlated to indices of peripheral oxygenation. The amplitude of change in cerebral TOI and muscle TOI was correlated to VO_2peak ($r = -0.78$, $P < 0.001$ for cerebral TOI and $r = 0.66$, $P < 0.01$ for muscle TOI) and predVO_2peak ($r = -0.70$, $P < 0.001$ for cerebral TOI and $r = 0.68$, $P < 0.01$ for muscle TOI).

4. Discussion

The main findings of the present study are first, that Fontan patients have a severely reduced cardiorespiratory capacity and exercise tolerance compared to healthy controls. Second, it was found that tissue oxygenation responses to exercise are altered in Fontan patients, possibly resulting in different mechanisms limiting exercise tolerance compared to healthy subjects. Third, it was found that the reduced VO_2peak was related to the level of arterial desaturation at rest, decreases with age, and was related to tissue desaturation responses at cerebral and muscular level. VO2peak did not correlate with the degree of desaturation during exercise, meaning that desaturation at rest is a more valuable parameter to gain insight into the patient his exercise capacity.

4.1. Analysis of exercise performance parameters in Fontan patients

It is known that exercise capacity is reduced in patients following any type of Fontan surgery [24,25]. At rest, we found an equal oxygen consumption and heart rate compared to healthy children. Heart rate at rest is mainly determined by sinus node function and cardiac autonomic nervous activity. Although both systems can be disturbed in Fontan patients [26], the results of the present study do not support this notion. The maximal heart rate in our patient population however is significantly lower, which has also been described in other literature [27–29]. Chronotropic incompetence in complex congenital heart disease tends to be one of the main reasons for a disturbed heart rate response [26]. We also confirm a seriously lower %predPPeak, and % VO_2peak during CPET in this patient sample. A 30–50% decrease in exercise tolerance is described in children after Fontan repair [30]. Diminished preload and cardiac output have been found to be the major reasons for this reduction in exercise performance [4]. Oxygen pulse, a

