Systolic Function in the Fontan Circulation Is Exercise, but Not Preload, Recruitable

Simone Goa Diab, MD, Assami Rösner, MD, PhD, Gaute Døhlen, MD, PhD, Henrik Brun, MD, PhD, Guro Grindheim, MD, PhD, Kanyalak Vithessonthi, MD, Mark K. Friedberg, MD, PhD, Henrik Holmstrøm, MD, PhD, and Thomas Möller, MD, PhD, *Oslo and Tromsø, Norway; Bangkok, Thailand; and Toronto, Ontario, Canada*

Background: Fontan circulatory failure with impaired systolic function is well documented; however, its mechanisms are not fully understood. The aim of this study was to explore myocardial functional reserve in adolescent patients with Fontan circulation in response to exercise or acute preload increase.

Methods: The study included 32 patients (median age, 16.7 years; range, 15.4–17.9 years; 12 female patients) with Fontan circulation. Echocardiographic imaging was performed during exercise using a recumbent cycle ergometer and during heart catheterization with a rapid infusion of 0.9% saline infusion at 5 mL/kg body weight. Myocardial peak longitudinal strain (LS) was measured in a four-chamber view during specific time intervals before, during, and after exercise (LS_{stress}) and volume load (LS_{cath}). During catheterization, central venous pressure and ventricular end-diastolic pressure were simultaneously recorded. A control group of 16 healthy individuals participated in the exercise test.

Results: Mean LS_{stress} was less negative for patients than for control subjects ($P \leq .001$ at all stages); however, it significantly improved from $-18.4 \pm 5.5\%$ at baseline to $-22.0 \pm 6.5\%$ ($P = .004$) at maximal loading. LS_{stress} at maximal loading did not correlate with changes in heart rate. During catheterization, mean LS_{cath} was $-19.6 \pm 6.0\%$ at baseline and did not improve significantly at 1.00 to 2.00 minutes and at 4.00 to 6.00 minutes after saline infusion. In more than half of the patients, LS_{cath} worsened or improved by less than -2% after saline infusion. Worsening of LS_{cath} correlated with central venous pressure and ventricular end-diastolic pressure in all conditions ($P \leq .017$). There was no difference in LS_{stress} or LS_{cath} between the morphologic right ventricle and the morphologic left ventricle.

Conclusions: Patients with Fontan circulation demonstrate systolic myocardial functional reserve that can be recruited with exercise stress but not with an acute increase in preload. (J Am Soc Echocardiogr 2024;■:■-■.)

Keywords: Fontan circulation, Myocardial function, Myocardial peak longitudinal strain, Exercise echocardiography, Preload challenge

Fontan operation is a necessary procedure in children with single-ventricle physiology[1] but inevitably leads to circulatory failure.[2,3] The associated exercise intolerance increasingly affects activities and quality of life throughout childhood and adolescence.[4-6] The pathophysiology of this failure is often divided into two groups: circulatory failure either with or without good systolic function of the single ventricle.[7] In the context of good systolic function, one explanation is that increased pulmonary vascular resistance limits venous return to the heart, particularly during periods of increased need, such as exercise. Several other aspects are also crucial, including diastolic dysfunction and the circulatory impact of increased caval pressure, such as portal hypertension and impaired lymphatic drainage.[2,3,8] In the context of impaired systolic function, the physiology is characterized by reverse remodeling of a single ventricle in

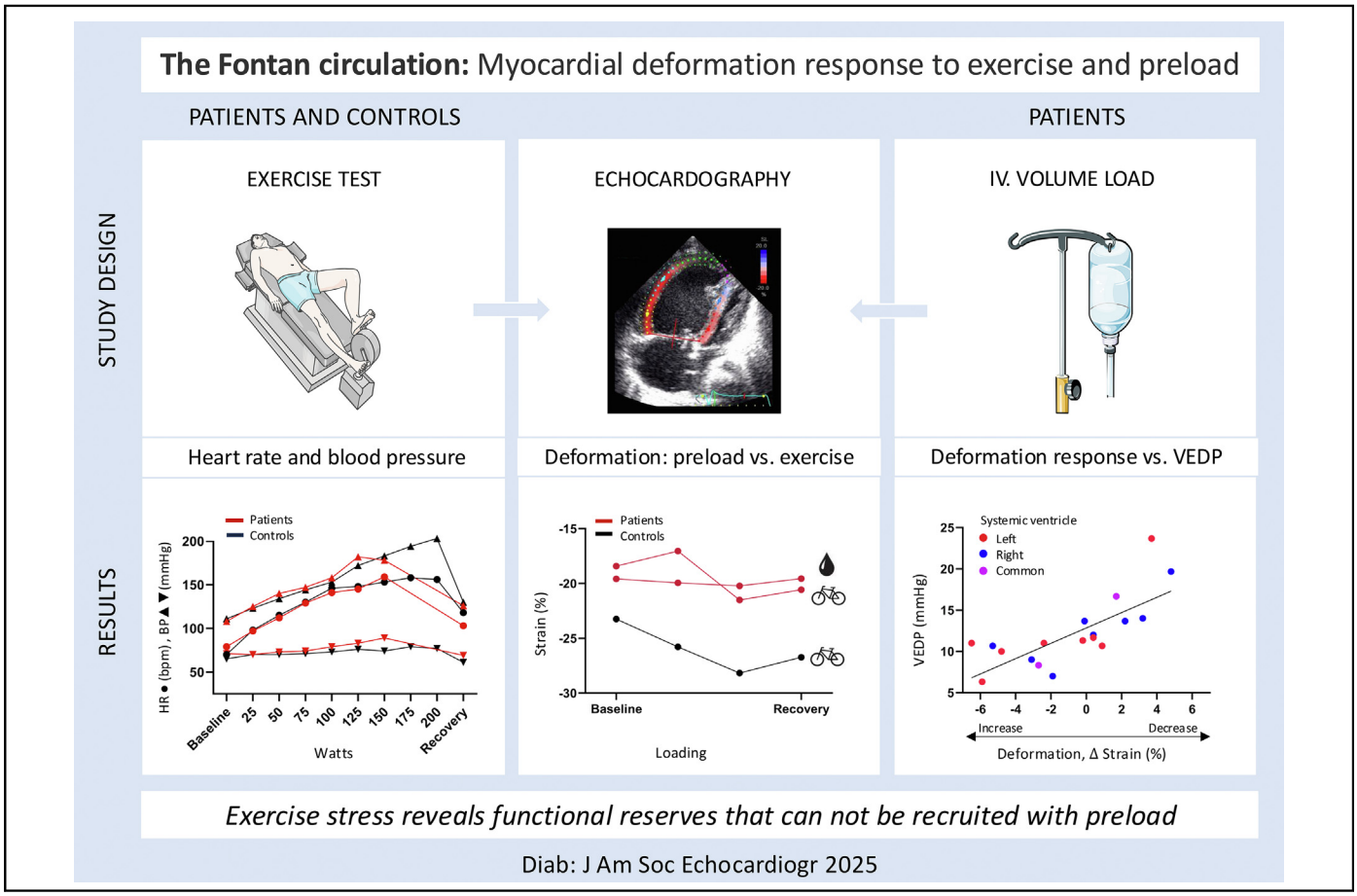
From the Department of Paediatric Cardiology, Oslo University Hospital, Rikshospitalet, Oslo, Norway (S.G.D., G.D., H.B., K.V., H.H., T.M.); Faculty of Medicine, Institute of Clinical Medicine, University of Oslo, Oslo, Norway (S.G.D.); Department of Cardiology, University Hospital of North Norway, Tromsø, Norway (A.R.); Department of Clinical Medicine, UiT, The Arctic University of Norway, Tromsø, Norway (A.R.); Division of Emergencies and Critical Care, Oslo University Hospital, Rikshospitalet, Oslo, Norway (G.G.); Division of Pediatric Cardiology, Department of Pediatrics, King Chulalongkorn Memorial Hospital, Bangkok, Thailand (K.V.); and The Labatt Family Heart Centre, The Hospital for Sick Children, Toronto, Ontario, Canada (M.K.F.).

