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Harteveld, L.M.; Blom, N.A.; Monteros, C.T.E.D.; Dijk, J.G. van; Kuipers, I.M.; Rammeloo, L.A.J.; ... ; Harkel, A.D.J. ten

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Determinants of exercise limitation in contemporary paediatric Fontan patients with an extra cardiac conduit

Lisette M. Harteveld [a,b,1,*], Nico A. Blom [a,b,c,1], Covadonga Terol Espinosa de Los Monteros [b,1], J. Gert van Dijk [d,1], Irene M. Kuipers [a,c,1], Lukas A.J. Rammeloo [a,c,1], Eco J.C. de Geus [e,1], Mark G. Hazekamp [a,f,1], Arend D.J. ten Harkel [a,b,1]

[a] The Centre for Congenital Heart Disease Amsterdam–Leiden, Leiden, the Netherlands
[b] Willem-Alexander Children's Hospital, Department of Paediatrics, Division of Paediatric Cardiology, Leiden University Medical Centre, the Netherlands
[c] Department of Paediatric Cardiology, Amsterdam University Medical Centre, Amsterdam, the Netherlands
[d] Department of Neurology and Clinical Neurophysiology, Leiden University Medical Centre, Leiden, the Netherlands
[e] Department of Biological Psychology, Faculty of Human Behavioural and Movement Sciences, Vrije Universiteit Amsterdam, Amsterdam Public Health Research Institute, Amsterdam, the Netherlands.
[f] Department of Cardiothoracic Surgery, Leiden University Medical Centre, the Netherlands

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ABSTRACT

Background: Although various determinants of exercise limitation in Fontan patients have been studied, most research has been performed in patients who underwent different surgical procedures with differing haemodynamic characteristics. The aim of the current study was to evaluate non-invasively measured cardiovascular parameters and their influence on exercise performance in paediatric Fontan patients with an extracardiac conduit and moderate-good systolic ventricular function.

Methods: Fontan patients, between 8 and 18 years of age, with moderate to good systolic ventricular function and an extracardiac conduit were included. Exercise performance and cardiovascular assessment, comprising echocardiography, aortic stiffness measurement and ambulatory measurement of cardiac autonomous nervous activity were performed on the same day. Healthy subjects served as controls.

Results: Thirty-six Fontan patients (age 14.0 years) and thirty-five healthy subjects (age 12.8 years) were included. Compared to controls, Fontan patients had reduced diastolic ventricular function and increased arterial stiffness. No differences were found in heart rate (HR) and cardiac parasympathetic nervous activity. In Fontan patients, maximal as well as submaximal exercise capacity was impaired, with the percentage of predicted capacity ranging between 54 and 72%. Chronotropic competence, however, was good with a peak HR of 174 (94% of predicted). Lower maximal and submaximal exercise capacity was correlated with a higher HR at rest, higher pulse wave velocity of the aorta and a lower ratio of early and late diastolic flow velocity.

Conclusion: Contemporary paediatric Fontan patients have an impaired exercise capacity with preserved chronotropic competence. Exercise performance correlates with heart rate at rest, diastolic function and aortic stiffness.

Abbreviations: ANS, Autonomic nervous system; E/A, Ratio between pulse wave Doppler peak early and late diastolic velocities; E/E', Ratio between pulse wave Doppler peak early and tissue Doppler peak early diastolic velocities; HR, heart rate; LF:HF ratio, ratio of low to high frequency power; OUES, Oxygen uptake efficiency slope; PEP, Pre-ejection period; PWVao, Aortic pulse wave velocity; VE/VCO_2 slope, Respiratory minute to CO_2 production slope; VO_2 peak, Peak oxygen uptake..

* Corresponding author: Department of Paediatric Cardiology, Leiden University Medical Centre, Albinusdreef 2, 2333ZA Leiden, the Netherlands. E-mail address: L.M.Harteveld@LUMC.nl

E-mail address: L.M.Harteveld@LUMC.nl (L.M. Harteveld).

[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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1. Introduction

Surgical Fontan techniques for palliation of a univentricular heart have evolved resulting in improved survival, however, patients still have a decreased life expectancy and significant morbidity, including arrhythmias, thromboembolic complications, heart failure and reduced exercise performance [1,2]. Exercise performance is reduced even in paediatric Fontan patients, and it decreases further with age [1]. An inability to increase ventricular preload during exercise prevents an appropriate increase in cardiac output, which is considered an important factor limiting exercise tolerance [3]. Other contributing factors included chronotropic incompetence, systolic and diastolic ventricular dysfunction and arterial stiffness [3–8]. As there is a direct relation between exercise performance and long-term outcome, a thorough understanding of the mechanisms influencing exercise capacity is important for efforts to improve outcome. Most exercise studies in Fontan patients included patients who underwent different surgical procedures or had different haemodynamic characteristics, which makes a comparison of results difficult. We therefore designed an exercise study in a homogeneous group of paediatric Fontan patients who had an extracardiac conduit and who had moderate to good systolic ventricular function. We evaluated various non-invasively measured cardiovascular function parameters, including echocardiographic parameters, arterial stiffness and cardiac autonomous nervous system activity, and determined their influence on exercise performance. Results were compared to those of healthy controls.

2. Methods

2.1. Study population & design

The study population consisted of Fontan patients aged 8–18 years with an extracardiac conduit, recruited from Leiden University Medical Centre and Amsterdam University Medical Centre. Patients with ventricular dysfunction and those who were unable to exercise were excluded. Healthy controls with a similar age were recruited through advertising in local schools. Written informed consent was obtained from all participants or their parents or guardians. The study was approved by the local ethics committee. Data were collected in a prospective way between July 2017 and October 2019 and all patients had all tests in one day. All participants underwent weight, height and arterial stiffness measurements, echocardiography, and an ambulatory cardiac autonomic nervous system (ANS) measurement as described below. As adequate reference values of exercise parameters of healthy children exist, cardiopulmonary exercise tests were only performed in Fontan patients and results expressed as percentage of predicted values.

