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Fluid responsiveness of ambulatory paediatric patients with a Fontan circulation by passive leg raising

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Abstract

Background: Passive leg raising is used to predict who will benefit from fluid therapy in critically ill patients, including children. Patients with a Fontan circulation may have a different haemodynamic response to a fluid challenge by passive leg raising. *Methods:* The haemodynamic response of 31 paediatric patients with a Fontan circulation from the outpatient clinic (median age 14.0 years) and 35 healthy controls (median age 12.8 years) to passive leg raising was evaluated non-invasively by echocardiography for the assessment of, e.g., velocity time integral across the (neo)aortic valve, blood pressure measurements, and respiration. Participants were considered responders when the velocity time integral increased $\geq$ 10.0%. *Results:* Overall, patients and controls did not differ in the haemodynamic response. Twelve patients (38.7%) and 8 controls (22.9%) were responders, which was not statistically different ($P = 0.22$). Responders in the patient and control group also had a similar echo-estimated velocity time integral increase of + 18.9% and + 15.2%, respectively ($P = 0.91$). There was no difference in echo-estimated velocity time integral change between patient and control non-responders with a decrease of −1.4% and −6.4%, respectively ($P = 0.70$) and no difference in the amount of patients who were negatively affected by passive leg raising, ith a decrease of $\leq$−10.0% in 7 patients (22.6%) and 9 controls (25.7%)($P = 0.77$). *Conclusion:* The haemodynamic response of ambulatory paediatric patients with a Fontan circulation to passive leg raising is like that of healthy controls. Patients who did not respond were similarly affected as healthy controls. Whether the haemodynamic response is different in critically ill patients warrants further investigation. *Trail registration:* The Netherlands National Trial Register (NTR), Trial: NL6415; date of registration 20-07-2017; Trial information: https://www.trialregister.nl/trial/6415.

Introduction

Paediatric and adult critical-care patients often receive fluid therapy to optimise intravascular volume. While fluid administration may improve haemodynamics, excessive administration can result in decreased stroke volume and unwanted side effects.[1] A fluid challenge, such as a passive leg raising manoeuvre, can be used in critical settings to predict fluid responsiveness. Passive leg raising is non-invasive and has proven to be reliable in predicting volume responsiveness in adult and paediatric populations.[2–7] Studies have shown that approximately 50.0% of critically ill paediatric and adult patients with a biventricular circulation increase their cardiac output in response to a fluid challenge.[2–5,8] However, little is known about the responsiveness of patients with a univentricular Fontan circulation. In patients palliated with a Fontan circulation, both caval veins are directly connected to the pulmonary arteries. Venous pressure is required to overcome pulmonary vascular resistance. This means that alterations of fluid balance may have negative consequences for the circulation: while a fluid bolus may result in an increased venous return and a beneficial increase in cardiac output, an increase in end-diastolic pressure might also lead to a decrease in transpulmonary gradient and reduced pulmonary blood flow, negatively affecting cardiac output.[9] Because these patients are often admitted to the ICU after procedures and may need fluid therapy, it is important to understand how they potentially react to a fluid challenge. Therefore, the aim of this study is to evaluate the haemodynamic response of ambulatory paediatric patients with a Fontan circulation to passive leg raising in comparison with healthy controls.

Materials and methods

Patients with a Fontan circulation between 8.0 and 18.0 years of age, who underwent surgery at the Leiden University Medical Centre, were recruited from the outpatient clinic from July 2017 to October 2019. To study a homogenous group, we included patients palliated with an extracardiac conduit and a subjective moderate to good systolic ventricular function. Patients with a pacemaker, an open fenestration, heart failure medications, antiarrhythmics, or diuretics were excluded from the study. Healthy children served as controls. The local ethics committee approved the study, and written informed consent was obtained from all participants or their parents or legal guardians as appropriate.

