Semi-Invasive Pressure-Flow Plots Obtained Using Exercise Echocardiography Relate to Clinical Status and Exercise Capacity in Patients With a Fontan Circulation

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Aims: Exercise echocardiography with peripheral venous pressure measurement (CPETecho-PVP) may provide superior insights into the pathophysiology of Fontan failure compared to standard cardiopulmonary exercise testing. Accordingly, we assessed (1) the clinical and hemodynamic correlates of pressure-flow plots obtained from CPETecho-PVP in Fontan patients and (2) the relationship between pressure-flow plots and exercise capacity.

Methods: Forty-one consecutive Fontan patients underwent CPETecho-PVP. Peripheral venous pressure was measured in the distal upper extremity using an 18- to 20-gauge intravenous line. A multipoint PVP/cardiac output (CO) slope was calculated as a linear approximation using linear regression analysis from individual pressure-flow plots. A PVP/CO >3 mm Hg/L/min was considered elevated.

Results: Median age was 28 (range, 17-60) years; left ventricle dominance was present in 32 (78%) patients. Compared to patients with a PVP/CO slope ≤3 mm Hg/L/min (n = 29), those with a PVP/CO slope >3 mm Hg/L/min were more likely to have New York Heart Association functional class III to IV (P = .005), lung pathology (P = .004), history of atrial arrhythmia (P = .009), or thromboembolism (P = .02). Additionally, a PVP/CO slope >3 mm Hg/L/min was associated with higher N-terminal prohormone of natriuretic peptide levels (325.0 [176.3-590.0] vs 150.5 [61.3-255.0] ng/L; P = .034), lower peak oxygen consumption (peak VO_2) 48.7% ± 13.3% vs 65.2% ± 15.3% predicted; P = .003), lower heart rate reserve (65% [42%-105%] vs 100% [75%-127%] predicted; P = .010), and lower peak cardiac index (3.8 ± 0.8 vs 6.3 ± 1.5 L/min.m^2; P < .001). Rest-to-peak change in heart rate (P < .001) and cardiac index (P = .006), percentage predicted forced vital capacity (P = .044), and PVP/CO slope (P = .009) were all related to percentage predicted peak VO_2.

Conclusions: A steeper PVP/CO plot is associated with worse clinical status, including lower exercise capacity. This supports the notion of implementing the CPETecho-PVP in the standard of care for Fontan patients. (J Am Soc Echocardiogr 2025;■:■-■.)

Keywords: Exercise echocardiography, Fontan patients, Adult congenital heart disease, Failing Fontan, Pressure-flow plots

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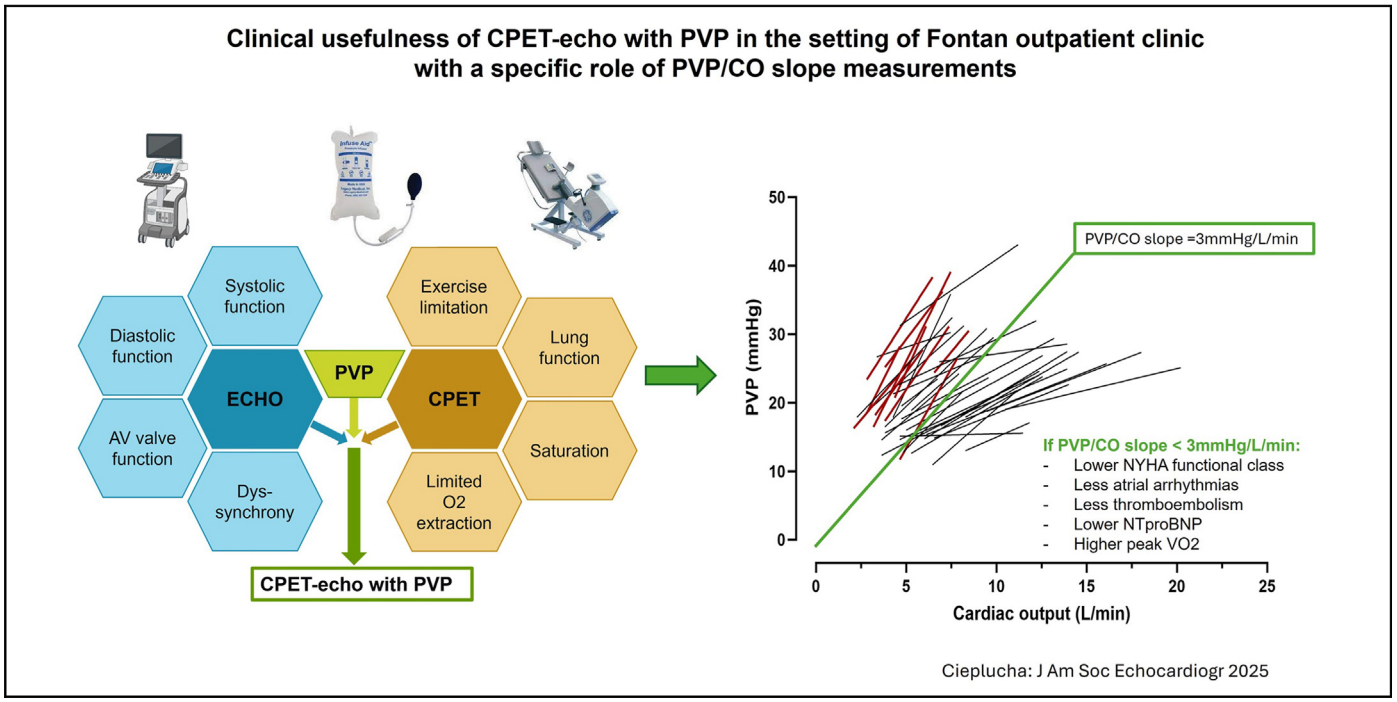