2.2. Arterial stiffness measurements

An oscillometric arteriograph device (Tensiomed, Hungary) [9] was used to measure aortic pulse wave velocity (PWVao), aortic augmentation index, systolic blood pressure and pulse pressure. Measurements were performed in supine position with the cuff on the left arm. The software determines measurement accuracy with a standard deviation (SD) of the PWVao [9]. However, as children have smaller pulse waves compared to adults, and as movement distorts pulse waves, we analysed each cardiac cycle separately. Measurements were considered valid after a visual check and when a reliable value could be calculated with an SD PWVao <1.0 m/s.

2.3. Echocardiography

Transthoracic echocardiograms were performed on a Vivid S6/S60 (GE healthcare, Norway) and images analysed offline using EchoPac (version 203, GE healthcare). If applicable, averages of three consecutive cardiac cycles were used for analysis. Conventional Doppler, Tissue Doppler imaging and speckle-tracking were performed to measure different systolic and diastolic parameters following previously published methods [10]. Ratio of peak early conventional and Tissue Doppler diastolic velocity (E/E') was calculated of the lateral wall. Longitudinal global peak strain was obtained if 5/6 segments could be recorded and showed acceptable curves. Furthermore, strain was conducted from both lateral walls when the ventricular septum defect was larger than one segment. In addition, Doppler recordings across the (neo)aortic valve were performed to assess aortic velocity time integral from which, together with heart rate (HR) and measured (neo)aortic annulus diameter, the cardiac index was calculated.

2.4. Ambulatory cardiac ANS measurement

We used the VU-ambulatory monitoring system (VU-AMS; VU university, Netherlands, 5 fs version) comprising an impedance measurement, an electrocardiogram, and the VU-Data Analysis and Management Software (VU-DAMS, VU University) to measure several heart rate variability parameters to determine the effect of ANS activity on the heart as described in previously published methods [11]. All participants completed a 4–5-min supine baseline measurement. Ectopic beats and artifacts were removed before analysis.

Pre-ejection period (PEP), reflecting cardiac sympathetic activity [12], and respiratory sinus arrhythmia (RSA), mainly reflecting cardiac parasympathetic activity [13], were calculated as described in previously published methods [11]. The root mean square of consecutive differences between the beats of normal sinus beats and the interval between the beats of normal sinus beats were calculated as additional cardiac parasympathetic activity parameters. Furthermore, we derived low-frequency (LF;0.04–0.15 Hz) and high-frequency (HF;0.15–0.4 Hz) power using the Fast Fourier Transformation and additionally calculated the LF:HF ratio, a disputed but frequently used measure of sympathovagal balance [14]. In addition, respiration rate was derived from the thorax impedance signal as well, as this, along with HR, could affect ANS parameters. To correct for HR remains, however, a subject of debate as adjustment may in fact remove possible important variance of outcomes related to autonomic control [13]. We therefore have chosen to report the outcomes of HR and respiration in parallel with the heart rate variability parameters over adjustment procedures.

2.5. Cardiopulmonary exercise test

Fontan patients performed an exercise test on an upright bicycle ergometer (Jaeger ER 900; Viasys Healthcare, Germany) with breath-by-breath analysis using a flowmeter (Triple V volume transducer) and a computerized gas analyser (Jaeger Oxycon Champion, Viasys Healthcare or Carefusion Vyntus, Vyaire Medical). Starting wattage and workload increment per minute were determined by patient's age. Patients were encouraged to exercise until exhaustion. From flow and gas analysis and HR measurements per 10 s exercise parameters as defined in previously published parameters could be derived or calculated [15,16]. Maximal exercise parameters were assessed from patients with a peak respiratory exchange ratio ≥ 1.0 and submaximal parameters from all patients. Besides absolute values, the percentage of predicted values adjusted for age and sex were calculated, where applicable, using previous published methods [15–17], except for peak oxygen uptake ($VO_{2\ peak}$) which was adjusted for age, sex, weight and height [18] and oxygen pulse for which we used the data of Ten Harkel et al. [16].

2.6. Statistical analysis

Data analysis was performed using SPSS (IBM, version 25). Variables were tested for normality using the Kolmogorov-Smirnov test as well as through visual inspection of histograms and normality plots. LF and HF their ratio were LN transformed before all statistical analyses to remove the significant skewness in the untransformed values so as not to violate

the assumption of normal distribution. Continuous data are reported as mean ± SD or as the median with first to third quartile [Q1-Q3] in case of non-normality, except for the percentage of predicted values which are reported as mean or median with 95% confidence intervals. Categorical data are presented as numbers with percentages. To compare groups, we used the Student's *t*-test or, in case of non-normality, the Mann-Whitney *U* test for continuous data and the Pearson Chi-Square test for categorical data. As aortic arch surgery could affect vascular function, cardiac ANS activity and chronotropic competence, we performed a sub-analysis between patients who did had aortic arch reconstruction and those who did not. Furthermore, a second sub-analyses was performed to show whether there were differences between cardiovascular and exercise parameters in patients with a morphological left of right ventricle. To test whether exercise parameters differed from their reference values, the one sample *t*-test or, in case of non-normality, the one sample Wilcoxon Signed Rank test was used. We tested correlations between exercise and cardiovascular parameters using the Pearson or Spearman correlation coefficients depending on data distribution. For correlation with HR at rest, only patients with a sinus rhythm were used for analysis.

3. Results

Thirty-six Fontan patients (median age 14.0 years) and 35 healthy controls (median age 12.8 years) were included (Table 1). Age, weight, height, body surface area and sex distribution between Fontan patients and controls were comparable. Twenty-one Fontan patients had a dominant left ventricle (58%), 12 a dominant right ventricle (33%) and 3 an indifferent or undefined ventricle (8%). Fifteen patients (42%) had aortic arch/Norwood surgery. Thirty-three patients (92%) had an initial fenestration at time of surgery and only one patient had a patent fenestration at time of the study (3%), in the remaining 32 patients the fenestration was closed naturally or by device. Furthermore, one other patient had a pacemaker (3%; dual chamber pacing; DDD). The median plasma N-terminal pro brain natriuretic peptide was low (80 ng/L) in the Fontan cohort.