To test the reaction to passive leg raising between patients and healthy controls, parameters were measured during supine rest and during passive leg raising. Therefore, in this study, we investigated heart rate, blood pressure, velocity time integral across the (neo) aortic valve, stroke volume index, and cardiac index for the haemodynamic response, peak hepatic vein flow, and inferior caval vein collapsibility index for an estimation of change in systemic venous return. Furthermore, since respiration may influence the haemodynamic response, we also evaluated the respiration rate during passive leg raising in this study. Additionally, we also evaluated if there were differences in baseline characteristics between non-responders and responders in patients as well as controls, such as e.g., age, sex, time of passive leg raising test during the day, BSA, BMI, but also age at operation, size of the extracardiac conduit, diastolic and systolic ventricular function, AV-valve regurgitation, and use of medication in patients with a Fontan circulation. As venous obstructions may influence the response to passive leg raising, prior catheterizations of patients were investigated. For this study, subjects started in supine position for baseline measurements, then the lower extremities were raised 45°, and after three minutes all measurements were performed again. Categorisation of responders was defined as $\geq$ 10.0% velocity time integral increase during passive leg raising. Fluid responsiveness is conventionally defined as an increase of at least 10.0–15.0% in stroke volume or cardiac output (or one of its surrogates, such as velocity time integral) with good sensitivity and specificity in adults as well as paediatric subjects.[3,4,6,10,11] In this study, velocity time integral was chosen as accurate measurement of the aortic annulus would be difficult in the Fontan population.

To measure velocity time integral, stroke volume index, cardiac index, hepatic venous flow, and inferior caval vein collapsibility index, transthoracic echocardiography was performed on a Vivid S6/S60 (GE healthcare, Norway). Velocity time integral, a measure of blood flow displacement (cm), was measured by pulse wave Doppler recordings across the (neo)aortic valve, from which, together with the (neo)aortic annulus (cm), stroke volume index (ml/m^2) and cardiac index (L/min/m^2) were calculated as follows: $\text{Stroke volume index} = \frac{\left(\left(\pi * \left(\frac{\text{aortic annulus}}{2}\right)^2\right) * \text{Velocity time integral}\right)}{\text{body surface area}}$ and cardiac index = heart rate* stroke volume index. For patients with two outlets, velocity time integral was measured at the dominant/largest outlet. In addition, Doppler recordings of the hepatic vein were performed to assess peak antegrade flow, and the maximum and minimum diameter of the inferior caval vein was measured by M-mode during a sniff-test, from which we calculated the proportional change, the inferior caval vein collapsibility index. Averages of three consecutive velocity time integral measurements were used for calculations and analysis. All measurements were reviewed independently by two clinicians to ensure accuracy, with discrepancies resolved by discussion. Blood pressure measurements were performed using an oscillometric arteriograph device with the cuff on the left arm (Tensiomed, Hungary). Furthermore, respiration was measured by impedance registration using the VU-ambulatory monitoring system (VU-AMS; VU university, Netherlands, 5fs version).

Analyses were conducted using SPSS statistics (IBM, version 25). To perform reliable inference in the small study group, non-parametric tests were used for all comparisons. Categorical data are reported as numbers with percentages and continuous data are presented as median with first to third quartile [Q1–Q3]. To assess the difference in categorical data, the Chi-square test was used. Differences between patient characteristics, baseline parameters, and percentage change to passive leg raising between the different groups were tested by the Mann–Whitney *U*-test. A *P*-value $\leq$ 0.05 was considered significant.