Central Illustration Clinical usefulness of CPET-echo with PVP in the setting of Fontan outpatient clinic with a specific role of PVP/CO slope measurements.

Abbreviations

2D = Two-dimensional

AV = Atrioventricular

CO = Cardiac output

CPETecho = Cardiopulmonary exercise echocardiography testing

FEV1 = Forced expiratory volume in the first second

FVC = Forced vital capacity

HR = Heart rate

HRR = Heart rate reserve

ICC = Intraclass correlation coefficient

mPAP = Mean pulmonary artery pressure

NT-pro-BNP = N-terminal prohormone of natriuretic peptide

PVP = Peripheral venous pressure

PW = Pulsed wave

SV = Stroke volume

SVi = Stroke volume indexed

VOT = Ventricular outflow tract

INTRODUCTION

The Fontan operation diverts systemic venous blood directly to the pulmonary arteries, hence providing definitive palliation for patients with a single anatomical or functional ventricle.[1] Although the Fontan circulation avoids mixture of oxygenated and deoxygenated blood and unloads the systemic ventricle, it also results in elevated systemic venous pressure and relatively low cardiac output (CO), which will eventually lead to Fontan circulatory failure.[2-4] This construct augments the importance of the pulmonary vasculature, which now determines the degree of upstream congestion and downstream low flow.[2,5,6] Nevertheless, the determinants of exercise capacity in adults after Fontan operation are multifactorial and not limited to pulmonary vascular resistance alone.[7,8] Changes in volume loading, surgical insults, and ventricular morphology may cause ventricular systolic or diastolic dysfunction.[8,9] Structural or functional atrioventricular valve regurgitation[10,11] and decreased heart rate (HR) reserve (HRR)[12] are common and are related to exercise capacity. Moreover, abnormal lung function, in particular restrictive lung disease, and reduced muscle strength further contribute to exercise limitations.[13,14]

The slope of pressure increase in the Fontan circulation versus CO augmentation (pressure-flow plot) is more sensitive in detecting abnormal hemodynamics when compared to the resting values.[15-17] However, in Fontan patients, this requires invasive pressure measurements. Since peripheral venous pressures (PVPs) correlate well with invasive pressures at rest and during exercise,[18] these pressure-flow plots can now be obtained noninvasively by combining exercise echocardiography with PVP measurements. The addition of cardiopulmonary exercise testing (CPETecho-PVP) improves phenotyping, provides prognostic information, and indicates alternative causes of exercise intolerance.[19] Accordingly, this study sought to assess (1) the clinical and hemodynamic correlates of pressure-flow plots obtained from CPETecho-PVP in Fontan patients compared to age- and gender-matched controls and (2) the relationship between pressure-flow plots and exercise capacity.