Table 2 shows the results of cardiovascular parameters. Fontan patients had a higher PWVao and augmentation index of the aorta, and a slightly higher systolic blood pressure and pulse pressure compared to healthy controls. Almost all diastolic function parameters showed a worse diastolic function in Fontan patients compared to controls with significant lower Doppler and Tissue Doppler velocities and ratio of peak early and late diastolic velocities (E/A) and higher E/E' ratio. All Fontan patients showed a subjective moderate to good ventricular systolic function on echocardiography. Although Tissue Doppler imaging showed lower systolic velocities in Fontan patients compared to controls, global strain was not significantly different. Cardiac index could be calculated in only 21 patients, as in 15 patients aortic annulus could not be determined. Cardiac index was comparable to healthy controls. Eight patients were excluded from cardiac ANS measurements because of a pacemaker in one patient, and frequent atrial ectopy or a dominant nodal rhythm in seven others. The heart rate variability parameters reflecting cardiac parasympathetic activity were comparable between Fontan patients and controls. PEP was significantly longer in Fontan patients, whereas the LF:HF ratio was higher. HR and respiration rate did not differ between patients and controls.

The results of the exercise test are shown in Table 3. Three patients (8.3%) were not able to achieve a respiratory exchange ratio > 1.0 and were excluded for the maximal exercise results. Furthermore, the patient with the pacemaker was excluded for the chronotropic parameters. There were no adverse events during the exercise tests. Fontan patients showed low exercise capacity, reflected by a low VO_{2peak} (mean 26.8 mL/kg/min), oxygen uptake efficiency slope (OUES) and plateau, and a high slope of respiratory minute volume to CO_2 (VE/VCO_2 slope) with percentage of predicted values ranging from 54 to 72% ($P < 0.001$) and 124% ($P < 0.001$). Oxygen pulse at peak exercise was also decreased with a percentage predicted of 59% ($P < 0.001$) which could reflect a lower stroke volume at peak exercise. Fontan patients showed a good chronotropic competence with a peak HR of 174 (94% of predicted; $P < 0.001$) and percentage HR recovery at 1 min of 35% (116% of predicted; $P < 0.01$).

Table 1
Patient Characteristics of Fontan patients and controls.

Characteristics	Fontan patients ($N = 36$)	Controls ($N = 35$)	*P*-value
Age (years)	14.0 [12.7–16.6]	12.8 [11.1–15.5]	0.202
Males (N,%)	23 (56.1)	18 (43.9)	0.288
Height (cm)	163.0 (14.1)	160.8 (13.5)	0.514
Weight (kg)	51.4 [42.8–60.3]	46.2 [37.0–56.9]	0.133
BSA (m^2)	1.55 (0.3)	1.46 (0.27)	0.189
Diagnosis (N,%)			
Tricuspid atresia	9 (25.0)		
Pulmonary atresia	2 (5.6)		
Double inlet left ventricle	5 (13.9)		
Double outlet right ventricle	1 (2.8)		
Hypoplastic left heart syndrome	8 (22.2)		
Unbalanced atrioventricular septum defect	4 (11.1)		
Other	7 (19.4)		
Main ventricle (N;%)			
Left	21 (58.3)		
Right	12 (33.3)		
Indifferent	3 (8.3)		
Aortic arch/Norwood surgery (N,%)			
Yes	15 (41.7)		
No	21 (58.3)		
Age at Glenn operation (years)	0.52 [0.38–0.79]		
Age at Fontan operation (years)	3.19 (0.65)		
Initial Fenestration (N,%)	33 (91.7)		
Open	1 (3.0)		
Closed (naturally or by device)	32 (97.0)		
Pacemaker (N,%)	1 (2.8)		
NT-pro BNP (ng/L)	80.2 [48.0–131.3]		
AV-valve regurgitation (N,%)			
No	16 (44.4)		
Mild	14 (38.9)		
Moderate	6 (16.7)		
Severe	0 (0.0)		
(Neo)Aortic regurgitation (N, %)			
No	31 (86.1)		
Mild	2 (5.6)		
Moderate	3 (8.3)		
Severe	0 (0.0)		
Cardiac medications (N, %)			
Acetylsalicylic acid	34 (94.4)		
Coumarin derivative	2 (5.9)		
β-blocker	1 (2.8)		
Diuretics	1 (2.8)		

Data expressed as n (%), mean (±SD), and median [Q1-Q3].
BSA = body surface area; NT-pro BNP = N-terminal pro brain natriuretic peptide; SpO_2 = oxygen saturation.

Table 4 shows the results of the sub-analyses between patients who did have aortic arch reconstruction and who did not. There were no significant differences in any of the analysed parameters, including vascular function, cardiac ANS activity, chronotropic competence and exercise capacity. Furthermore, a second sub-analyses showed that there were no differences in cardiovascular and exercise parameters between patients with a dominant left and right ventricle (Supplementary Tables S1–2).

Among the cardiovascular parameters, HR at rest (r = -0.540, $P = 0.001$ and r = -0.452, $P = 0.006$), PWVao (r = -0.455, $P = 0.018$ and r = -0.361, $P = 0.046$) and E/A (r = 0.625, $P < 0.001$ and r = 0.421, $P = 0.010$) were found to be correlated with both VO_{2peak} and OUES and are

Table 2
Cardiovascular parameters in Fontan patients and controls at rest.

