Haemodynamics in children with a Fontan circulation: effects of afterload reduction

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Chapter 5

Fluid responsiveness of ambulant paediatric Fontan patients by passive leg raising

Under review Cardiology in the Young

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Abstract

Background

Passive leg raising (PLR) 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 hemodynamic response to a fluid challenge by PLR.

Methods

The hemodynamic response of 35 paediatric Fontan patients from the outpatient clinic (median age 14.0 years) and 35 healthy controls (median age 12.8 years) to PLR was evaluated non-invasively by echocardiography for assessment of e.g., velocity time integral (VTI) across the (neo)aortic valve, blood pressure measurements and respiration. Participants were considered responders when the VTI increased by ≥10%.

Results

Overall, Fontan patients and controls did not differ in the hemodynamic response to PLR. Twelve patients (36%) in the Fontan group and 8 controls (23%) were responders, which was not statistically different (*P*=0.222). Responders in the Fontan and control group also had a similar VTI increase of +18.9% and +15.2% respectively (*P*=0.910). There was no difference in VTI change between Fontan and control non-responders with a decrease of -1.4% and -6.4% respectively (*P*=0.655) and no difference in the amount of patients who were negatively affected by PLR, with a decrease of ≤-10% in VTI in 7 patients (33%) en 9 controls (33%)(*P*=1.00).

Conclusion

The hemodynamic response of ambulant paediatric Fontan patients to PLR is similar to that of healthy controls. Fontan patients who did not respond to PLR were similarly affected as healthy controls. Whether the hemodynamic response is different in critically-ill Fontan patients warrants further investigation.

Introduction

Paediatric and adult critical-care patients often receive fluid therapy to optimize 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 (PLR) manoeuvre, can be used in critical settings to predict fluid responsiveness. PLR is non-invasive, reversible and has proven to be reliable in predicting volume responsiveness in adult and paediatric populations (2-7).

Studies have shown that approximately 50% 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 Fontan patients with a univentricular circulation. In Fontan patients 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 preload 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 Fontan patients are often admitted to the intensive care unit 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 hemodynamic response of ambulant paediatric Fontan patients to PLR in comparison with healthy controls.

Methods

Patients between 8 and 18 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 and an open fenestration 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 PLR between patients and healthy controls, parameters were measured during supine rest and during PLR. Therefore, in this study, we investigated heart rate, blood pressure, velocity time integral (VTI) across the (neo) aortic valve, stroke volume index (SVI) and cardiac index (CI) for the hemodynamic response, peak hepatic vein flow and inferior vena cava (IVC) collapsibility index for an estimation of change in systemic venous return. Furthermore, since respiration may influence the hemodynamic response, we also evaluated the respiration rate during PLR in this study. Furthermore, we also evaluated if there were differences in baseline characteristics between non-responders and responders in Fontan patients as well as controls, such as e.g., age, sex, BSA, BMI, but also age at operation and diastolic and systolic ventricular function.

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. Categorization of responders was defined as ≥10% VTI increase during PLR. Fluid responsiveness is conventionally defined as an increase of at least 10-15% in stroke volume or cardiac output (or one of its surrogates, such as VTI) with good sensitivity and specificity in adults as well as paediatric subjects (3, 4, 6, 10, 11). In this study, VTI was chosen as accurate measurement of the aortic annulus would be difficult in the Fontan population.

To measure VTI, SVI, CI, hepatic venous flow and IVC collapsibility index, transthoracic echocardiography was performed on a Vivid S6/S60 (GE healthcare, Norway). VTI, 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), SVI (ml/m^2) and CI (L/min/m^2) were calculated as follows: $SVI = \frac{\left(\left(\pi * \left(\frac{\text{aortic annulus}}{2}\right)^2\right) * \text{VTI}\right)}{\text{body surface area}}$ and CI=heart rate*SVI.

In addition, Doppler recordings of the hepatic vein were performed to assess peak antegrade flow and the maximum and minimum diameter of the inferior vena cava (IVC) was measured by M-mode during a sniff-test, from which we calculated the proportional change, the IVC collapsibility index. Averages of three consecutive VTI measurements were used for calculations and analysis.

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 PLR between the different groups were tested by the Mann-Whitney *U*-test. A P-value ≤0.05 was considered significant.