Results

Thirty-one ambulatory patients with a Fontan circulation and a good functional status (median age 14.0 years) and low median plasma NT-Pro BNP of 86.0 ng/L and 35 controls (median age 12.8 years) were included in the study (Table 1). Nineteen patients had a dominant left ventricle (61.3%), 10 a dominant right ventricle (32.3%), and 2 an indifferent or undefined ventricle (6.5%). Furthermore, seventeen patient had an extracardiac conduit size of 16 mm (54.8%), 13 a size of 18 mm (41.9%), and from 1 patient the size was unknown (3.2%). None of the patients had an interrupted inferior caval vein or an inferior caval vein stent. Prior catheterisations of all patients showed no evidence of venous obstructions, which were also absent during the present study. Twenty-eight patients were in sinus rhythm, and three patients had a dominant junctional rhythm during all tests. Although all patients had a subjective moderate to good systolic ventricular function, global longitudinal strain was slightly lower in Fontan patients compared to healthy controls and Tissue Doppler imaging showed significant lower systolic velocities in patients compared to controls. Furthermore, diastolic ventricular function was lower in patients compared to controls. A total of 14 (45.2%) patients had no AV-valve regurgitation, 11 (35.5%) had mild, 6 (19.4%) had moderate, and none had severe AV-valve regurgitation. All patients received anticoagulation therapy via acetylsalicylic acid ($N = 29$, 93.5%) or a coumarin derivative ($N = 2$, 6.5%).

Table 2 shows the baseline parameters during supine rest and percentage change during passive leg raising between patients and controls. At baseline, patients had a higher systolic blood pressure and lower echo-estimated velocity time integral, peak hepatic vein flow, and inferior caval vein collapsibility index compared to controls. Overall, patients and controls showed a similar response to passive leg raising, except for stroke volume index, which increased in Fontan patients but showed a decrease in controls (+7.6% in patients versus -1.3% in controls, $P = 0.05$).

A total of 12 patients (38.7%) and 8 controls (22.9%) responded to passive leg raising with an increase of $\geq$ 10.0% in echo-estimated velocity time integral, which was not statistically different ($P = 0.22$). In patients, baseline characteristics did not differ between responders and non-responders, including type of main ventricle, age at Glenn and Fontan operation, extracardiac conduit size, and AV-valve regurgitation, while in controls, responders had a higher age, body surface area, and body mass index, were

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Table 1. Patient characteristics

Characteristics	Fontan patients (N = 31)	Controls (N = 35)	*P*-value
Age (years)	14.0 [12.7–16.2]	12.8 [11.1–15.5]	0.18
Males (N,%)	19 (61.3)	18 (51.4)	0.42
BMI (kg/m^2)	19.2 [17.0–21.1]	17.5 [16.1–19.6]	0.07
BSA (m^2)	1.5 [1.4–1.7]	1.4 [1.2–1.7]	0.10
Time of PLR test (HH:MM)	12:57 [11:25–13:47]	13:56 [11:10–14:41]	0.32
Main ventricle (N;%)			
Left	19 (61.3)		
Right	10 (32.3)		
Indifferent	2 (6.5)		
Diagnosis (N;%)			
Tricuspid atresia	9 (29.0)		
Pulmonary atresia	1 (3.2)		
Double inlet left ventricle	5 (16.1)		
Double outlet right ventricle	0 (0.0)		
Hypoplastic left heart syndrome	8 (25.8)		
Unbalanced atrioventricular septal defect	3 (9.7)		
Other	5 (16.1)		
Age at Glenn operation (years)	0.5 [0.4–0.8]		
Age at Fontan operation (years)	3.1 [2.7–3.6]		
Extracardiac Conduit Size (N,%)			
16 mm	19 (57.6)		
18 mm	13 (39.4)		
Unknown*	1 (3.0)		
NT pro-BNP	86.0 [43.2–136.1]		
Systolic ventricular function			
Global longitudinal strain (%)	15.2 [12.5–17.5]	16.6 [14.4–18.2]	0.04
TDI septal S' (cm/s)	4.3 [3.0–5.0]	8.0 [7.0–8.3]	**<0.001**
TDI lateral free wall S' (cm/s)	5.9 [4.7–7.1]	10.7 [9.3–12.3]	**<0.001**
Diastolic ventricular function			
E/A	1.5 [1.1–2.1]	2.3 [2.0–2.7]	**<0.001**
E/E'	8.2 [6.0–12.6]	5.7 [5.1–7.1]	**0.002**
AV-valve regurgitation (N,%)			
No	14 (45.2)		
Mild	11 (35.5)		
Moderate	6 (19.4)		
Severe	0 (0.0)		
Cardiac medications (N,%)			
Acteylsalicylic acid	29 (93.5)		
Coumarin derivative	2 (6.5)		

Data expressed as number (%) or median [Q1-Q3]. *The conduit size of for the 33rd patient was unknown. E/A = ratio of peak early and late diastolic velocity; E/E' = ratio of peak early conventional and Tissue Doppler diastolic velocity; BMI = Body mass index; BSA = body surface area; NT-pro BNP = N-terminal pro brain natriuretic peptide; PLR = Passive leg raising; S'= peak systolic TDI velocity.

predominantly female, and had a better diastolic function measured by E/E' compared to the non-responders (Table 3).