	Fontan patients (N = 36)	Controls (N = 35)	*P*-value
Heart rate (bpm)	71.3 (15.6)	71.0 (10.2)	0.918
SpO_2 (%)	95.1 [94.2–96.3]	99.0 [98.4–99.5]	<0.001
Vascular function			
SBP (mmHg)	118.7 (9.1)	108.9 (8.6)	<0.001
PP (mmHg)	52.9 (8.3)	46.9 (6.8)	0.001
PWVao (m/s)	5.5 (1.1)	4.7 (0.6)	<0.001
AIXao	17.5 (9.9)	11.2 (7.8)	0.006
Ventricular function			
Systolic			
Aortic annulus width (mm)	23.0 (3.1)	20.1 (2.2)	0.001
VTI (cm)	16.1 [14.2–20.9]	21.1 [18.9–23.3]	0.001
CI (L/min/m^2)	3.4 (0.7)	3.3 (0.6)	0.546
TDI septal S′ (m/s)	0.04 [0.03–0.05]	0.08 [0.07–0.08]	<0.001
TDI lateral free wall S′ (m/s)	0.058 (0.02)	0.106 (0.03)	<0.001
Global strain (%)	−15.3 (3.2)	−16.6 (2.4)	0.062
Diastolic			
E (m/s)	0.66 [0.55–0.82]	0.98 [0.89–1.03]	<0.001
A (m/s)	0.49 (0.20)	0.42 (0.08)	0.069
E/A	1.43 [1.1–2.1]	2.32 [2.0–2.7]	<0.001
TDI septal E' (m/s)	0.072 (0.03)	0.143 (0.03)	<0.001
TDI septal A' (m/s)	0.041 (0.02)	0.053 (0.01)	0.003
TDI lateral free wall E' (m/s)	0.085 (0.04)	0.178 (0.04)	<0.001
TDI lateral free wall A' (m/s)	0.047 [0.03–0.06]	0.055 [0.05–0.07]	0.017
E/E'	8.51 [6.5–12.5]	5.71 [5.13–7.09]	<0.001
Cardiac autonomous nervous activity			
PEP (ms)	122.4 (17.6)	81.3 (15.9)	<0.001
RSA (ms)	68.7 [26.1–110.3]	84.5 [54.7–123.5]	0.104
RMSSD (ms)	60.6 [20.8–107.2]	62.5 [49.4–100.4]	0.611
SDNN (ms)	79.9 [28.0–126.1]	70.7 [55.1–95.9]	0.843
LF (ms^2)	1271 [69–4832]	1243 [575–2173]	0.380
HF (ms^2)	1063 [37–3136]	1264 [559–1264]	0.056
LF:HF ratio	1.48 [0.82–2.64]	0.88 [0.47–1.33]	0.009
Respiration rate (breaths/min)	18.8 (3.0)	18.5 (3.2)	0.686

Data expressed as mean (±SD), and median [Q1–Q3]. A = peak late diastolic velocity; A' = peak late diastolic TDI velocity; AIXao = Augmentation index of the aorta; CI = cardiac index; E = peak early diastolic velocity; E' = peak early diastolic TDI velocity; HF = high frequency power spectral values; LF = low frequency power spectral values; LF:HF = low frequency/high frequency ratio; PEP = pre-ejection period; PP = pulse pressure; PWVao = pulse wave velocity of the aorta; RMSSD = root mean square of successive differences between normal sinus beats; RSA = respiratory sinus arrhythmia zero; S′ = peak systolic TDI velocity; SBP = systolic blood pressure; SDNN = standard deviation of the inter-beat interval of normal sinus beats; SpO_2 = oxygen saturation; TDI = tissue doppler imaging; VTI = velocity time integral.

shown Fig. 1. An overview of all correlations between VO_{2peak} and OUES and the various cardiovascular parameters is shown in Supplementary Table S3.

4. Discussion

Our study demonstrates reduced maximal and submaximal exercise performance in contemporary Fontan patients with moderate to good systolic ventricular function. Stroke volume was reduced at peak exercise, reflected by a decreased oxygen pulse, although chronotropic competence was preserved. A reduced exercise performance was related to impaired diastolic function, increased aortic stiffness and an increased HR at rest.

Table 3
Cardiopulmonary exercise test results Fontan patients.

	Absolute values	Percentage of predicted
Maximal exercise (*N* = 33)		
RER_{peak}	1.13 (0.09)	–
WR_{peak} (watt)	118.6 (38.2)	61.3 (56.3–66.3)**
WR_{peak}/kg (watt/kg)	2.2 (0.6)	63.5 (58.0–69.0)**
HR_{peak} (bpm)	173.5 (16.0)	93.5 (90.2–96.7)**
HR reserve (bpm)	94.9 (25.7)	–
HR01 percentage (%)	35.0 [25.2–48.3]	115.8 (102.3–131.0)*
VO_{2peak} (L/min)	1434.5 (337)	–
VO_{2peak} (ml/kg/min)	26.8 (4.7)	54.4 (51.3–57.5)**
Peak O_2 pulse (ml/beat)	8.65 [7.1–9.4]	58.6 (54.6–62.7)**
Submaximal exercise (*N* = 36)		
VE/VCO2 slope	36.5 [33.5–41.0]	123.8 (118.9–140.5)**
OUES	1402.7 (386.2)	–
OUES/kg	27.2 (5.9)	58.4 (54.3–62.5)**
OUEP	31.6 [29.4–33.8]	72.2 (68.4–74.7)**

Absolute values expressed as mean (±SD), and median [Q1–Q3].
Percentage of predicted expressed as mean or median (95% CI).
HR01 percentage = percentage heart rate recovery at 1 min after exercise; HR_{peak} = heart rate at peak exercise; $HR_{recovery01}$ = heart rate at peak exercise - heart rate at 1 min after exercise; HR reserve = heart rate at peak exercise – heart rate at rest; HR_{rest} = heart rate at rest; OUEP = oxygen uptake efficiency plateau; OUES = oxygen uptake efficiency slope; Peak O_2 pulse = peak oxygen uptake per heart beat; RER_{peak} = respiratory exchange ratio at peak exercise; VE = ventilatory efficiency; VE/VCO2 slope = slope of respiratory minute to CO2 production; VO_{2peak} = oxygen uptake at peak exercise; WR_{peak} = maximal work rate achieved.
* P-value < 0.01 for difference between exercise values and reference values.
** *P*-value < 0.001.

Exercise requires an adequate increase in cardiac output, which in turn requires an adequate increase in or at least a preserved stroke volume and a sufficient increase in HR. A limited increase in stroke volume during exercise is known to be one of the main limiting factors in a Fontan circulation; the absence of a sub-pulmonary ventricle results in an inability to augment venous return [19]. Other factors that may also contribute to a limited increase in stroke volume during exercise in Fontan patients are reduced diastolic and systolic ventricular function and increased arterial stiffness.