Results

Thirty-five ambulant Fontan patients with a good functional status (median age 14.0 years) and low median plasma NT-Pro BNP of 79.3ng/L and 35 controls (median age 12.8 years) were included in the study (Table 1). Nineteen Fontan patients had a dominant left ventricle (58%), 11 a dominant right ventricle (33%) and 3 an indifferent or undefined ventricle (9%). Although all Fontan patients had a subjective moderate to good systolic ventricular function and a comparable global longitudinal strain compared to healthy controls on echocardiography, Tissue Doppler imaging showed lower systolic velocities in Fontan patients compared to controls. Furthermore, diastolic ventricular function was lower in Fontan patients compared to controls (Table 1).

Table 2 shows the baseline parameters during supine rest and percentage change during PLR between Fontan patients and controls. At baseline, patients had a higher systolic blood pressure and lower VTI, peak hepatic vein flow and IVC collapsibility index compared to controls. Overall, Fontan patients and controls showed similar response to PLR with no difference in percentage change of all parameters.

Table 1. Patient Characteristics

Characteristics	Fontan patients (N=33)	Controls (N=35)	*P*-value
Age (years)	14.0 [12.7-16.5]	12.8 [11.1-15.5]	0.187
Males (N,%)	21 (63.64)	18 (51.4)	0.309
BMI (kg/m^2)	19.2 {17.1-21.0]	17.5 [16.1-19.6]	0.070
BSA (m^2)	1.5 [1.4-1.7]	1.4 [1.2-1.6]	0.103
Main ventricle (N;%)			
Left	19 (57.6)		
Right	11 (33.3)		
Indifferent	3 (9.1)		
Age at Glenn operation (years)	0.5 [0.4-0.7]		
Age at Fontan operation (years)	3.1 [2.7-3.5]		
NT pro-BNP	79.3 [44.4-126.5]		
Systolic ventricular function			
Global longitudinal strain (%)	15.4 [12.8-17.6]	16.6 [14.4-18.2]	0.084
TDI septal S' (cm/s)	4.3 [3.1-5.0]	8.0 [7.0-8.3]	<0.001
TDI lateral free wall S' (cm/s)	5.9 [4.7-7.3]	10.7 [9.3-12.3]	<0.001
Diastolic ventricular function			
E/A	1.5 [1.1-2.2]	2.3 [2.0-2.7]	0.001
E/E'	8.2 [6.2-12.4]	5.7 [5.1-7.1]	<0.001

Data expressed as n (%), mean (±SD), and median [Q1-Q3].
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; S'= peak systolic TDI velocity.

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

	Fontan patients		Healthy controls	
	Supine rest	**Percentage change**	**Supine rest**	**Percentage change**
Haemodynamics				
Heart rate (bpm)	64.9 [57.9-89.5]	-5.1 [-12.0-1.4]	69.5 [64.9-76.9]	-4.5 [-12.1-3.1]
VTI (cm)	15.9 [13.8-20.9]	+4.6 [-4.5-14.4]	21.1 [18.9-23.3] *	-0.5 [-10.6-8.3]
SVI (ml/min/ m^2)	50.0 [43.6-54.8]	+6.5 [-1.3-17.6]	47.1 [41.0-52.5]	-1.3 [-10.6-8.1]
CI (L/min/m^2)	3.3 [2.9-4.0]	-0.7 [-9.2-4.9]	3.4 [2.8-3.7]	-3.8 [-13.6-8.5]
Systolic BP (mmHg)	120.0 [115.0-125.5]	0.0 [-3.7-2.5]	108.0 [102.8-115.3] **	-0.4 [-1.9-2.2]
Diastolic BP (mmHg)	65.5 [60.3-71.0]	+0.6 [-3.0-6.5]	61.5 [72.8-83.0]	-0.7 [-6.6-8.0]
Systemic venous return				
Peak hepatic flow (m/s)	0.25 [0.21-0.29]	-5.6 [-16.9-12.2]	0.46 [0.34-0.52] **	-2.2 [-16.2-8.3]
IVC collapsibility index (%)	35.1 [24.5-47.7]	-0.6 [-11.6-13.2]	72.6 [59.7-85.6 **	-3.4 [-13.2-5.6]
Respiration				
Respiration (breaths/min)	19.2 [15.9-20.5]	-0.7 [-6.5-6.9]	18.1 [16.0-20.9]	-0.9 [-5.6-4.7]

Data expressed as mean (±SD), and median [Q1-Q3].