The parameters of responders and non-responders of patients and controls during supine rest and percentage change during passive leg raising are depicted in Table 4. Overall, baseline characteristics and reaction to passive leg raising did not differ much. At baseline, inferior caval vein collapsibility index of Fontan responders were higher compared to Fontan non-responders and during passive leg raising the inferior caval vein collapsibility index decreased in Fontan responders, while in Fontan non-responders it did not change. In contrast, control responders had a lower inferior caval vein collapsibility index compared to non-responders; however, there was no difference in percentage change during passive leg raising between both groups. Echo-estimated velocity time integral and stroke volume index increased significantly during passive leg raising in Fontan as well as control responders, while echo-estimated cardiac index only increased more in control responders compared to control non-responders. In reaction to passive leg raising, echo-estimated velocity time integral increased similarly in both responder groups (+18.9% in patients versus + 15.2% in controls; $P = 0.91$). Change of echo-estimated velocity time integral in Fontan and control non-responders did also not differ, with −1.4% and −6.4%, respectively ($P = 0.70$). Furthermore, there was no difference in the number of subjects who were negatively affected by passive leg raising, with a decrease of ≤ −10% in echo-estimated velocity time integral in 7 patients (22.6%) and 9 controls (25.7%; $P = 0.77$).

Discussion

Our study demonstrates that ambulatory paediatric patients with a Fontan circulation respond similarly to a fluid challenge by passive leg raising as healthy controls. Furthermore, patients who did not respond were similarly affected by passive leg raising as healthy controls.

The proportion of responders in both groups, approximately 30.0%, was lower as compared to previous paediatric studies performed in biventricular patients, where around 50.0% were responders.[3,4] However, these studies have only been conducted in critical care settings where patients are more likely to be fluid depleted. Passive leg raising studies in healthy subjects have so far only been performed in adults and have shown a fluid

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Table 2. Cardiovascular parameters during supine rest and the percentage change during passive leg raising in fontan patients versus healthy controls

	Fontan patients		Healthy controls		*P*-value Supine rest F versus C	*P*-value % Change F versus C
	Supine rest	Percentage change	Supine rest	Percentage change		
Hemodynamics						
Heart rate (bpm)	64.9 [58.0–89.4]	−5.5 [−12.4–1.9]	69.5 [64.9–76.9]	−4.5 [−12.1–3.1]	0.73	0.56
VTI (cm)	15.9 [13.5–20.8]	+ 5.5 [−3.1–14.4]	21.1 [18.9–23.3]	−0.5 [−10.6–8.3]	<**0.001**	0.18
SVI (ml/m^2)	50.1 [44.3–54.9]	+ 7.6 [−1.4–18.6]	47.1 [41.0–52.5]	−1.3 [−10.6–8.1]	0.47	**0.05**
CI (L/min/m^2)	3.2 [2.9–3.8]	−0.6 [−9.7–5.3]	3.4 [2.8–3.7]	−3.8 [−13.6–8.5]	0.99	0.53
Systolic BP (mmHg)	120.0 [114.3–123.5]	0.0 [−3.5–2.6]	108.0 [102.8–115.3]	−0.4 [−1.9–2.2]	<**0.001**	0.91
Diastolic BP (mmHg)	65.5 [60.0–71.0]	+ 0.6 [−2.9–6.8]	61.5 [72.8–83.0]	−0.7 [−6.6–8.0]	0.09	0.52
Systemic venous return						
Peak hepatic flow (m/s)	0.25 [0.21–0.30]	−5.6 [−17.9–12.2]	0.46 [0.34–0.52]	−2.2 [−16.2–8.3]	<**0.001**	0.97
IVC collapsibility index (%)	33.0 [23.4–54.0]	−0.6 [−13.5–10.9]	72.6 [59.7–85.6	−3.4 [−13.2–5.6]	<**0.001**	0.50
Respiration						
Respiration (breaths/min)	19.2 [15.7–20.4]	−0.7 [−6.1–7.0]	18.1 [16.0–20.9]	−0.9 [−5.6–4.7]	0.81	0.70