Diastolic dysfunction may be caused by an increased stiffness of the systemic ventricle and thereby limit the preload affecting stroke volume. Our study showed that an impaired diastolic function, reflected by an increased E/A ratio, was a determinant of diminished exercise capacity. This finding is in line with a previous echocardiographic study in adult Fontan patients, in which an increased diastolic dysfunction, reflected by an E/E' ratio ≥ 12, was associated with a lower VO_{2peak} [8]. In our study, E/E' was not correlated with exercise performance, however, the E/E' was much lower (median 8.5), which could indicate that only a significant increased E/E', indicating significant diastolic dysfunction, might be correlated with reduced exercise capacity. Diastolic dysfunction can already be present shortly after the Fontan operation [20] and is most likely explained by the immediate pre-load reduction post-operatively, resulting in a greater mass to volume ratio altering relaxation and diastolic performance. On the long term, impaired diastolic function tends to persist or even further deteriorate [20,21]. The aetiology of diastolic dysfunction in Fontan patients is not completely understood, and factors such as myocardial fibrosis possibly induced by volume overload and cyanosis pre-operatively, long-term shunts, previous pulmonary artery banding, systemic ventricular outflow tract obstructions, or by renin-angiotensin-aldosterone system activation may play an important role [22].

Systolic ventricular function clearly plays a role in the preservation

Table 4
Comparison of vascular function, cardiac autonomic nervous activity, chronotropic competence and exercise capacity between patients who had aortic arch reconstruction and who did not.

Characteristics	Aortic arch surgery ($N = 15$)	No aortic arch surgery ($N = 21$)	*P*-value
Vascular function			
SBP (mmHg)	120.0 [112.0–125.0]	120.0 [115.0–123.0]	1.000
PP (mmHg)	54.1 (9.7)	52.1 (7.3)	0.486
PWVao (m/s)	5.9 [4.8–6.8]	4.9 [4.8–5.7]	0.149
AIXao	13.0 [10.5–18.9]	16.3 [13.3–24.4]	0.215
Cardiac autonomous nervous activity			
PEP (ms)	130.4 [105.4–141.8]	117.6 [112.1–129.5]	0.486
RSA (ms)	64.7 [19.1–103.5]	82.1 [26.1–115.6]	0.664
RMSSD (ms)	50.5 [15.7–126.7]	77.3 [24.2–107.2]	0.568
SDNN (ms)	64.1 [20.4–119.7]	89.6 [39.5–137.7]	0.371
LF	942.4 [37–5531]	1518.7 [385–4832]	0.516
HF	475.5 [17–3920]	1657.9 [74.0–3136]	0.399
LF:HF	1.53 [1.0–2.9]	1.28 [0.7–2.3]	0.516
Respiration rate (breaths/min)	19.9 (2.9)	18.0 (2.9)	0.089
Chronotropic competence			
Patients with maximal exercise (N)	14	19	
HR_{peak} (bpm)	169.0 (15.8)	177.0 (15.7)	0.165
% HR_{peak}	90.9 (9.1)	95.5 (8.6)	0.147
$HR_{01\%}$ (%)	37.7 [30.0–49.3]	32.8 [22.2–45.1]	0.316
% $HR_{01\%}$	125.7 (51.8)	117.0 (40.4)	0.602
Exercise capacity			
Maximal exercise (*N*)	14	19	
VO_{2peak} (ml/kg/min)	26.8 (3.9)	26.8 (5.3)	0.997
% VO_{2peak}/kg	52.1 (7.3)	56.1 (9.7)	0.198
Submaximal exercise (*N*)	15	21	
OUES/kg	26.6 [23.7–31.6]	26.9 [22.3–29.8]	0.505
% OUES/Kg	58.2 [56.7–64.4]	58.5 [49.4–63.6]	0.680

Data expressed as mean (±SD), and median [Q1-Q3]. AIXao = Augmentation index of the aorta; HF = high frequency power spectral values; HR_{peak} = maximal heart rate at peak exercise; HR01 percentage = percentage heart rate recovery at 1 min after exercise; LF = low frequency power spectral values; LF:HF = low frequency/high frequency ratio; OUES = oxygen uptake efficiency slope; PEP = pre-ejection period; PP = pulse pressure; PWVao = pulse wave velocity of the aorta; RMSSD = root mean square of successive differences between normal sinus beats; RSA = respiratory sinus arrhythmia zero; SBP = systolic blood pressure; SDNN = standard deviation of the inter-beat interval of normal sinus beats; VO_{2peak} = oxygen uptake at peak exercise.

of stroke volume during exercise and previous Fontan studies also showed that significant systolic ventricular dysfunction was related to limited exercise performance [3]. In the present study, which included only patients with moderate to good systolic ventricular function, we found no correlation between systolic function parameters and exercise performance. However, Tissue Doppler imaging values were lower compared to controls, indicating that even in this relatively healthy and young Fontan cohort systolic ventricular function was also decreased and progression of systolic dysfunction in time may contribute to the deterioration of exercise performance on the long term [1].

Increased arterial stiffness leads to a higher afterload which subsequently results in a higher workload of the single ventricle, negatively affecting diastolic and systolic ventricular function and volumes [4,23]. We showed that a higher arterial stiffness, measured as PWVao, was correlated with reduced exercise capacity. AIX was not correlated with exercise performance. However, AIX is an indirect measure of arterial stiffness and is also be influenced by heart rate and stroke volume. The correlation with a higher arterial stiffness corresponds with the majority of studies in paediatric and adult Fontan patients [4,7,24]. A small study in 17 paediatric and adult Fontan patients, using the same non-invasive methodology, did not show an effect of arterial stiffness on exercise capacity, which may be explained by the small sample size [6].

Furthermore, we showed no difference in arterial stiffness between patients who had aortic arch reconstruction and who did not. Previous studies have shown that not only the non-compliant patch used for aortic reconstruction relates to aortic stiffness, but that also other Fontan patients show arterial stiffness, suggesting other wall abnormalities are present [25,26]. Arterial stiffness could be related to vascular fibrosis, endothelial dysfunction, inflammation and elevated sympathetic activity [25,27,28] and has been shown to increase with age [4].