BP= Blood pressure; CI= Cardiac index; IVC= inferior vena cava; SVI= stroke volume index; VTI= velocity time integral.

* *P*-value <0.01 for differences in supine rest and percentage change between Fontan patients and healthy controls.

** *P*- value <0.001.

A total of 12 patients (36%) and 8 controls (23%) responded to PLR with an increase of ≥10%, which was not statistically different (*P*=0.222). In patients, baseline characteristics did not differ between responders and non-responders, including type of main ventricle, age at Glenn and Fontan operation, while in controls, responders had a higher age, body surface area and body mass index, and were predominantly female compared to the non-responders (Table 3).

The parameters of responders and non-responders of Fontan patients and controls during supine rest and percentage change during PLR are depicted in Table 4. Overall, baseline characteristics and reaction to PLR did not differ much. At baseline, IVC collapsibility index of Fontan responders were higher compared to Fontan non-responders and during PLR the IVC collapsibility index decreased in Fontan responders, while in Fontan non-responders it did not change. In contrast, control responders had a lower IVC collapsibility index compared to non-responders, however, there was no difference in percentage change during PLR between both groups. VTI and SVI increased significantly during PLR in Fontan as well as control responders, while CI only increased more in control responders compared to control non-responders. In reaction to PLR, VTI increased similarly in both responder groups (+18.9% in patients versus +15.2% in controls; *P*=0.910). Change of VTI in Fontan and control non-responders did also not differ, with -1.4% and -6.4% respectively (*P*=0.655). Furthermore, there was no difference in the number of patients who were negatively affected by PLR, with a decrease of ≤-10% in VTI in 7 patients (33%) and 9 controls (33%; *P*=1.00).

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=21)*	**Responders** *(N=8)*	**Non-responders** *(N=27)*
Age (years)	13.6 [11.9-16.0]	14.1 [12.7-17.2]	15.3 [14.4-17.4]	11.7 [10.6-15.3] **
Males (N,%)	6 (50.0)	15 (71.4)	1 (12.5)	17 (63.0) *
BMI (kg/m^2)	18.1 [16.5-20.1]	19.8 [17.5-21.8]	19.0 [17.7-21.0]	17.0 [15.9-18.0] *
BSA (m^2)	1.5 [1.4-1.6]	1.7 [1.4-1.8]	1.6 [1.5-1.7]	1.4 [1.2-1.7] *
Main ventricle (N;%)				
Left	6 (50.0)	13 (61.9)		
Right	5 (41.7)	6 (28.6)		
Indifferent	1 (8.3)	2 (9.5)		
Age at Glenn operation (years)	0.51 [0.37-0.75]	0.50 [0.38-0.73]		
Age at Fontan operation (years)	3.2 [2.6-3.8]	3.0 [2.7-3.4]		
NT pro-BNP	123.3 [42.5-270.6]	78.4 [50.5-105.4]		
Systolic ventricular function				
Global longitudinal strain (%)	13.6 [12.0-16.4]	15.2 [13.0-17.2]	16.0 [13.4-17.5]	17.0 [14.6-18.8]
TDI septal S' (cm/s)	4.0 [3.0-6.0]	4.7 [3.7-5.3]	8.2 [7.8-8.9]	7.8 [7.0-8.3]
TDI lateral free wall S' (cm/s)	6.7 [5.0-7.0]	6.0 [5.7-8.0]	11.5 [9.8-12.8]	10.8 [9.3-12.0]
Diastolic ventricular function				
E/A	1.4 [1.2-2.9]	1.7 [1.0-1.9]	2.6 [1.9-2.7]	2.2 [1.9-2.7]
E/E'	7.9 [4.8-8.4]	6.8 [5.2-9.2]	5.2 [4.3-6.0]	5.9 [5.3-7.1]

Data expressed as mean (±SD), and median [Q1-Q3].

See Table 1 for previously used abbreviations.

* *P*-value <0.05 for differences between responders and non-responders per group.