Data expressed as median [Q1-Q3]. *P*-value supine rest F versus C and % Change F versus C for differences in supine rest and percentage change between Fontan patients and healthy controls.BP = Blood pressure; CI = Cardiac index; IVC = inferior caval vein; SVI = stroke volume index; VTI = velocity time integral.

Table 3. Baseline characteristics of responders and non-responders of fontan patients and healthy controls

	Fontan patients			Healthy controls		
	Responders *(N = 12)*	Non-responders *(N = 19)*	*P*-value	Responders *(N = 8)*	Non-responders *(N = 27)*	*P*-value
Age (years)	13.6 [11.9–16.0]	14.1 [12.7–17.2]	0.44	15.3 [14.4–17.4]	11.7 [10.6–15.3]	**0.007**
Males (N,%)	6 (50.0)	13 (68.4)	0.31	1 (12.5)	17 (63.0)	**0.01**
BMI (kg/m^2)	18.1 [16.5–20.1]	20.0 [17.6–22.0]	0.11	19.0 [17.7–21.0]	17.0 [15.9–18.0]	**0.04**
BSA (m^2)	1.5 [1.4–1.6]	1.7 [1.4–1.8]	0.09	1.6 [1.5–1.7]	1.4 [1.2–1.7]	**0.03**
Time of PLR test (HH:MM)	13:42 [11:25–14:08]	12:29 [11:25–13:37]	0.46	14:23 [11:42–15:28]	13:28 [11:05–14:29]	0.21
Main ventricle (N;%)			0.59			
Left	6 (50.0)	13 (68.4)				
Right	5 (41.7)	5 (26.3)				
Indifferent	1 (8.3)	1 (5.3)				
Age at Glenn operation (years)	0.5 [0.4–0.8]	0.5 [0.4–0.8]	0.80			
Age at Fontan operation (years)	3.2 [2.6–3.8]	3.0 [2.7–3.4]	0.62			
Extracardiac Conduit Size (N,%)*			0.86			
16 mm	6 (54.5)	11 (57.9)				
18 mm	5 (45.5)	8 (42.1)				
NT pro-BNP	123.3 [42.5–270.6]	79.3 [55.4–110.3]	0.31			
Systolic ventricular function						
Global longitudinal strain (%)	14.5 [12.1–16.2]	15.2 [13.1–17.6]	0.49	16.0 [13.4–17.5]	17.3 [14.8–19.0]	0.15
TDI septal S' (cm/s)	4.0 [2.3–4.7]	4.7 [3.8–5.3]	0.10	8.2 [7.8–8.9]	7.7 [7.0–8.3]	0.14
TDI lateral free wall S' (cm/s)	5.0 [4.4–6.9]	6.0 [5.3–7.4]	0.47	11.5 [9.8–12.8]	10.7 [9.2–12.0]	0.33
Diastolic ventricular function						
E/A	1.4 [1.2–2.4]	1.7 [1.0–1.9]	0.89	2.6 [1.9–2.7]	2.2 [2.0–2.7]	0.44
E/E'	8.0 [6.7–13.5]	8.7 [5.3–12.6]	0.83	5.2 [4.3–6.0]	6.3 [5.3–7.2]	**0.05**

(*Continued*)

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Table 3. (*Continued*)