Chronotropic incompetence, defined as the inability to increase heart rate normally with exercise, negatively affects cardiac output, limiting exercise performance [5,29]. In our study, chronotropic competence was preserved and HR at peak was not correlated with exercise performance. However, the degree of chronotropic impairment may vary in Fontan patients. A reduction in maximal HR can be the result of reduction in cardiac filling at exercise [30], sinus node dysfunction or altered ANS control. As markedly impaired cardiac autonomic nerve activity has been described in adult Fontan patients [31], this may negatively affect chronotropic competence on the long term.

In addition, we showed that there was no difference in HR at peak and ANS control between patients who had aortic arch surgery and who did not. A difference could be expected as at time of arch reconstruction there can be transection of the peri-arterial network of cardiac innervation influencing ANS values and chronotropic competence. Our results suggest that the cardiac innervation in these patients is relatively preserved.

We did find a correlation between a higher resting HR and decreased exercise performance. This finding is intriguing as there is concern about sinus node dysfunction in Fontan patients, which is associated with lower exercise tolerance. However, sinus node dysfunction not only includes bradycardia, but also includes a non-sinus rhythm, lower peak HR at exercise or long pauses [32]. Our results are confirmed by a previous study, which showed that sinus bradycardia on its own was not associated with decreased functional status in a group of Fontan patients [33]. A lower resting HR is therefore not necessarily unfavourable in Fontan patients.

A possible explanation could be that a lower resting HR provides mechanical advantages by prolonging diastolic filling time to support the preload dependent Fontan circulation [33]. Conversely, HR at rest could be increased in patients as a compensation for reduced stroke volume to maintain adequate cardiac output. The correlation with a higher HR might, however, also be caused by sympathovagal disbalance, as can be seen in patients with heart failure [34]. Although LF:HF ratio was increased suggesting sympathetic dominance in chronotropic cardiac control, PEP was increased as well suggesting the opposite. Because PEP is also influenced by changes in preload and afterload, it may be a less reliable parameter for sympathetic activity in Fontan patients [35]. On the other hand, the LF:HF ratio as sympathovagal balance remains controversial, as LF reflects a mixture of cardiac vagal and cardiac sympathetic activity [14]. Therefore, more invasive parameters should be considered in future research to validly measure sympathetic activity and sympathovagal balance in Fontan patients.

Besides limiting factors, there are modifiable factors which are positively associated with exercise capacity, such as the ventilatory and skeletal muscle pump [36]. Although not investigated in our study, both factors may augment venous return and are, therefore, important factors in a circulation where a subpulmonary ventricle is lacking. The peripheral muscle pump is the largest contributor to venous return and lean leg mass has been found to be closely correlated with the increase in cardiac index during exercise [36,37]. Regular physical activity and improving leg muscle strengthening may, therefore, result in better exercise performance [38,39]. While many studies have described potential short-term benefits of physical activity, the benefits of long-term physical activity rehabilitation programs from an early age onwards have not yet been investigated.