METHODS

Subjects

Forty-one consecutive Fontan patients age >16 years were prospectively included in the study between April 2022 and August 2023 at the University Hospitals Leuven, Leuven, Belgium. All Fontan patients undergo a full cardiac catheterization before being transferred to the Adult Congenital Heart Disease clinic to assess pressures, connections, and complications. Forty-one age- and gender-matched controls without apparent heart disease based on a negative history, clinical exam, and echocardiography were retrospectively collected. All Fontan patients provided written informed consent for the protocol, which was

HIGHLIGHTS

- Exercise intolerance in Fontan patients is frequent and multifactorial.
- CPETecho with PVP is feasible in Fontan patients.
- Pressure-flow plots obtained by CPETecho-PVP correlate with exercise capacity.
- CPETecho-PVP provides a comprehensive insight into exercise physiology.
- CPETecho-PVP can be performed in the outpatient clinic and may change management.

approved by the local research ethics committee Clinical Trial Center of the University Hospitals Leuven, Leuven, Belgium (S67408).

Data Collection

Demographics, type of congenital heart defect and surgical/interventional history, clinical characteristics, and medical therapy were collected at the time of inclusion. Patient records were studied retrospectively with regard to episodes of arrhythmia, thromboembolic events, and stroke. Current and past mental health issues were defined as episodes of depression, alcohol addiction, or concentration problems demanding medical therapy. Skeletal issues were defined as the presence of scoliosis, kyphosis, or documented mobility impairment. Advanced Fontan-associated liver disease was defined as the presence of nodular or cirrhotic lesions in the liver parenchyma, esophageal varices, or hepatocellular carcinoma.[20] Venous blood samples were collected and analyzed for hemoglobin, creatinine, liver function, albumin, alfa-fetoprotein, and N-terminal prohormone of natriuretic peptide (NT-pro-BNP) as per clinical indication.

Exercise Echocardiography With Simultaneous Cardiopulmonary Testing and PVP Measurement (CPETecho-PVP)

Exercise Echocardiography. All patients underwent a maximal, symptom-limited bicycle ergometry test in a semisupine position on a tiltable ergometer (Schiller, CS-200, Ergo-Spiro) with simultaneous acquisition of echocardiographic data by experienced echocardiographers (A.C. or A.V.D.B.) using a GE Vivid Scanner (General Electric Healthcare). After acquiring a complete resting echocardiographic study, all subjects conducted a continuous ramp protocol. In Fontan patients, the ramp protocol started at 10 W and increased by 10 W every minute until the maximum tolerated load; patients were asked to maintain 60 to 65 rotations per minute against a continuous workload. Images were acquired with 20 W increments.

Control subjects conducted a tailored ramp protocol to achieve 10 to 15 minutes of exercise with the protocol being halted twice: once around the first ventilatory threshold or to ensure an HR <100 bpm and once close to peak exertion to enable acquisition of a full set of echo images at the same workload.

Secondary data analysis was done offline using EchoPac (General Electric Healthcare) blinded for the cardiopulmonary testing data. The standardized imaging protocol included (1) a routine resting two-dimensional (2D) echo, color Doppler, pulsed-wave and continuous-wave Doppler assessment of Fontan patient using subcostal, suprasternal, parasternal, and apical views, with a particular focus on measuring the ventricular outflow tract (VOT) diameter for calculations of stroke volume (SV) and CO; CO was calculated as SV * HR; (2) an exercise 2D assessment on every stage of exercise aiming to obtain at least 5 time points with acquisition of full set of exercise echo images. This set included (1) 2D grayscale acquisition for contractility and annular plane systolic excursion of the dominant ventricle; (2) tissue Doppler imaging for s′ of the basal segment of the lateral wall of the dominant ventricle; (3) tissue Doppler imaging pulsed wave (PW) of the lateral annular attachment of the atrioventricular valve (AV) valve; (4) PW of the inflow of the AV valve; (5) color Doppler for the severity of AV valve regurgitation; (6) PW of the VOT. Ejection fraction was calculated from the apical 4-chamber view with tracing of the endocardial borders of the single dominant ventricle at end systole and end diastole, including the septum or both lateral walls when adjacent ventricles functioned as a common chamber. Adequate tracking of the wall movement was verified and adjusted if necessary.[21] The time points of acquisition were as follows: (1) with legs down; (2) immediately after rising the legs and installing feet in pedals; (3) at rest, that is, legs up with stabilized pressure, approximately 30 to 60 seconds after the legs-up maneuver; (4) every 20 W throughout the exercise; and (5) during the recovery period 2 minutes after finishing the test.