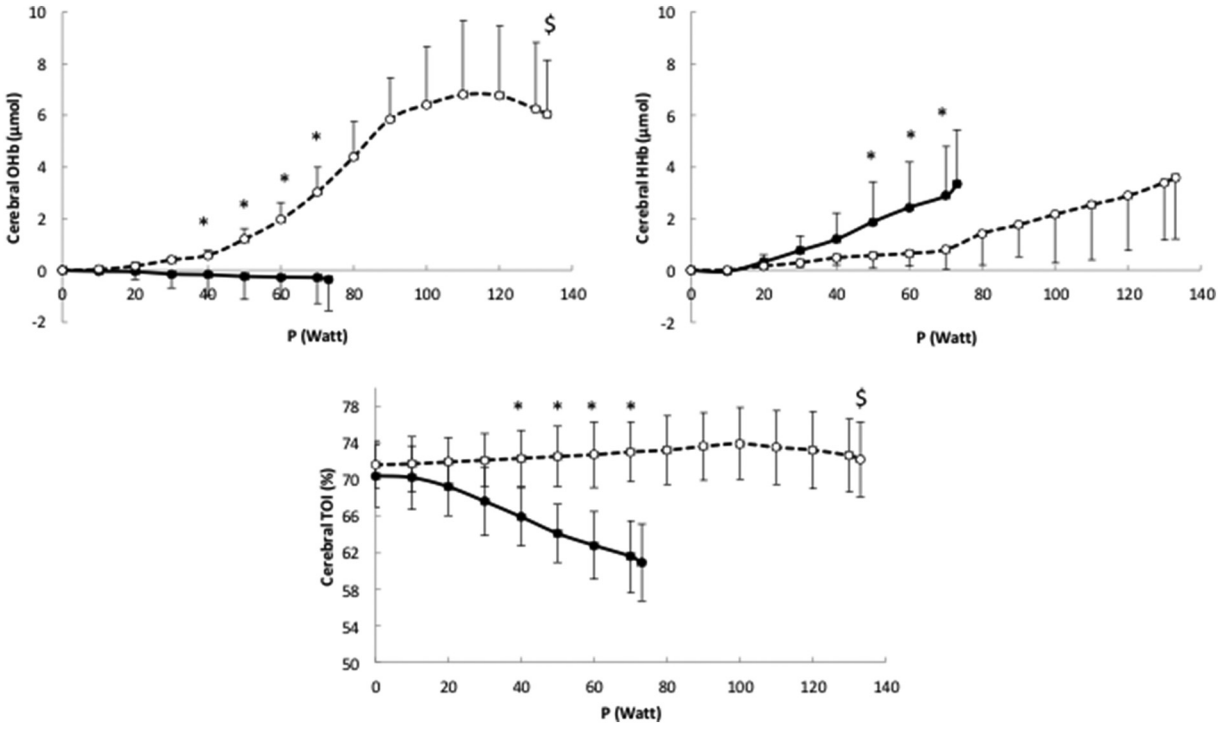

Fig. 1. Mean cerebral O_2Hb, HHb, and TOI responses to incremental ramp exercise in Fontan patients (black dots) compared to healthy controls (white dots). *Indicates significantly different between the two groups for the value at the specific work rate. $Indicates significantly different between the two groups at Ppeak.

parameter of stroke volume during exercise, is lower in our patient group with UVH, pointing towards a combined chronotropic and contractility problem during exercise in this patient group. We also demonstrated a negative relationship between age and VO_2peak. This means that, as described by others [31], exercise performance worsens with aging in Fontan physiology. VO_2 at the GET is lower in Fontan patients, although the patients reach GET at an equal heart rate compared to healthy children. As there is a lot of debate about aerobic and anaerobic thresholds, we defined GET as described by Binder et al. [32]. They divide exercise into 3 phases, divided by the aerobic (first lactate