Dr. Diab's research employment was supported by a doctoral grant from the South-Eastern Norway Health Authority (grant 2021015). The research project and Dr Möller's research employment were supported by a postdoctoral research grant from the South-Eastern Norway Health Authority (grant 2014077).

Reprint requests: Simone Goa Diab, MD, Department of Pediatric Cardiology, Oslo University Hospital, PO Box 4950 Nydalen, Oslo 0424, Norway (E-mail: *simonediab@gmail.com*).

0894-7317

https://doi.org/10.1016/j.echo.2024.11.005



Central Illustration The Fontan circulation: myocardial deformation response to exercise and preload. We aimed to study the systolic myocardial functional reserve of the single ventricle using echocardiographic LS assessment during exercise and/or an intravenous volume challenge. We found that the single ventricle has contractile reserves that are recruitable during exercise but less so than in healthy individuals, despite a similar heart rate and blood pressure response. During an intravenous volume challenge, the contractile response was blunted and had a negative correlation with VEDP.

Abbreviations

CVP = Central venous pressure

GLS = Global longitudinal strain

LS = Longitudinal strain

LV = Left ventricle

RV = Right ventricle

RVE = Rapid volume expansion

VEDP = Ventricular end-diastolic pressure

response to nonphysiologic changes in volume and pressure loading. Volume overload is observed in fetal life, persists until the later surgical stages, and can be exaggerated at any stage by valve regurgitation.[3,9] Pressure load is particularly evident for the morphologic right ventricle (RV) exposed to the systemic blood pressure after palliation. Some evidence suggests that the morphologic left ventricle (LV) adapts more effectively to the hemodynamic requirements of the Fontan circulation.[10-12] Nonetheless, the underlying mechanisms remain incompletely delineated.

In this study, we aimed to describe the systolic myocardial functional reserve of the single ventricle in Fontan circulation using echocardiographic longitudinal strain (LS) assessment. We hypothesized that an exercise and/or volume challenge can identify a subgroup of patients with myocardial limitations and that these limitations are related to ventricular morphology.

METHODS

Patient Population and Inclusion

This study was part of the Norwegian Fontan Project (ClinicalTrials.gov identifier NCT02378857) at Oslo University Hospital, which is a multidisciplinary observational study of adolescents living with Fontan circulation.[13] The protocol was approved by the Regional Committee for Medical and Health Research Ethics (REK Sør-Øst, 2013/1331). All participants provided informed consent before enrollment. The study was conducted in accordance with the Declaration of Helsinki II.

We included patients 15 to 18 years of age undergoing routine hospital admission, which involves a comprehensive clinical workup before the transition to adult cardiac care. Heart catheterization was performed in all enrolled patients unless they had undergone clinically indicated heart catheterization shortly before the start of the project or shortly before they turned 16 years old. A control group

HIGHLIGHTS

- During exercise, GLS increases in single ventricles but is lower than in controls.
- During volume load, GLS is unchanged in single ventricles.
- GLS response during exercise differs between single LVs and single RVs.
- GLS response during volume load is negatively correlated to VEDP.

was recruited among relatives and acquaintances of the hospital staff and included for noninvasive examinations.

Stress Echocardiography

Stress echocardiography was performed using a recumbent cycle ergometer with a 45° inclination (Ergoselect EL; Ergoline). Starting at 25 W, the workload was increased by 25 W every 3 minutes. Images were obtained during the second and third minute at each stage. The test was stopped when the participants reached volitional physical exhaustion or when they could no longer obtain a pedal frequency of 60 ± 5 rpm. Heart rate and blood pressure were defined at baseline, the initial loading step of 25 W, maximal workload, and 1 to 3 minutes of recovery.

Heart Catheterization Procedure With a Preload Challenge

Heart catheterization was performed using femoral arterial and femoral venous access in accordance with clinical routine. The procedure was performed either with conscious sedation while maintaining spontaneous respirations or under general anesthesia. Hemodynamic measurements using liquid-filled catheters were obtained from the ventricular cavity in systole, ventricular cavity in end-diastole (ventricular end-diastolic pressure [VEDP]), and inferior vena cava (central venous pressure [CVP]). Patients without Fontan obstruction underwent a preload challenge by performing a rapid volume expansion (RVE). Five milliliters of 0.9% saline solution per kilogram body weight was infused over approximately 15 to 30 seconds. The bolus size was chosen on the basis of clinical routine, maintaining the total infused volume during the procedure at 10 mL/kg. To facilitate the fastest possible volume expansion, the infusion was performed manually and simultaneously through at least two venous accesses. Serial pressure readings were recorded at the following time intervals after the end of the saline infusion: every 15 seconds for the first 2 minutes, every 30 seconds for the next 2 minutes, and every minute until 6 minutes after the infusion. Whereas measurements at baseline were collected as a single value, measurements during and after volume load were obtained by averaging values obtained during 1.00 to 2.00 minutes (average of five measurements) and 4.00 to 6.00 minutes (average of three measurements), respectively. A CVP of 14 mm Hg or higher and a VEDP of 12 mm Hg or higher at any stage was considered elevated on the basis of previously published data.[14-16]

When evaluating the hemodynamic effects of the intravenous fluid bolus, we considered a significant increase in CVP to be a nonspecific marker of downstream circulatory limitation. This limitation may be at the pulmonary, cardiac, or systemic arterial level. In contrast, a simultaneous increase in VEDP was considered a specific marker of circulatory limitation attributable to the reduced function of the single ventricle.