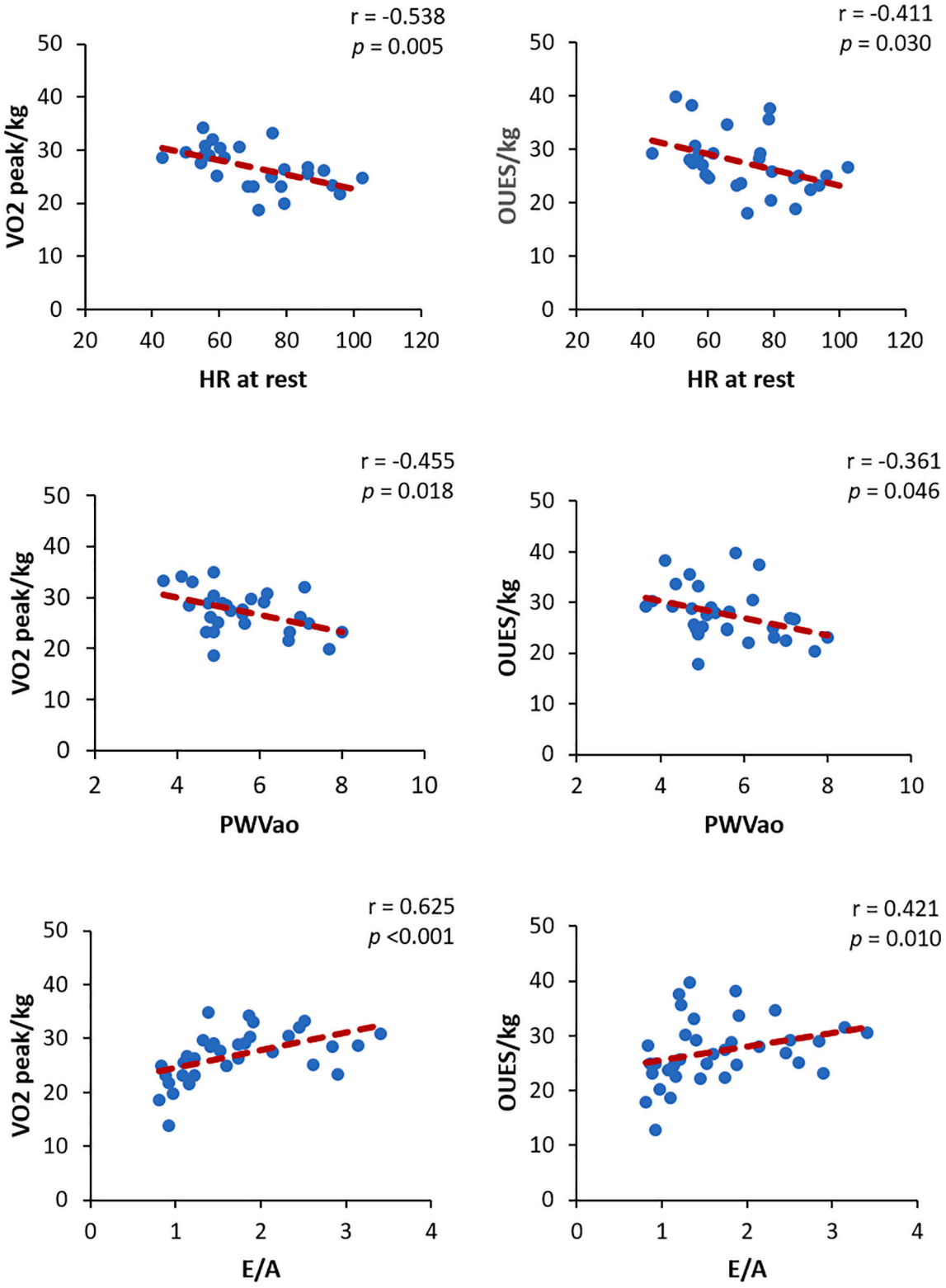

Fig. 1. Correlation between VO_2 peak or OUES and HR, PWVao and E/A.
E/A = ratio of peak early and late diastolic velocity; HR = heart rate; OUES = oxygen uptake efficiency slope; PWVao = aortic pulse wave velocity; VO_2peak = oxygen uptake peak.

5. Limitations

This study is limited by its cross-sectional design. As in all other Fontan studies, the underlying cardiovascular defect is heterogeneous. However, our group was more homogeneous than in most studies including only paediatric patients with an extracardiac conduit and moderate-good systolic ventricular function. Although we did investigate multiple possible cardiovascular factors of exercise limitation, even more other possible factors have been described previously in Fontan patients, such as skeletal muscle mass/strength, lung function and pulmonary vascular resistance. Measuring all possible factors was not feasible, however could have fully completed the understanding of limited exercise performance in this cohort. In addition, echocardiography has its limitations in assessing diastolic function or ventricular dimensions. Finally, as exercise data in the control group is lacking, we were unable to explore the relationship between different cardiovascular parameters and exercise capacity in the normal population. We were therefore unable to provide a context to what to expect when exploring these relationships in the Fontan population and how to interpret our findings in the Fontan population.

6. Conclusion

Paediatric Fontan patients with moderate to good systolic ventricular function have an impaired exercise capacity with a preserved chronotropic competence. In this group of young patients impaired diastolic function, increased aortic stiffness and an increased HR at rest seemed to be important determinants of reduced exercise performance. Given that diastolic function further decreases, and aortic stiffness increases over time, both parameters may contribute to the deterioration of exercise capacity in Fontan patients. Further longitudinal studies investigating the effect of changes in these cardiovascular parameters on exercise deterioration are warranted to determine the prognostic value of these markers in Fontan patients.

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None.

Declaration of competing interest

The authors report no relationships that could be construed as a conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2021.08.012.