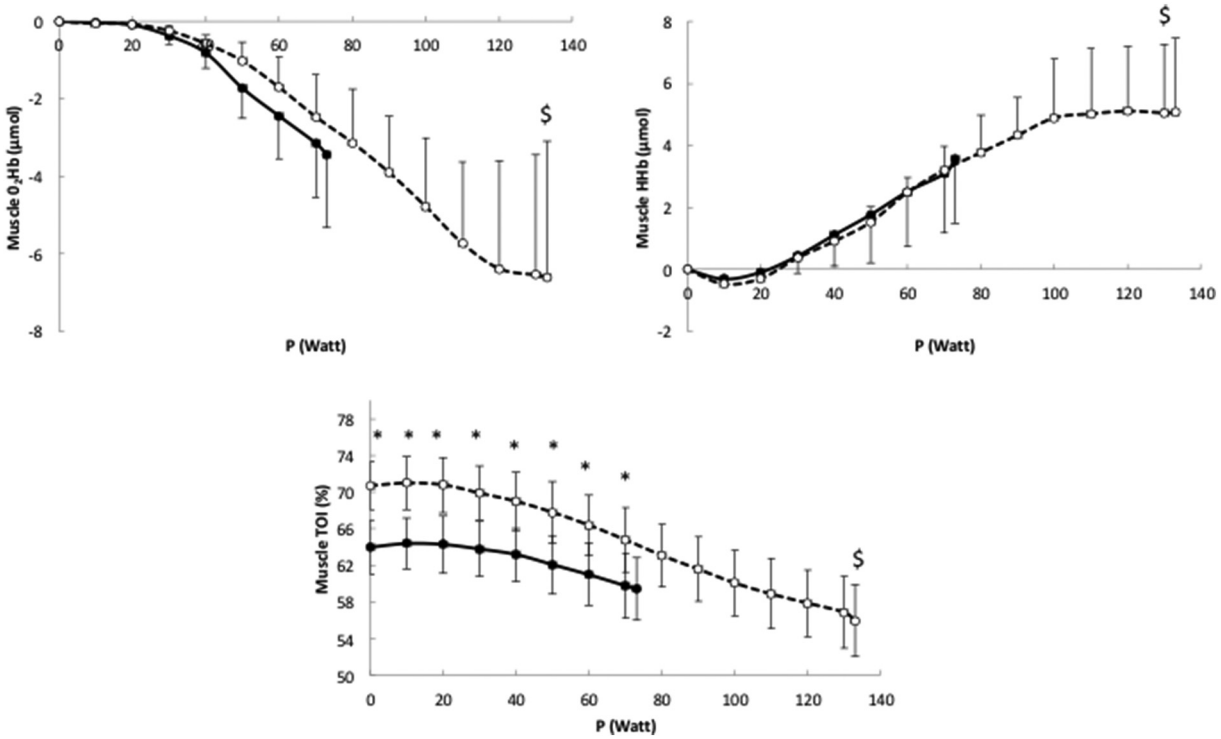

Fig. 2. Mean muscle O_2Hb, HHb, and TOI responses to incremental ramp exercise in Fontan patients (black dots) compared to healthy controls (white dots). *Indicates significantly different between the two groups for the value at the specific work rate. $Indicates significantly different between the two groups at Ppeak.

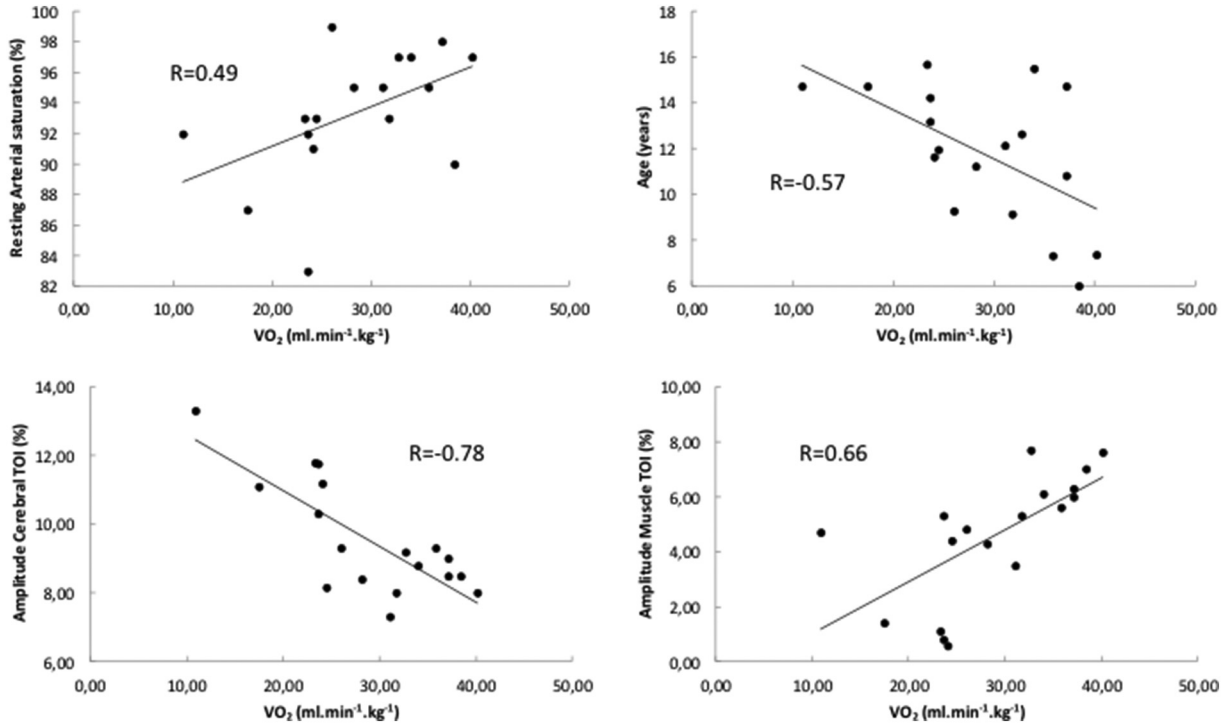

Fig. 3. Correlations between VO_2peak and resting arterial saturation (upper left), age (upper right), amplitude of cerebral TOI (lower left), and amplitude of the muscle TOI (lower right).