** *P*-value <0.01.

*** *P*-value <0.001.

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	
	Supine rest	**Percentage change**	**Supine rest**	**Percentage change**
Fontan patients	*N=12*		*N=21*	
Heart rate (bpm)	77.1 [60.9-88.8]	-10.1 [-17.6-1.6]	63.1 [56.5-92.8]	-4.2 [-10.6-1.4]
VTI (cm)	15.3 [13.1-17.3]	+18.9 [13.3-26.2}	16.9 [14.2-22.1]	-1.4 [-12.9-4.1] ***
SVI (ml/min/ m^2)	46.1 [42.3-52.3]	+18.6 [13.6-23.9]	52.3 [43.4-55.4]	-0.9 [-12.0-5.5] ***
CI (L/min/m^2)	3.3 [3.0-4.2]	+3.4 [-8.2-20.5]	3.0 [2.9-3.8]	-4.7 [-10.9- -0.5]
Systolic BP (mmHg)	120.0 [115.0-122.0]	+1.7 [-1.6-6.3]	120.0 [113.5-125.0]	-0.8 [-4.5-2.2]
Diastolic BP (mmHg)	65.0 [56.0-72.0]	0.0 [-2.7-5.4]	66.0 [60.5-71.0]	+1.3 [-5.7-8.3]
Peak hepatic flow (m/s)	0.25 [0.21-0.26]	0.0 [-13.5-12.2]	0.26 [0.21-0.31]	-6.8 [-21.0-10.3]
IVC collapsibility index (%)	40.5 [35.5-62.3]	-7.8 [24.9-0.7]	30.3 [20.9-40.3] *	+1.9 [-8.7-19.5] *
Respiration (breaths/min)	19.2 [16.3-21.7]	-0.01 [-7.4-6.0]	19.2 [15.7-20.3]	-1.5 [-6.2-7.2]
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]
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] ***
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] ***
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] **
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]
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]
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]
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]
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]

Data expressed as mean (±SD), and median [Q1-Q3].

BP= Blood pressure; CI= Cardiac index; IVC= inferior vena cava; SVI= stroke volume index; VTI= velocity time integral.

* *P*-value: ≤0.05 for differences in supine rest and percentage change between responders and non-responders in Fontan patients and healthy controls.

** *P*-value <0.01.

*** *P*-value <0.001.

Discussion

Our study demonstrates that ambulant paediatric Fontan patients respond similarly to a fluid challenge by PLR as healthy controls. Furthermore, Fontan patients who did not respond were similarly affected by PLR as healthy controls.

The proportion of responders in both groups, approximately 30%, was lower as compared to previous paediatric studies performed in biventricular patients, where around 50% were responders (3, 4). However, these studies have only been conducted in critical care settings where patients are more likely to be fluid depleted. PLR studies in healthy subjects have so far only been performed in adults and have shown a fluid responsiveness of about 45% (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 SVI between Fontan patients and controls to PLR. It might be expected that the increased venous pressure in Fontan patients along with venous congestion can result in a reduced response to PLR. On the other hand, Fontan non-responders were not more negatively affected by PLR than controls, which is important to notice as Fontan patients often receive fluid therapy post-operatively in the intensive care unit. In Fontan patients, responders had a higher IVC collapsibility index at baseline and the index decreased during PLR, while in the responders group it did not change. This difference from the control group but can be explained by the fact that the Fontan circulation is a preload dependent circulation requiring venous pressure to overcome pulmonary vascular resistance. While the IVC Collapsibility Index may be useful in Fontan 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 preload (15), it was shown that in response to a fluid challenge during catheterization most Fontan patients increased their cardiac output, but some showed a substantial decrease in transpulmonary gradient (9). A fluid challenge by PLR prior to fluid administration is thus useful to avoid adverse effects of an unnecessary fluid bolus. Because Fontan patients exhibit a critical fluid balance, the use of a PLR test in the intensive care unit can be very helpful to evaluate hemodynamic status and prevent hypo- or hypervolemia.

This study has some limitations. We included paediatric patients who were not critically-ill, signifying that these results cannot be directly translated to critically-ill patients on the intensive care unit. 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 PLR reflects the effects of fluid administration (2-5), however, the predictability of fluid responsiveness in Fontan patients may be different because of their increased venous pressure and dependence on adequate preload.

Conclusion

Paediatric Fontan patients have a similar hemodynamic response to PLR as healthy controls. Furthermore, patients who did not respond were not more negatively affected by PLR than healthy controls. Whether the hemodynamic response is different in critically-ill Fontan patients warrants further investigation. However, the use of a PLR test in the intensive care unit can be very helpful to evaluate hemodynamic status and to prevent hypo- or hypervolemia, especially in Fontan patients who exhibit a delicate fluid balance.

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