References

[1] A.M. Atz, V. Zak, L. Mahony, et al., Longitudinal outcomes of patients with single ventricle after the Fontan procedure, J. Am. Coll. Cardiol. 69 (2017) 2735–2744.
[2] K.N. Pundi, J.N. Johnson, J.A. Dearani, et al., 40-year follow-up after the Fontan operation: long-term outcomes of 1,052 patients, J. Am. Coll. Cardiol. 66 (2015) 1700–1710.
[3] M.H. Gewillig, U.R. Lundström, C. Bull, R.K. Wyse, J.E. Deanfield, Exercise responses in patients with congenital heart disease after Fontan repair: patterns and determinants of performance, J. Am. Coll. Cardiol. 15 (1990) 1424–1432.
[4] Y. Hayama, H. Ohuchi, J. Negishi, et al., Progressive stiffening and relatively slow growth of the dilated ascending aorta in long-term Fontan survivors-serial assessment for 15 years, Int. J. Cardiol. 316 (2020) 87–93.
[5] A. Hebert, A.S. Jensen, U.R. Mikkelsen, et al., Hemodynamic causes of exercise intolerance in Fontan patients, Int. J. Cardiol. 175 (2014) 478–483.
[6] L.C.M. Noortman, E.A. Haapala, T. Takken, Arterial stiffness and its relationship to cardiorespiratory fitness in children and young adults with a Fontan circulation, Pediatr. Cardiol. 40 (2019) 784–791.
[7] H. Ohuchi, Y. Hayama, J. Negishi, et al., Determinants of aortic size and stiffness and the impact on exercise physiology in patients after the Fontan operation, Int. Heart J. 58 (2017) 73–80.
[8] L. Tomkiewicz-Pajak, P. Podolec, L. Drabik, J. Pajak, J. Kolcz, W. Plazak, Single ventricle function and exercise tolerance in adult patients after Fontan operation, Acta Cardiol. 69 (2014) 155–160.
[9] I.G. Horvath, A. Nemeth, Z. Lenkey, et al., Invasive validation of a new oscillometric device (Arteriograph) for measuring augmentation index, central blood pressure and aortic pulse wave velocity, J. Hypertens. 28 (2010) 2068–2075.
[10] C. Terol, V.P. Kamphuis, M.G. Hazekamp, N.A. Blom, Ten Harkel ADJ, Left and right ventricular impairment shortly after correction of tetralogy of fallot, Pediatr. Cardiol. 41 (2020) 1042–1050.
[11] I. Nederend, A.D.J. Ten Harkel, N.A. Blom, G.G. Berntson, E.J.C. de Geus, Impedance cardiography in healthy children and children with congenital heart disease: improving stroke volume assessment, Int. J. Psychophysiol. 120 (2017) 136–147.
[12] E.S. Mezzacappa, R.M. Kelsey, E.S. Katkin, The effects of epinephrine administration on impedance cardiographic measures of cardiovascular function, Int. J. Psychophysiol. 31 (1999) 189–196.
[13] E.J.C. de Geus, P.J. Gianaros, R.C. Brindle, J.R. Jennings, G.G. Berntson, Should heart rate variability be "corrected" for heart rate? Biological, quantitative, and interpretive considerations, Psychophysiology 56 (2019), e13287.
[14] A.D. Goedhart, G. Willemsen, J.H. Houtveen, D.I. Boomsma, E.J. De Geus, Comparing low frequency heart rate variability and preejection period: two sides of a different coin, Psychophysiology 45 (2008) 1086–1090.
[15] B.C. Bongers, E.H. Hulzebos, W.A. Helbing, A. Ten Harkel, M. van Brussel, T. Takken, Response profiles of oxygen uptake efficiency during exercise in healthy children, Eur. J. Prev. Cardiol. 23 (2016) 865–873.
[16] A.D. Ten Harkel, T. Takken, M. Van Osch-Gevers, W.A. Helbing, Normal values for cardiopulmonary exercise testing in children, Eur. J. Cardiovasc. Prev. Rehabil. 18 (2011) 48–54.
[17] American Thoracic SaPACoC, ATS/ACCP statement on cardiopulmonary exercise testing, Am. J. Respir. Crit. Care Med. 167 (2003) 211–277.
[18] C.F. Mylius, W.P. Krijnen, C.P. van der Schans, T. Takken, Peak oxygen uptake reference values for cycle ergometry for the healthy Dutch population: data from the LowLands fitness registry, ERJ Open Res. 5 (2019).
[19] S.M. Paridon, P.D. Mitchell, S.D. Colan, et al., A cross-sectional study of exercise performance during the first 2 decades of life after the Fontan operation, J. Am. Coll. Cardiol. 52 (2008) 99–107.
[20] Y.F. Cheung, D.J. Penny, A.N. Redington, Serial assessment of left ventricular diastolic function after Fontan procedure, Heart 83 (2000) 420–424.
[21] Y. Nakamura, T. Yagihara, K. Kagisaki, I. Hagino, J. Kobayashi, Ventricular performance in long-term survivors after Fontan operation, Ann. Thorac. Surg. 91 (2011) 172–180.
[22] M. Sugimoto, H. Saiki, A. Tamai, et al., Ventricular fibrogenesis activity assessed by serum levels of procollagen type III N-terminal amino peptide during the staged Fontan procedure, J. Thorac. Cardiovasc. Surg. 151 (2016) 1518–1526.
[23] M. Schäfer, A. Younoszai, U. Truong, et al., Influence of aortic stiffness on ventricular function in patients with Fontan circulation, J. Thorac. Cardiovasc. Surg. 157 (2019) 699–707.
[24] B.H. Goldstein, E.M. Urbina, P.R. Khoury, et al., Endothelial function and arterial stiffness relate to functional outcomes in adolescent and young adult Fontan survivors, J. Am. Heart Assoc. 5 (2016).
[25] I. Voges, M. Jerosch-Herold, J. Hedderich, et al., Maladaptive aortic properties in children after palliation of hypoplastic left heart syndrome assessed by cardiovascular magnetic resonance imaging, Circulation 122 (2010) 1068–1076.
[26] H. Senzaki, S. Masutani, H. Ishido, et al., Cardiac rest and reserve function in patients with Fontan circulation, J. Am. Coll. Cardiol. 47 (2006) 2528–2535.
[27] E. Lambert, Y. D'Udekem, M. Cheung, et al., Sympathetic and vascular dysfunction in adult patients with Fontan circulation, Int. J. Cardiol. 167 (2013) 1333–1338.
[28] L. Tomkiewicz-Pajak, H. Dziedzic-Oleksy, J. Pajak, et al., Arterial stiffness in adult patients after Fontan procedure, Cardiovasc. Ultrasound 12 (2014) 15.
[29] F.S. Ridderbos, B.E. Bonenkamp, S.L. Meyer, et al., Pulmonary artery size is associated with functional clinical status in the Fontan circulation, Heart 106 (2020) 233–239.
[30] G. Claessen, A. La Gerche, A. Van De Bruaene, et al., Heart rate reserve in Fontan patients: chronotropic incompetence or hemodynamic limitation? J. Am. Heart Assoc. 8 (2019), e012008.
[31] C.H. Davos, D.P. Francis, M.F. Leenarts, et al., Global impairment of cardiac autonomic nervous activity late after the Fontan operation, Circulation 108 Suppl 1 (2003) Ii180–5.
[32] S.S. Bossers, N. Duppen, L. Kapusta, et al., Comprehensive rhythm evaluation in a large contemporary Fontan population, Eur. J. Cardiothorac. Surg. 48 (2015) 833–840 (discussion 40-1).
[33] A.D. Blaufox, L.A. Sleeper, D.J. Bradley, et al., Functional status, heart rate, and rhythm abnormalities in 521 Fontan patients 6 to 18 years of age, J. Thorac. Cardiovasc. Surg. 136 (2008), 100-7, 7.e1.
[34] D.M. Kaye, J. Lefkovits, G.L. Jennings, P. Bergin, A. Broughton, M.D. Esler, Adverse consequences of high sympathetic nervous activity in the failing human heart, J. Am. Coll. Cardiol. 26 (1995) 1257–1263.
[35] J. Krohova, B. Czippelova, Z. Turianikova, Z. Lazarova, I. Tonhajzerova, M. Javorka, Preejection period as a sympathetic activity index: a role of confounding factors, Physiol. Res. 66 (2017) S265–s75.
[36] K.M. Shafer, J.A. Garcia, T.G. Babb, D.E. Fixler, C.R. Ayers, B.D. Levine, The importance of the muscle and ventilatory blood pumps during exercise in patients without a subpulmonary ventricle (Fontan operation), J. Am. Coll. Cardiol. 60 (2012) 2115–2121.

[37] R. Cordina, Y. d'Udekem, Long-lasting benefits of exercise for those living with a Fontan circulation, Curr. Opin. Cardiol. 34 (2019) 79–86.
[38] D.L. Tran, C. Rodrigues, K. du Plessis, et al., Decline is not inevitable: exercise capacity trajectory in an Australian and New Zealand Fontan cohort, Heart Lung Circ. 30 (2021) 1356–1363.
[39] S.J. Weinreb, K.M. Dodds, D.S. Burstein, et al., End-organ function and exercise performance in patients with Fontan circulation: what characterizes the high performers? J. Am. Heart Assoc. 9 (2020), e016850.