Echocardiographic Assessment of Ventricular Function

Transthoracic echocardiography was performed during the exercise test, and transthoracic or transesophageal echocardiography was performed during catheterization. All imaging was performed using a GE Vivid 9 ultrasound scanner (GE Ultrasound) with a 5-MHz transducer for transthoracic imaging and a 6-VT transducer for transesophageal imaging. Grayscale images of the ventricle in an apical four-chamber view were stored as cine loops with at least three sequential heart cycles. Echocardiographic studies were excluded from the offline analysis in cases of insufficient data quality or availability (such as poor image quality, angle error, overly small image sector, or storage failure). All image data were reviewed and analyzed by two experienced specialists (A.R. and S.G.D.), and nine cine loops were repeated to analyze interobserver variations. Offline analysis of the image data was performed using EchoPAC SW Only version 206 (GE Ultrasound).

Echocardiographic strain during bicycle exercise (LS_{stress}) was calculated as global wall shortening by manually tracing the

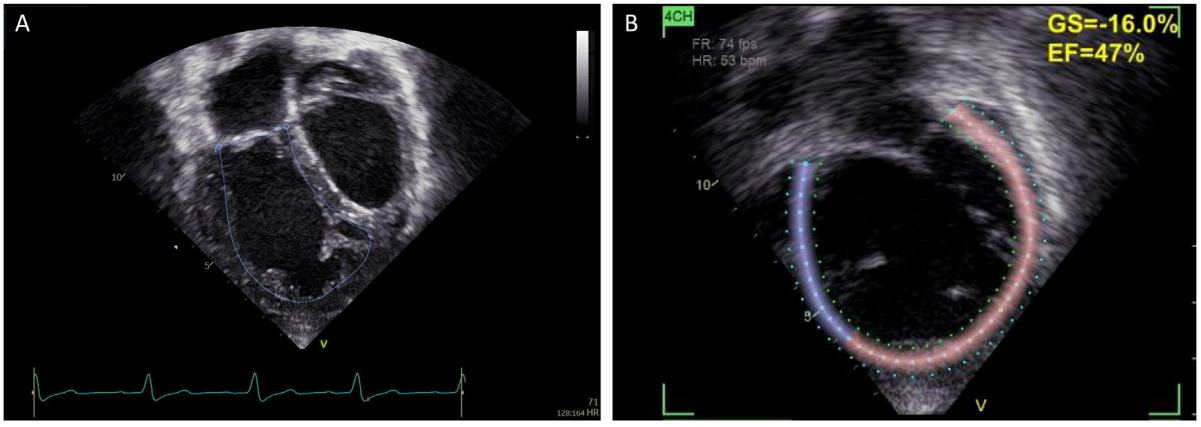


Figure 1 **(A)** Tracing of the endocardial border in both diastole and systole for calculation of LS_{stress} by global wall shortening: LS_{stress} = (wall length systole – wall length diastole)/wall length diastole × 100%. **(B)** Measuring of global endocardial LS *(inner green dotted line)* by offline analysis using EchoPAC SW Only. *4CH*, Four-chamber; *EF*, ejection fraction; *GS*, global strain.

Table 1 General characteristics of the patient population

Characteristic	Patients			Control subjects
	All (*n* = 32)	Catheterization (*n* = 20)	Stress echocardiography (*n* = 30)	All (*n* = 16)
Age, y	16.7	16.6 (16.1-17.7)	16.7	18.9 (18.1-23.1)
Sex (female/male)	12 (38)/20 (62)	7 (35)/13 (65)	10 (33)/20 (66)	8 (50)/8 (50)
Median body mass index, kg/m^2	21.3 (15.3-29.9)	21.4 (16.4-28.4)	21.3 (15.3-29.9)	20.0 (16.9-25.0)
Median oxygen saturation at rest, %	96 (84-98)	96 (92-98)	96 (84-98)	
Echocardiographic features at inclusion				
Fractional area change, %	34 ± 9			45 ± 3
Ejection fraction, %	50 ± 8			53 ± 3
Longitudinal to transverse diameter	1.4 ± 0.3			1.9 ± 0.3
Fontan-specific characteristics				
Age at Fontan completion, y	1.6 (1.0-5.5)	1.6 (1.0 – 5.5)	1.6 (1.0-5.5)	
Fontan type (extracardiac/lateral tunnel)	22 (69)/10 (31)	15 (75)/5 (25)	20 (66)/10 (33)	
Atrioventricular valve regurgitation (none/mild/moderate)	10 (31)/18 (56)/4 (13)	4 (20)/13 (65)/3 (15)	9 (30)/17 (57)/4 (13)	
Systemic ventricular morphology LV/RV/common	16 (50)/14 (44)/2 (6)	8 (40)/10 (50)/2 (10)	15 (50)/13 (43)/2 (7)	
Open fenestration	1 (3)	0 (0)	1 (3)	
Complications				
Protein-losing enteropathy	3 (9)	1 (5)	2 (7)	
Anatomic diagnoses				
Hypoplastic left heart syndrome	11 (34)	8 (35)	11 (37)	
Tricuspid atresia	4 (13)	4 (20)	3 (10)	
Double-outlet RV	2 (6)	2 (10)	2 (7)	
Double-inlet LV	6 (19)	3 (15)	5 (17)	
Pulmonary atresia / intact ventricular septum	3 (9)	0 (0)	3 (10)	
Other (unbalanced AVSD, hypoplastic RV, etc.)	6 (19)	3 (20)	6 (20)	
Devices				
Pacemaker	5 (16)	4 (20)	5 (17)	
ICD	0 (0)	0 (0)	0 (0)	
Medications				
Acetylsalicylic acid	23 (72)	16 (80)	21 (70)	
Warfarin	7 (22)	4 (20)	7 (23)	
ACE inhibitor	6 (19)	4 (20)	6 (20)	
Pulmonary vasodilator	3 (9)	1 (5)	3 (10)	
Diuretic	4 (13)	2 (10)	4 (13)	
Aldosterone antagonist	3 (9)	2 (10)	3 (10)	
β-blocker	2 (6)	1 (5)	2 (7)	
Antiarrhythmic drug (non-β-blocker)	0 (0)	0 (0)	0 (0)	

ACE, Angiotensin-converting enzyme; *AVSD*, atrioventricular septal defect; *ICD*, implantable cardioverter-defibrillator.
Data are expressed as median (interquartile range), number (percentage), or mean ± SD.

endocardial border in end-diastole and end-systole (LS_{stress} = [wall length systole − wall length diastole]/wall length diastole × 100%; Figure 1). The echocardiographic images obtained during catheterization were analyzed using speckle-tracking for strain measurements. We traced the wall of the single dominant ventricle, including the septum, or both lateral walls when adjacent ventricles functioned as a common chamber. Adequate tracking of the wall movement was verified or adjusted if necessary. To assess systolic ventricular function