	Fontan patients			Healthy controls		
	Responders (*N = 12*)	Non-responders (*N = 19*)	*P*-value	Responders (*N = 8*)	Non-responders (*N = 27*)	*P*-value
AV-valve regurgitation (N,%)			0.85			
No	5 (41.7)	9 (47.4)				
Mild	5 (41.7)	6 (31.6)				
Moderate	2 (16.7)	4 (21.1)				
Severe	0 (0.0)	0 (0.0)				

Data expressed as number (%) or median [Q1-Q3]. * Of 1 patient the conduit size is unknown, therefore the analysis was performed in 32 patients. P-value for differences between responders and non-responders per group (Fontan patients and Healthy controls. See Table 1 for previously used abbreviations.

Table 4. Cardiovascular parameters during supine rest and percentage change during passive leg raising between responders and non-responders in fontan patients and healthy controls

	Responders		Non-responders		*P*-value Supine rest Res versus Non-res	*P*-value % Change Res versus Non-res
	Supine rest	Percentage change	Supine rest	Percentage change		
Fontan patients	*N = 12*		*N = 19*			
Heart rate (bpm)	77.1 [60.9–88.8]	−10.1 [−17.6–1.6]	63.1 [56.7–91.4]	−4.3 [−11.4–2.0]	0.35	0.35
VTI (cm)	15.3 [13.1–17.3]	+ 18.9 [13.3–26.2}	16.9 [14.2–21.0]	−1.4 [−13.4–4.6]	0.29	<**0.001**
SVI (ml/min/ m^2)	46.1 [42.3–52.3]	+ 18.6 [13.6–23.9]	53.4 [43.8–55.6]	−0.1 [−12.6–5.5]	0.28	<**0.001**
CI (L/min/m^2)	3.3 [3.0–4.2]	+ 3.4 [−8.2–20.5]	3.0 [2.8–3.5]	−2.8 [−14.9–0.13]	0.45	0.18
Systolic BP (mmHg)	120.0 [115.0–122.0]	+ 1.7 [−1.6–6.3]	120.0 [112.0–125.0]	−0.8 [−3.8–2.4]	0.77	0.35
Diastolic BP (mmHg)	65.0 [56.0–72.0]	0.0 [−2.7–5.4]	66.0 [60.0–71.0]	+ 1.3 [−3.1–8.3]	0.71	0.83
Peak hepatic flow (m/s)	0.25 [0.21–0.26]	0.0 [−13.5–12.2]	0.26 [0.22–0.32]	−6.8 [−22.5–10.2]	0.27	0.22
IVC collapsibility index (%)	40.5 [35.5–62.3]	−7.8 [−24.9–0.7]	29.6 [20.9–38.1]	+ 1.9 [−9.6–22.1]	**0.02**	**0.04**
Respiration (breaths/min)	19.2 [16.3–21.7]	−0.01 [−7.4–6.0]	19.2 [15.4–20.2]	−1.5 [−5.1–7.7]	0.60	0.86
Controls	*N = 8*		*N = 27*			
Heart rate (bpm)	67.1 [52.2–82.0]	−9.1 [−13.3–4.1]	70.2 [66.1–76.2]	−2.6 [−11.7–4.9]	0.52	0.12
VTI (cm)	20.6 [16.0–22.8]	+ 15.2 [13.5–26.2]	21.1 [18.9–23.6]	−6.4 [−12.4–3.0]	0.38	<**0.001**
SVI (ml/min/ m^2)	42.9 [33.9–55.3]	+ 15.0 [13.1–28.1]	47.8 [42.3–51.6]	−6.4 [−12.4–3.0]	0.34	<**0.004**
CI (L/min/m^2)	2.7 [2.3–3.7]	+ 8.2 [−0.5–19.9]	3.4 [3.1–3.7]	−7.6 [−14.5–7.3]	0.08	**0.005**
Systolic BP (mmHg)	116.5 [108.5–119.8]	+ 0.5 [−3.3–4.3]	106.0 [102.0–111.0]	−0.9 [−1.9–2.2]	**0.04**	0.49
Diastolic BP (mmHg)	65.5 [55.8–71.8]	+ 3.0 [−6.0–13.5]	61.0 [55.0–67.0]	−2.3 [−6.9–7.0]	0.44	0.44
Peak hepatic flow (m/s)	0.40 [0.31–0.48]	−2.1 [−16.0–8.3]	0.47 [0.34–0.53]	−2.4 [−17.1–9.2]	0.31	0.81
IVC collapsibility index (%)	59.4 [37.9–68.3]	+ 5.1 [−10.1–34.1]	74.3 [62.2–87.1]	−6.0 [−13.4–1.6]	**0.003**	0.07
Respiration (breaths/min)	18.0 [16.1–21.7]	−0.5 [−5.7–4.3]	18.1 [16.0–20.8]	−1.4 [−5.6–4.7]	0.86	0.95