threshold) and anaerobic threshold (second lactate threshold). We were unable to detect respiratory compensation point in some patients hence this parameter was not taken into account. The onset of the aerobic threshold at a lower oxygen consumption means that patients reach the aerobic threshold at an earlier level, starting the "second phase" of exercise. VE/VCO_2 slope, a known prognostic parameter in cardiac failure [33] is higher in Fontan patients, which is in line with other research [34,35]. The oxygen uptake efficiency slope has been poorly investigated in children and is a parameter at debate in Fontan patients [36–38]; in our patient group, we also found lower OUES-values in the Fontan group compared to healthy adults. Although there is no agreement on this [36], OUES is seen by some groups as a valid effort-independent parameter of cardiorespiratory fitness [37].

4.2. The patterns of muscle and cerebral oxygenation during exercise in Fontan patients

It was observed in the present study that muscle TOI is lower at rest and unloaded cycling in Fontan patients compared to healthy controls, whereas cerebral TOI did not differ. These results indicate that, even at very low intensities Fontan patients show a reduced oxygen supply (QO_2) to the tissues, not only related to desaturation at rest but possibly also related to the reduced cardiac output inherent to the disease. Local redistribution at rest of cardiac output however, results in a sufficient QO_2 to the brain, whereas muscle QO_2 is limited. As such it can be expected that fractional O_2 extraction at rest and low intensity exercise at the level of the muscle is already increased in Fontan patients. However, this cannot be extracted from the local O_2Hb and HHb responses measured with this NIRS device as only changes from baseline values can be measured. The most important finding from the present study is that cerebral TOI decreases from the onset of CPET to maximal exercise in Fontan patients whereas cerebral TOI remains stable in healthy controls. The cerebral O_2Hb and HHb pattern show that the increased metabolic load of the brain to provide the central command to the exercising muscles is provided predominantly by increasing fractional O_2 extraction and not by increasing cerebral perfusion. In healthy children cerebral O_2 supply increases significantly at low to moderate intensities with only a small increase in fractional O_2 extraction (i.e., only a small increase in cerebral HHb from 0 to 80 W). As work rate increases to high intensities in healthy controls, also cerebral HHb starts to increase more progressively (from 80 W), whereas cerebral O_2Hb levels off and even decreases slightly. This decrease in cerebral O_2Hb can be related to a hypocapnia that occurs in relation to the hyperventilatory response to the metabolic acidosis [13], even though the metabolic rate increases in the motor areas of the brain [39]. The pattern of a decreasing cerebral O_2Hb and increasing HHb, which has been reported previously in healthy subjects [9,11], triggered the question whether this might affect motor drive to the muscles and thus that the brain would limit maximal incremental exercise performance [40].

Studies in hypoxic conditions, in which the hypocapnia-induced limitation of cerebral blood flow is more pronounced, found a relationship between exercise performance and cerebral deoxygenation [41–44]. Additionally, studies in which rapid administration of O_2 near maximal exercise in hypoxic conditions enhanced performance support this hypothesis [45,46]. On the other hand, it should be noted that in normoxic conditions, and also in the present study, that cerebral O_2Hb at maximal exercise is still above resting values and that TOI remains stable in healthy subjects throughout exercise. Additionally, clamping $PETCO_2$ to maintain cerebral blood flow avoiding a decrease in cerebral O2Hb, had no beneficial effect on exercise performance [47]. Therefore, currently the consensus indicates that the brain does not limit incremental exercise performance in normoxic conditions in healthy subjects. However, the cerebral oxygenation patterns of the present study suggest that cerebral blood flow and oxygenation could play an important role in the termination of incremental exercise in Fontan patients. Cerebral O_2Hb does not increase throughout the exercise test, whereas cerebral HHb increases progressively from the onset of the exercise test. It should be noted that the maximal change in cerebral HHb from baseline values in Fontan patients does not differ from that of