Table 2 Echocardiographic strain measurements (%) from the exercise test and invasive volume challenge

	Patients							Control subjects	
	All	*P* value vs baseline	LV	*P* value vs baseline	RV	*P* value vs baseline	*P* value, LV vs RV	*P* value vs control subjects	All	*P* value vs baseline
Stress exercise	(*n* = 30)*		(*n* = 15)		(*n* = 13)				(*n* = 16)	
Baseline	−18.4 ± 5.5		−17.3 ± 5.6		−20.5 ± 4.7		0.113	**<.001**	−23.3 ± 3.0	
At 25 W	−17.0 ± 4.9	.236	−18.7 ± 5.2	.222	−14.9 ± 4.3	**.007**†	0.183†	**<.001**	−25.8 ± 3.0	**.045**
Median (IQR)					−16.6 (8.0)					
At maximal load	−22.0 ± 6.5	**.004**	−22.7 ± 7.0	**<.001**	−20.5 ± 4.8	.969	0.344	**<.001**	−28.4 ± 2.7	**<.001**
At recovery	−20.6 ± 6.4	**.030**	−21.3 ± 5.6	**.002**	−19.8 ± 8.0	.987	0.576	**.001**	−26.7 ± 3.0	**.010**
Volume challenge	(*n* = 20)*		(*n* = 8)		(*n* = 10)					
Baseline	−19.6 ± 6.0		−20.2 ± 6.9		−19.4 ± 6.0		0.803			
At 1.00-2.00 min after RVE	−20.2 ± 3.9	.329	−22.0 ± 3.6	.170	−19.4 ± 3.5	.711	0.145			
At 4.00-6.00 min after RVE	−19.6 ± 4.6	.971	−20.2 ± 4.9	.995	−19.0 ± 4.7	.550	0.609			

IQR, Interquartile range.
Data are expressed as mean ± SD. Healthy control subjects were included for exercise test only.
Statistical significance is indicated with boldface type.
*Common ventricle, *n* = 2.
†Statistical analyses using a nonparametric method (Mann-Whitney *U* test and related-samples Wilcoxon signed rank test).

during catheterization, the trace of global endocardial LS (LS_{cath}) was collected.

During exercise, echocardiographic, LS_{stress} was defined at baseline, at an initial workload of 25 W, at maximal loading (the highest workload with adequate image quality), and at 1 to 3 minutes of recovery. During catheterization, echocardiographic LS_{cath} was defined at baseline, during the first 1.00 to 2.00 minutes after saline infusion, and upon reaching a new steady state 4.00 to 6.00 minutes after the saline infusion (see "Heart Catheterization Procedure With a Preload Challenge"). All other measurements were performed similarly. Echocardiographic LS_{stress} was compared with LS_{cath} at the predefined time points. As the group size differed, a sensitivity test was performed comparing LS_{stress} and LS_{cath} in only the 18 patients who underwent both tests (excluding the 12 patients who did not undergo RVE).

Statistical Analysis

Continuous variables are reported as mean ± SD. For nonparametric variables, we also report the median (interquartile range). Comparisons were made using paired or unpaired two-tailed Student's *t* test in the case of normally distributed variables and using the Mann-Whitney *U* test or two-sided analysis of variance, as suitable for the number of groups. The normality of the distribution was tested using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Variable relationships were analyzed using Pearson correlation in the case of a normal distribution and otherwise by Spearman correlation. Interobserver variability was determined by calculating the intraclass correlation coefficient for continuous variables.[17] Statistical analyses were performed using SPSS Statistics for Windows version 25.0 (IBM). A two-tailed *P* value of <.05 was considered to indicate statistical significance.

RESULTS

Study Group

Stress echocardiography using a recumbent cycle ergometer was performed on 30 patients and 16 healthy individuals in the control group. Among the patients who consented to undergo RVE during the routine catheterization procedure,[13] analyzable echocardiography recordings were available for 20. Eighteen patients underwent echocardiography both during catheterization and stress testing. The general characteristics of the study groups, including baseline echocardiographic features, are presented in Table 1. The interobserver analysis of LS_{cath} showed high reliability, with an intraclass correlation of 0.836.

As previously described,[13] catheterization was performed under conscious sedation or general anesthesia. Among the 20 patients included in this study, 12 underwent general anesthesia (nine were intubated, and three were administered a laryngeal mask). In our previous study,[13] no differences in heart rate, CVP, VEDP, or ventricular systolic pressure values were observed between the two groups. Cardiac output data were not collected.

Exercise Test

The mean LS_{stress} of the patient group was −18.4 ± 5.5% at baseline, unchanged (−17.0 ± 4.9%) at initial loading (25 W), followed by a significant improvement compared with baseline values: −22.0 ± 6.5% at maximal loading and −20.6 ± 6.4% at recovery

Table 3 Collected variables during the exercise test and invasive volume challenge