Data expressed as median [Q1-Q3]. *P*-value supine rest Res versus Non-res and % Change Res versus Non-res for differences in supine rest and percentage change between responders and non-responders in Fontan patients and healthy controls. BP = Blood pressure; CI = Cardiac index; IVC = inferior caval vein; SVI = stroke volume index; VTI = velocity time integral.

responsiveness of about 45.0%.[10,12,13] The response rate in our healthy subjects was lower compared to these adult studies and may be due to the fact that adults have a larger blood pool in the lower extremities compared to paediatric subjects.[14]

There was no difference in the response of echo-estimated stroke volume index between patients and controls to passive leg raising. It might be expected that the increased venous pressure in patients with a Fontan circulation along with venous congestion can result in a reduced response to passive leg raising. On the other hand, patient non-responders were not more negatively affected by passive leg raising than controls, which is important to notice as these patients often receive fluid therapy postoperatively in the ICU. In patients, responders had a higher inferior caval vein collapsibility index at baseline, which decreased during passive leg raising. However, in the non-responders group, the index did not change. This differs from the control group but can be explained by

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the fact that the Fontan circulation requires venous pressure to overcome pulmonary vascular resistance. While the inferior caval vein collapsibility index may be useful in patients to predict fluid response, the effect of fluid loading cannot always be predicted in advance. Although a Fontan circulation is highly dependent on an adequate venous return,[15] it was shown that in response to a fluid challenge during catheterisation most patients with a Fontan circulation increased their cardiac output, but some showed a substantial decrease in transpulmonary gradient.[9] A fluid challenge by passive leg raising prior to fluid administration is thus useful to avoid adverse effects of an unnecessary fluid bolus. The use of a passive leg raising test in the intensive care unit can be very helpful to evaluate hemodynamic status and prevent hypo- or hypervolemia.

This study has some limitations. Although no significant baseline differences were found between dominant RV and LV patients,[16] subtle physiological differences cannot be entirely ruled out. However, the small sample size limits further subgroup analyses. We included paediatric patients who were not critically ill, signifying that these results cannot be directly translated to critically ill patients on the ICU. However, by studying a more homogeneous group, we were able to determine the reaction to a fluid challenge in patients with a well-functioning Fontan circulation. Furthermore, previous studies have shown that passive leg raising reflects the effects of fluid administration;[2–5] however, the predictability of fluid responsiveness in patients with a Fontan circulation may be different because of their increased venous pressure and dependence on adequate venous return. Furthermore, we also did not investigate possible factors that may have influenced the volume status of participants, such as venous insufficiency and timing of the test in relation to the menstrual cycle of the female participants. At last, measuring cardiac output by echocardiography is less reliable than other known measurements, such as invasive techniques like catheterisation. Furthermore, validation of echocardiography is limited in children as well as in patients with CHDs.

In conclusion, ambulant paediatric patients with a Fontan circulation have a similar haemodynamic response to passive leg raising as healthy controls. Furthermore, patients who did not respond were not more negatively affected by passive leg raising than healthy controls. Whether the haemodynamic response is different in critically ill patients with a Fontan circulation warrants further investigation.

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Ethical standard. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation of the Netherlands and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the Medical Ethics Committee of the Leiden University Medical Centre.

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