healthy controls, indicating a similar fractional O_2 extraction at the level of the brain. Interestingly in this concern, muscle HHb does not reach a levelling-off at peak exercise in Fontan patients, whereas a plateau is traditionally observed during incremental exercise in healthy subjects [9,48]. This indicates that the locomotor muscles do not reach a level of maximal fractional O_2 extraction and are probably not pushed to the limit, probably due to a limited motor command originating from the command center in the brain. Altogether, these results suggest that the limitations to incremental exercise performance might have shifted in Fontan patients to the level of the brain, where a decreased oxygenation leads to a reduced motor command to the locomotor muscles. Only two other studies evaluated overall tissue oxygenation in Fontan patients during exercise. Loomba et al. investigated the effect of Fontan fenestration on tissue oxygenation and concluded there was no effect from the presence of a fenestration on local tissue oxygenation [16]. Another study evaluated local oxygenation processes at different sites in 5 patients compared to 33 normal subjects; this research already points at the role of early cerebral deoxygenation as possible cause of exercise limitation.

We did not find correlations between VO_2peak or oxygen pulse and O_2Hb or HHb, but there was a negative correlation between amplitude of cerebral TOI and a positive correlation with the amplitude of muscular TOI. This negative correlation again supports the preceding discussion with regards to cerebral perfusion: increased diminishing of the local tissue oxygenation can lead to decreased cerebral perfusion, starting the initiation of exercise limitation. Children who have lower cerebral tissue oxygenation, tend to have lower overall exercise performance. In the muscles of the leg, the opposite conclusion can be made: a higher amplitude in tissue oxygenation is seen in patients with higher exercise performance. Increasing lean muscle mass might improve local muscular oxygenation and hence, besides the effect of muscle strength, lead to improved fitness [49]. Further on, there might also be a contribution of increased muscle pump when increasing lean muscle mass leading to better venous return and hence increased cardiac output. Therefore, rehabilitation programs combining cardiovascular training as well as muscle strengthening might be recommended in children with Fontan circulation.

4.3. Study limitations

Our study has some limitations. This experimental setup was performed in nearly 20 children after Fontan operation; larger (multicenter) studies are needed to gain more insight to evaluate prognostic value of NIRS in exercise testing. NIRS is a technique demonstrating relative changes from the baseline rather than giving absolute measurements, hence interpretation should be done with caution and by experienced investigators. This makes the routine implementation of NIRS while performing CPET more complicated. Adipose tissue thickness might have an influence on the NIRS signal measured and was not measured in our study. All patients and controls from our study were lean children, hence the confounding because of ATT can be minimized. This study is however the first to describe both O_2Hb and HHb patterns, besides the overall TOI, in children with Fontan physiology.

5. Conclusion

Children after Fontan operation have severely diminished exercise capacity in combination with different patterns of oxygenated and deoxygenated hemoglobin and tissue oxygenation at the level of the brains and at the muscular level. Exercise performance decreases with aging and in the condition of lower arterial saturation. At cerebral level, there is less offer of oxygenated hemoglobin and a faster deoxygenation process, leading to a persistent decrease in tissue oxygenation. At muscular level, tissue oxygenation is constantly lower, however the pattern of deoxygenation process seems to be equal up to the point of exhaustion. This points towards the fact that cerebral tissue oxygenation might play an important role in the cessation of exercise in patients with Fontan circulation.

Funding

Kristof Vandekerckhove received a grant as clinical PhD fellow by the Flemish Scientific Research Board (FWO Vlaanderen) (Grant number 1701418N).

Declaration of Competing Interest

No conflicts of interest to declare.

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