Variable	Patients						Control subjects	
	All (n = 30)*	P value vs baseline	LV (n = 15)	RV (n = 13)	P value, LV vs RV	P value vs control subjects	(n = 16)	P value vs baseline
Exercise echocardiography								
Maximal workload, W	96.7 ± 36.4		103 ± 35	96 ± 35	NS	**.009**†	129.7 ± 34.4	
Median (IQR)	100.0 (50)						125.0 (44)	
Time, min	11.4 ± 4.8		12.4 ± 5.0	11.3 ± 4.3	NS	**.004**†	15.7 ± 4.1	
Median (IQR)							15.1 (5.1)	
Heart rate (patients without pacemakers), beats/min	(n = 25)		(n = 11	(n = 12)				
Baseline	79 ± 16		79 ± 16	76 ± 17	NS	NS	70 ± 9	
At 25 W	97 ± 20	<.001	96 ± 18	92 ± 19	NS	NS	98 ± 12	**<.001**
Maximal	152 ± 21	<.001	158 ± 24	144 ± 18	NS†	NS†	162 ± 23	**<.001**†
Median (IQR)			164 (32)				170 (41)	
Recovery	103 ± 19	<.001	107 ± 20	98 ± 20	NS	**.005**	118 ± 15	**<.001**
BP, mm Hg								
Baseline systolic BP	108 ± 12		107 ± 12	112 ± 14	NS	NS	111 ± 15	
Diastolic BP	71 ± 9		68 ± 9	75 ± 8	NS	NS	65 ± 7	
Maximal Systolic BP	160 ± 30	**<.001**	156 ± 30	166 ± 32	NS	NS	169 ± 24	**<.001**
Diastolic BP	79 ± 16	**.042**†	77 ± 16	83 ± 17	NS†	NS†	75 ± 12	**.002**
Median (IQR)	74 (21)		74 (16)					
Recovery systolic BP	126 ± 34	NS†	126 ± 35	127 ± 37	NS†	NS†	130 ± 21	**.010**
Median (IQR)	116 (27)		116 (27)					
Diastolic BP	69 ± 15	NS†	66 ± 9	73 ± 17	NS†	NS†	61 ± 10	**NS**
Median (IQR)	67 (12)			69 (16)				
Heart catheterization	(n = 20)		(n = 8)	(n = 10)				
Inferior vena cava pressure, mm Hg								
Baseline	13.2 ± 3.5		12.0 ± 4.2	14.1 ± 1.9				
Median (IQR)			10.0 (6.0)					
Average 1.00-2.00 min after RVE	15.7 ± 3.3	**<.001**	14.9 ± 4.3	16.3 ± 1.5				
Median (IQR)			13.3 (4.3)					
Steady state	14.8 ± 3.1	**<.001**	13.5 ± 3.7	15.7 ± 1.4				
Median (IQR)			12.2 (4.2)					
VEDP, mm Hg								
Baseline	10.6 ± 4.4		10.5 ± 5.0	10.3 ± 3.3				
Median (IQR)	10.0 (3.0)		9.3 (3.0)					
Average 1.00-2.00 min after RVE	13.2 ± 4.5	**<.001**†	13.1 ± 5.2	12.9 ± 3.7				
Median (IQR)	12.3 (2.6)		12.5 (0.7)					
Steady state	12.3 ± 4.1	**<.001**†	12.0 ± 5.0	12.4 ± 3.5				
Median (IQR)	11.2 (3.8)		11.0 (1.4)					

(*Continued*)

Table 3 (*Continued*)

Variable	Patients						Control subjects	
	All (n = 30)*	P value vs baseline	LV (n = 15)	RV (n = 13)	P value, LV vs RV	P value vs control subjects	(n = 16)	P value vs baseline
Ventricular peak systolic pressure, mm Hg								
Baseline	96.8 ± 18.6		102.8 ± 25.8	93.2 ± 11.4				
Median (IQR)	92.0 (15.0)		2.0 (23.0)					
Average 1.00-2.00 min after RVE	99.6 ± 16.6	**.008**†	104.4 ± 22.9	96.7 ± 11.1				
Median (IQR)	95.6 (15.1)		97.3 (22.7)					
Steady state	98.5 ± 17.2	NS†	102.4 ± 23.7	96.6 ± 11.8				
Median (IQR)	93.5 (15.5)		2.2 (23.1)					
Heart rate (patients without pacemakers), beats/min	(n = 17)		(n = 6)	(n = 9)				
Baseline	77 ± 13		80 ± 13	72 ± 13				
Average 1.00-2.00 min after RVE	72 ± 12	**.001**	74 ± 12	70 ± 12				
Steady state	74 ± 12	**.017**	74 ± 12	71 ± 12				

NS, Nonsignificant.
Data are expressed as mean ± SD except as indicated. Healthy control subjects were included for exercise test only.
Statistical significance is indicated with boldface type.
*Common ventricle, n = 2.
†Statistical analyses using a nonparametric method as appropriate (related-samples Wilcoxon signed rank test or Mann-Whitney U test).

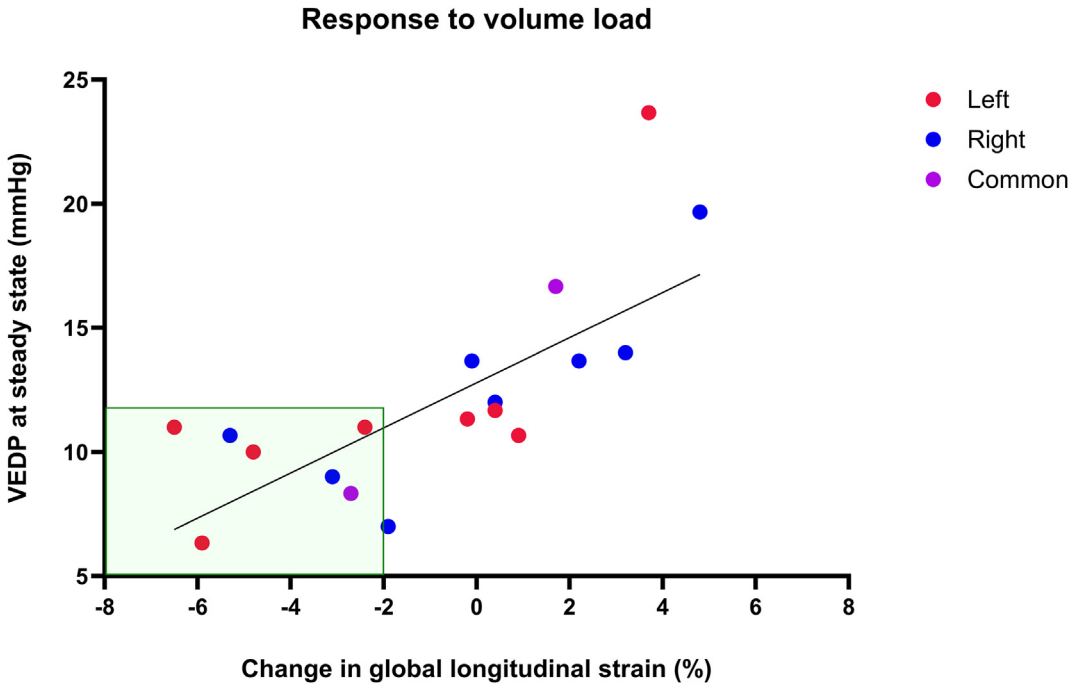


Figure 2 Correlation between VEDP at steady state and change in absolute GLS (ΔLS_{stress}) from baseline to averaged value 1.00 to 2.00 minutes after an invasive volume load. The *green box* indicates the area of expected results after the volume challenge in healthy individuals.

($P = .004$ and $P = .030$, respectively; Table 2, Supplemental Figure 1). LS_{stress} values at the maximal workload did not correlate with changes in heart rate. LS_{stress} values did not differ significantly between morphologic LVs and RVs at any stage. However, subgroup analysis revealed that only morphologic LVs had improved strain during maximal loading and recovery, and morphologic RVs had worsened strain at initial loading (25 W). The sensitivity of the LS_{stress} results was assessed by excluding patients who did not undergo RVE. The remaining 18 patients still showed a significant improvement in global LS (GLS) during exercise from −19.3% to −22.8% ($P = .014$), while GLS at recovery (−21.5%) was not significantly improved ($P = .107$). For healthy control subjects, the mean LS_{stress} at baseline was −23.3 ± 3.0%, followed by significant improvements at initial loading (−25.8 ± 3.0%), maximal loading (−28.4 ± 2.7%), and recovery (−26.7 ± 3.0%) compared with baseline values ($P = .045$, $P < .001$, and $P = .010$, respectively).