Spirometry, Ventilation, and Gas Exchange. Immediately before the exercise test, patients underwent spirometry measurements of forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1). The ratio of FEV_1 to FVC was calculated (Tiffeneau index). Lung function suggestive of restriction was characterized by a normal FEV_1/FVC ratio (>0.70) and a reduction in FVC below 80% with the flow-volume curve showing a convex shape. Obstructive lung function was defined as FEV_1/FVC ratio of < 0.70[22,23] Supine exercise testing was performed on a bicycle ergometer (Schiller, CS-200, Ergo-Spiro). The initial workload of 10 W was increased by 10 W every minute until exhaustion. A 12-lead electrocardiogram, blood pressure, and respiratory data through breath-by-breath analysis were continuously registered. Oxygen saturation was monitored by pulse oximetry throughout the test. Oxygen and carbon dioxide concentration were continuously measured in the inspired and expired air to determine oxygen uptake (VO_2) and carbon dioxide output (VCO_2). Peak oxygen consumption (peak VO_2) was defined as the highest 30 second average of VO_2 at the end of the test. The percentage predicted peak VO_2 was calculated according to the Gläser formula.[24] Patients were encouraged to reach maximal exertion, defined as a respiratory exchange ratio of >1.05. Ventilatory reserve was defined as the ratio of peak minute ventilation divided by estimated maximal voluntary ventilation. Heart rate reserve was calculated according to the formula (peak HR − rest HR)/(APMHR − rest HR) *100%, where APMHR (age-predicted maximal HR) was calculated as (119 + 0.5 * rest HR − 0.5 * age).[25]

Peripheral Venous Pressure and Mean Pulmonary Artery Pressure Measurements. Peripheral venous pressure was measured invasively in one of the veins of the distal upper extremity. Using a 3-way stopcock, PVP was continuously recorded via an 18- to 20-gauge intravenous line.[18] The peripheral line was cautiously secured, positioned at the midaxillary level, and connected to a pressure transducer zeroed at the same level. The pressure was continuously recorded during exercise and analyzed offline using LabChart V8 (AD Instruments). Peripheral venous pressure was averaged off over 10 consecutive cardiac cycles at specific time points: (1) with legs down, (2) immediately after raising the legs and installing the feet in the pedals, (3) with legs up after stabilizing the pressures for approximately 30 to 60 seconds after the legs-up maneuver, and (4) throughout exercise. Measurement of PVP was not possible in