For patients with Fontan circulation, the mean peak power output was 93.6 ± 39.8 W with a mean exercise duration of 11.4 ± 4.8 minutes (Table 3). The corresponding values for healthy control subjects were 129.7 ± 34.4 W and 15.7 ± 4.1 minutes, respectively. In all cases, the reason for termination was physical exhaustion. The mean heart rate for the patient group was 79 ± 16 beats/min at baseline; it increased during exercise to 152 ± 21 beats/min at maximal workload (Table 3, Central Illustration). Heart rate values for control subjects were lower than those for patients at baseline but higher at the remaining stages; however, the difference between the study groups reached statistical significance only at recovery. The mean systolic and diastolic blood pressure values were normal at baseline in both groups and increased adequately during exercise, with no statistical differences between the groups (Table 3, Central Illustration).

Heart Catheterization With a Volume Challenge

Mean LS_{cath} was −19.6 ± 6.0% at baseline and unchanged after RVE and at postinfusion steady state (−20.2 ± 3.9% and −19.6 ± 4.6%, respectively; Table 2, Supplemental Figure 1). In 11 patients, LS worsened or improved by less than −2% after RVE. This finding did not differ between morphologic LVs and RVs (Figure 2).

Hemodynamic parameters during heart catheterization have been previously described in detail.[13] For the subgroup of 20 patients with available echocardiographic data, the baseline heart rate was 77 ± 13 beats/min, which dropped significantly after RVE to 72 ± 12 beats/min ($P = .001$) and remained significantly lower than baseline values at the steady state ($P = .017$). There was no correlation between changes in heart rate and changes in LS_{cath}. CVP at baseline was elevated in nine patients. Baseline CVP correlated with the worsening in LS_{cath} at baseline, after RVE, and at steady state ($P = .012$, $P = .004$, and $P = .007$, respectively). Eight of 20 patients showed increases in CVP of >20% during volume load. All of these patients showed concomitant increases in VEDP and no significant increases in the transpulmonary pressure gradient. VEDP at baseline was elevated in four patients. Univariate analysis demonstrated that the worsening in LS_{cath} correlated significantly with VEDP both at baseline, after RVE, and at steady state ($P = .017$, $P = .003$, and $P < .001$, respectively; Figure 2).

Comparison of Preload and Stress Response

The change in strain during exercise did not correlate with the change in strain during volume load. Mean LS_{stress} in patients with unchanged or worsened LS_{cath} during volume did not differ significantly from mean LS_{stress} in patients with improved LS_{cath} during volume load of at least −2% (Supplemental Figure 2).

DISCUSSION

In this study, we compared the effects of physical exercise with those of a rapid preload increase on echocardiographic LS in patients with Fontan circulation (Central Illustration). We report the following findings:

- During exercise, mean LS improved significantly during maximal loading and recovery but was less negative than in healthy control subjects, despite a similar heart rate response.
- Although LS strain during exercise did not differ significantly between morphologic RVs and LVs, only LVs showed improved strain with increased load.
- During catheterization, mean LS was unchanged at 1.00 to 2.00 minutes and at 4.00 to 6.00 minutes after an RVE.
- Preload-sensitive ventricles with unchanged or worsening LS after an RVE also showed an attenuated strain response to exercise.

Exercise and volume challenges with simultaneous echocardiographic assessment allowed us to study associations between loading changes and myocardial performance. We found a significantly different response in LS in these two settings. Our findings raise concerns regarding the use of fluid challenge in lieu of exercise.

Exercise Response

In our study, mean LS_{stress} was less negative for patients than for control subjects at all stages, corresponding to reduced systolic function. The difference in LS_{stress} between patients and control subjects could not be attributed to heart rate. In contrast to a recent study by Claessen *et al.*,[18] we found a similar slope of the relationship between heart rate and workload in patients and control subjects up to 125 W, with no difference in maximal heart rate. Atrioventricular valve regurgitation to a moderate degree was present in only four patients and is not considered to explain the findings.

Similar differences in deformation between the systemic ventricle in patients with Fontan circulation and the LV in healthy control subjects have been observed in other studies.[19,20] The findings suggest deviating myocardial properties of the systemic ventricle in Fontan circulation. Previous studies have shown echocardiographic indices of diastolic dysfunction, suggestive of decreased lusitropic effect that could be even more pronounced with exercise.[21,22] Another factor with potential impact is myocardial fibrosis. Magnetic resonance imaging studies have shown fibrosis in approximately 30% of patients with Fontan circulation, with a wide myocardial distribution and affecting both systolic and diastolic function.[23,24] In early childhood, fibrosis may be caused by a vicious cycle of systemic hypoxemia and ventricular volume loading with chronically elevated myocardial wall stress and myocardial oxygen supply-demand mismatch.[25] Furthermore, altered prevailing direction of deformation might play a role, with underestimation of maximal strain by conventional measurement angles.[26]

In both patients and control subjects, mean LS_{stress} improved, indicating myocardial contractile reserve. This finding aligns with a recent study of adolescents with Fontan circulations and age-matched control subjects, demonstrating an exercise induced increase in GLS in both groups: from −15.7 ± 2.8% at baseline to −18.8 ± 3.4% at

maximal workload for patients and from −19.9 ± 3.1% to −25.6 ± 1.8% for control subjects.

In healthy adolescents, Pieles *et al.*[27] demonstrated that baseline strain was more negative in the RV compared with the LV, but strain in the LV improved more during exercise (from −17.6 ± 2.9% to −23.6 ± 4.9% for the LV and from −25.1 ± 6.0 to −28.6 ± 4.4% for the RV). When studying morphologically right and left single ventricles, we found a corresponding trend. Although the difference in LS_{stress} at baseline was not significant, during maximal workload and recovery, left but not right single ventricles had significantly improved strain. In our healthy control group, our findings for the LV are similar to those of Pieles *et al.*

A remarkable difference between patients with Fontan circulation and control subjects was found at 25 W of exercise load, at which mean LS_{stress} significantly improved in control subjects but was unchanged in patients and even worsened in patients with morphologic RVs. The finding could not be attributed to differences in heart rate or blood pressure. Differences in venous return and volumes were not addressed in our study. However, Claessen *et al.*[18] recently demonstrated in a magnetic resonance imaging–based study that the end-diastolic volume of the single ventricle increased at initial exercise before a subsequent volume decrease. One could speculate whether the lack of strain response at the onset of exercise in the present study is due to increased ventricular volume and altered geometry.

All participants performed the bicycling in a recumbent position with a 45° inclination. A previous study[28] showed how maximum power (watts) in a recumbent position is reduced compared with upright bicycling. To optimize echocardiography, participants were additionally tilted leftward. In our study, maximum power among patients with Fontan circulation and control subjects was higher than in a similar Japanese study from 2021, examining a comparable age group.[20] Therefore, we believe that our participants achieved maximal effort.

Preload Response

In a healthy circulation, volume load improves left ventricular LS. An animal study with a preload increase by intravenous infusion of dextran (7% of body weight) showed that LS of the healthy LV changed from −26.4 ± 10.3% to −38.1 ± 14.3%.[29] Other studies in human subjects have shown preload-dependent increase in ejection fraction and stroke volume of the healthy LV,[30,31] also with a comparable low bolus size.[30] The infusion rate in our study was done more rapid than described in other studies of both the healthy LV and the single ventricle in Fontan.[30-34] In contrast to the volume response observed in healthy individuals, half of the patients in our study showed no change or even a worsening in LS after saline infusion. This systolic incompetence could not be explained by an increase in the transpulmonary pressure gradient. Figure 2 illustrates that in patients with Fontan circulation, the improvement in LS_{cath} during volume load was inversely correlated with VEDP at steady state. Only one-third of the patients had strain responses and VEDP levels consistent with levels typically observed in healthy individuals, revealing a circulatory limitation at the level of the heart in numerous Fontan patients. The strain response did not differ between the morphologic right and left systemic ventricles. Although opposed to our expectations, the finding aligns well with our previous observations of only a slightly higher mean CVP in morphologic RVs than LVs and no difference in heart rate, ventricular systolic pressure, or VEDP.[10]

In normal circulation, ventricle stretching before contraction increases the strength of contraction via the Frank-Starling mechanism. However, Rösner *et al.*[19,29] previously showed an inverse relationship between circumferential strain and the degree of sphericity in single ventricles. Of note, in another study, the same group demonstrated a significant association between increased sphericity and poor outcome in single ventricles of patients with Fontan circulation.[35] Chronic volume overload in early childhood and remodeling of the ventricle to a more spherical shape could cause the myofibers to be prestretched beyond the optimal Frank-Starling curve point, resulting in minimal or even negative effects from additional volume load. Furthermore, the volume load may acutely unfavorably affect ventricular volumetrics and consequently contractility (as further discussed below).

Comparison of Preload and Stress Response

Our findings suggest that the single ventricle has contractile reserves that are recruitable during exercise but less recruitable by a preload challenge. Most patients demonstrated little contractile reserve to a volume load, while contractile reserve during exercise appeared to be present even in patients with blunted preload response (Supplemental Figure 2). These observations question the perception of the single ventricle being chronically preload deprived. In a recent report describing exercise hemodynamics in the Fontan circulation, Miranda *et al.*[16] also challenged this theory and referred to the lack of benefit of pulmonary vasodilators in this patient group.

The different stress and preload responses can be explained by known physiologic mechanisms. During exercise, the sympathetic pathway is activated, with a positive chronotropic and inotropic effect mediated by β-receptors. Although we did not find a correlation between the increase in heart rate and the improvement in LS_{stress}, the β-receptor effect is assumed to play an important role. The rise in blood pressure and increased ventricular wall tension also promote contraction during exercise.

The increase in heart rate is accompanied by reduced duration of diastole compared with systole.[36] This reduces ventricular filling, and it has been documented that the size of the ventricle decreases; that is, it is less volume loaded during exercise.[37] In patients with Fontan circulation, one could speculate whether the reduced volume has a beneficial effect on geometry and myofiber orientation, promoting contractility.

In our patient group, the contractile response to preload was diverging, potentially because of altered myocardial properties. Although fibrosis may contribute to lower baseline contractility, it does not explain the different responses during exercise stress and preload challenges. Unfavorable geometry with larger and spherical ventricles and disarray of the muscle fibers might be more likely. In our two experimental settings, one could speculate whether the first exercise step is comparable with the volume load, both representing an acute negative impact on geometry by increased venous return. Myocardial properties as well as the effect of exercise training on favorable cardiac remodeling should be further investigated.

Limitations

Twelve of the 20 patients were sedated during heart catheterization, which may have affected the strain response during volume challenge and added inaccuracies in comparison with the strain response during stress echocardiography. When evaluating strain in patients with Fontan circulation in general, the lack of normative data sets is a limitation. In this study, the echocardiographic images allowed only two-dimensional LS, while circumferential strain might also be of

importance.[38] During catheterization, patients were in a supine position, causing suboptimal image acquisition, and in six cases, only one of the walls (typically the visually best contracting wall) allowed accurate strain tracking. In the patients undergoing transesophageal echocardiography, four-chamber views likely had some degree of foreshortening. Both factors might have resulted in overestimation of LS values during catheterization but still allowed the evaluation of a change in LS values during RVE. During exercise echocardiography, poorer image quality with increasing loading forced the exclusion of images at the highest loading stages, which might have underestimated peak strain values in general. Furthermore, echocardiographic images obtained during bicycle exercise had an insufficient frame rate for automated deformation analysis by speckle-tracking, and LS was collected manually. For invasive testing, although a control group was desirable, it could not be met with the current Norwegian ethics policy. Furthermore, not all effects of the saline infusion with potential influence on contractility (e.g., blood pressure) have been addressed. Regarding the hemodynamic assessment of patients with Fontan circulation, the evaluation is limited by the lack of a generally accepted definition of the limits of CVP and VEDP. For comparison of (patho)physiology during exercise and volume load, testing the effect with an infusion of an inotrope or even invasive exercise testing would have been valuable.

CONCLUSION

Patients with Fontan circulation demonstrate systolic functional reserves that can be recruited with exercise stress but not with an acute preload increase. Our results call into question the perception of the systemic ventricle in Fontan being preload deprived and suggest that investigation of myocardial properties beyond the ventricular morphology necessitates further research.

CONFLICTS OF INTEREST

None.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.echo.2024.11.005.

REFERENCES

1. Kverneland LS, Kramer P, Ovroutski S. Five decades of the Fontan operation: a systematic review of international reports on outcomes after univentricular palliation. Congenit Heart Dis 2018;13:181-93.
2. Mori M, Aguirre AJ, Elder RW, et al. Beyond a broken heart: circulatory dysfunction in the failing Fontan. Pediatr Cardiol 2014;35:569-79.
3. Gewillig M, Brown SC. The Fontan circulation after 45 years: update in physiology. Heart 2016;102:1081-6.
4. Hedlund ER, Lundell B, Villard L, et al. Reduced physical exercise and health-related quality of life after Fontan palliation. Acta Paediatr 2016;105:1322-8.
5. Suter B, Kay WA, Kuhlenhoelter AM, et al. Does reduced cardiopulmonary exercise testing performance predict poorer quality of life in adult patients with Fontan physiology? Cardiol Young 2021;31:84-90.
6. Grosch IB, Andresen B, Diep LM, et al. Quality of life and emotional vulnerability in a national cohort of adolescents living with Fontan circulation. Cardiol Young 2022;32:874-82.
7. Book WM, Gerardin J, Saraf A, et al. Clinical phenotypes of Fontan failure: implications for management. Congenit Heart Dis 2016;11:296-308.
8. Veldtman GR, Opotowsky AR, Wittekind SG, et al. Cardiovascular adaptation to the Fontan circulation. Congenit Heart Dis 2017;12:699-710.
9. King G, Buratto E, Celermajer DS, et al. Natural and modified history of atrioventricular valve regurgitation in patients with Fontan circulation. J Am Coll Cardiol 2022;79:1832-45.
10. Ghelani SJ, Colan SD, Azcue N, et al. Impact of ventricular morphology on fiber stress and strain in Fontan patients. Circ Cardiovasc Imaging 2018;11:e006738.
11. Aly S, Mertens L, Friedberg MK, et al. Longitudinal changes in ventricular mechanics in adolescents after the Fontan operation. J Am Soc Echocardiogr 2023;36:998-1007.
12. Erikssen G, Aboulhosn J, Lin J, et al. Survival in patients with univentricular hearts: the impact of right versus left ventricular morphology. Open Heart 2018;5:e000902.
13. Möller T, Klungerbo V, Diab S, et al. Circulatory response to rapid volume expansion and cardiorespiratory fitness in Fontan circulation. Pediatr Cardiol 2022;43:903-13.
14. Ohuchi H. Where is the "optimal" Fontan hemodynamics? Korean Circ J 2017;47:842-57.
15. Miranda WR, Hagler DJ, Taggart MW, et al. Elevated ventricular filling pressures and long-term survival in adults post-Fontan. Catheter Cardiovasc Interv 2020;95:803-9.
16. Miranda WR, Jain CC, Borlaug BA, et al. Exercise catheterization in adults post-Fontan with normal and abnormal haemodynamic criteria: insights into normal Fontan physiology. Eur J Heart Fail 2024;26:314-23.
17. Bland JM, Altman DG. Measuring agreement in method comparison studies. Stat Methods Med Res 1999;8:135-60.
18. Claessen G, La Gerche A, Van De Bruaene A, et al. Heart rate reserve in Fontan patients: chronotropic incompetence or hemodynamic limitation? J Am Heart Assoc 2019;8:e012008.
19. Rösner A, Khalapyan T, Pedrosa J, et al. Ventricular mechanics in adolescent and adult patients with a Fontan circulation: relation to geometry and wall stress. Echocardiography 2018;35:2035-46.
20. Yamazaki S, Akazawa Y, Obinata H, et al. Ventricular myocardial response to exercise in patients with Fontan circulation. J Echocardiogr 2021;19:212-21.
21. Cheung YF, Penny DJ, Redington AN. Serial assessment of left ventricular diastolic function after Fontan procedure. Heart 2000;83:420-4.
22. Chowdhury SM, Graham EM, Taylor CL, et al. Diastolic dysfunction with preserved ejection fraction after the Fontan procedure. J Am Heart Assoc 2022;11:e024095.
23. Rathod RH, Prakash A, Powell AJ, et al. Myocardial fibrosis identified by cardiac magnetic resonance late gadolinium enhancement is associated with adverse ventricular mechanics and ventricular tachycardia late after Fontan operation. J Am Coll Cardiol 2010;55:1721-8.
24. Kato A, Riesenkampff E, Yim D, et al. Pediatric Fontan patients are at risk for myocardial fibrotic remodeling and dysfunction. Int J Cardiol 2017;240:172-7.
25. Ho PK, Lai CT, Wong SJ, et al. Three-dimensional mechanical dyssynchrony and myocardial deformation of the left ventricle in patients with tricuspid atresia after Fontan procedure. J Am Soc Echocardiogr 2012;25:393-400.
26. Sato T, Matsubara D, Wang Y, et al. Contraction patterns of post-Fontan single right ventricle versus normal left and right ventricles in children: Insights from principal strain analysis. J Am Soc Echocardiogr 2023;36:878-87.
27. Pieles GE, Gowing L, Forsey J, et al. The relationship between biventricular myocardial performance and metabolic parameters during incremental exercise and recovery in healthy adolescents. Am J Physiol Heart Circ Physiol 2015;309:H2067-76.
28. Wehrle A, Waibel S, Gollhofer A, et al. Power output and efficiency during supine, recumbent, and upright cycle ergometry. Front Sports Act Living 2021;3:667564.

29. Rösner A, Bijnens B, Hansen M, et al. Left ventricular size determines tissue Doppler-derived longitudinal strain and strain rate. Eur J Echocardiogr 2009;10:271-7.
30. Sanghvi VR, Khaja F, Mark AL, et al. Effects of blood volume expansion on left ventricular hemodynamics in man. Circulation 1972;46:780-7.
31. Kumar A, Anel R, Bunnell E, et al. Effect of large volume infusion on left ventricular volumes, performance and contractility parameters in normal volunteers. Intensive Care Med 2004;30:1361-9.
32. Averin K, Hirsch R, Seckeler MD, et al. Diagnosis of occult diastolic dysfunction late after the Fontan procedure using a rapid volume expansion technique. Heart 2016;102:1109-14.
33. De Mey W, Cools B, Heying R, et al. Can a volume challenge pinpoint the limiting factor in a Fontan circulation? Acta Cardiol 2015;70:536-42.
34. Peck D, Averin K, Khoury P, et al. Occult diastolic dysfunction and adverse clinical outcomes in adolescents and young adults with Fontan circulation. J Am Heart Assoc 2023;12:e026508.
35. Rösner A, McElhinney DB, Diab SG, et al. Classic-pattern dyssynchrony is associated with outcome in patients with Fontan circulation. J Am Soc Echocardiogr 2022;35:513-22.
36. Obara S, Yamaguchi H, Bando E, et al. Comparison of left ventricular systolic and diastolic times in exercise between trained and untrained men. Jpn J Phys Fitness Sports Med 1991;40:145-55.
37. Tomai F, Ciavolella M, Crea F, et al. Left ventricular volumes during exercise in normal subjects and patients-with dilated cardiomyopathy assessed by first-pass radionuclide angiography. Am J Cardiol 1993;72:1167-71.
38. Pieles GE, Gowing L, Ryding D, et al. Characterisation of LV myocardial exercise function by 2-D strain deformation imaging in elite adolescent footballers. Eur J Appl Physiol 2021;121:239-50.