Table 1 Demographic, clinical characteristics, and medical history

Parameter	Control group $n = 41$	Fontan group $n = 41$	P value*	PVP/CO slope ≤ 3 mm Hg/L/min $n = 29$	PVP/CO slope > 3 mm Hg/L/min $n = 11$	P value†
Age, years (range)	29 (23-36)	28 (22-37)	.61	26 (21-36)	32 (25-38)	.42
Body mass index, kg/m^2 (range)	26 (21-29)	22 (20-26)	.11	23 (21-26)	21 (20-27)	.55
Sex, male	23 (56)	24 (59)	.10	17 (59)	7 (64)	.77
Left ventricle dominant	—	32 (72)	—	23 (79)	8 (73)	.66
Extracardiac conduit	—	29 (71)	—	21 (72)	7 (64)	.589
Intra-atrial tunnel	—	7 (17)	—	5 (17)	2 (18)	.944
NYHA class II	—	14 (34)		9 (31)	4 (36)	.75
NYHA class III-IV	—	5 (12)		1 (3)	4 (36)	**.005**
Comorbidities						
Overweight	10 (24)	10 (24)	.43	9 (31)	1 (9)	.15
Obesity	5 (12)	3 (7)	.26	1 (3)	2 (18)	.11
Restrictive lung function	0 (0)	21 (51)	**<.001**	12 (41)	9 (82)	**.02**
Obstructive lung function	2 (5)	5 (12)	.30	3 (10)	2 (18)	.50
Any lung function abnormality	0 (0)	26 (63)	**<.001**	15 (52)	11 (100)	**.004**
Mental health issues	—	9 (22)	—	3 (10)	6 (55)	**.003**
Skeletal issues	—	2 (5)	—	1 (3)	1 (9)	.47
Hypertension	—	1 (2)	—	1 (3)	0 (0)	.83
Diabetes	—	0 (0)	—	0 (0)	0 (0)	—
Complications						
Advanced Fontan-associated liver disease	—	9 (22)	—	5 (17)	4 (36)	.19
Protein losing enteropathy	—	5 (12)	—	4 (14)	1 (9)	.67
Hepatic malignancy	—	2 (5)	—	1 (3)	1 (9)	.47
Diaphragm paresis	—	2 (5)	—	2 (7)	0 (0)	.37
Atrial arrhythmia	—	16 (39)	—	8 (28)	8 (73)	**.009**
Atrial fibrillation	—	6 (15)	—	3 (10)	3 (27)	.188
Pacemaker	—	11 (27)	—	7 (24)	4 (36)	.44
Implanted cardiac defibrillator	—	2 (5)	—	0 (0)	2 (18)	**.02**
Thromboembolism	—	6 (15)	—	2 (7)	4 (36)	**.02**
Stroke/transient ischemic attack	—	3 (7)	—	2 (7)	1 (9)	.81

Data are presented as n (%) unless otherwise indicated. Significant differences are marked with bold font.
*P value calculated for controls vs Fontan group.
†P value calculated for Fontan patients with normal vs elevated PVP/CO slope.

one patient due to technical issues (lack of venous access), thus only a CPETecho test was performed in this individual. In Fontan patients, we considered PVP a surrogate of the pressure in the Fontan pathway and hence a surrogate of the mean pulmonary artery pressure (mPAP).[26] Peripheral venous pressure has been validated against invasive pulmonary artery pressure with excellent agreement.[18] In the control group we used the Chemla formula to calculate mPAP from the tricuspid regurgitation velocity signal.[27]

Hemodynamic Calculations. All the measurements were averaged from 3 consecutive beats for patients in sinus rhythm, and 5 for patients in atrial fibrillation. Systemic ventricular SV and CO were calculated from the flow velocity-time integral in the VOT. During exercise echocardiography, CO was recorded with 10 to 20 W increments and at peak exercise. The multipoint PVP/CO slope, starting legs down, was calculated as a linear approximation using linear regression analysis from pressure-flow plots for each patient. Changes in PVP during the leg raise maneuver were recorded, but precautions were taken to exclude any transient increase in PVP into the multipoint linear approximation. An elevated PVP/CO slope was defined as >3 mm Hg/L/min.[16]

Tissue Doppler s′ velocity of the dominant ventricle lateral wall annulus was recorded with 10 to 20 W increments and at peak exercise and calculated offline with EchoPac Q-analysis. Atrioventricular valve regurgitation was assessed visually according to the current guidelines European Association of Cardiovascular Imaging recommendations.[28] Systolic and diastolic durations were measured from pulsed tissue Doppler sampled at the lateral annulus of the dominant ventricle.[29]

Statistical Analysis

Data were tested for normality with the Kolmogorov-Smirnov test. Descriptive data for continuous variables were displayed as means ± SD or as medians with interquartile ranges as appropriate. Descriptive data for discrete variables were displayed as percentages or frequencies. Continuous variables were evaluated between subgroups using 1-way analysis of variance, and, if significant, subgroups were compared

Table 2 Clinical characteristics and current medical status

Parameter	Control group *n* = 41	Fontan group *n* = 41	*P* value*	PVP/CO slope ≤3 mm Hg/L/min *n* = 29	PVP/CO slope >3 mm Hg/L/min *n* = 11	*P* value†
Biochemical profile						
NT-pro-BNP, ng/L	50 (25-74)	177.5 (86.5-286.5)	**<.001**	150.5 (61.3-255.0)	325.0 (176.3-590)	**.03**
Creatinine clearance, mL/min	102 (90-115)	112 (100-124)	.10	112 (100-125)	113 (108-120)	.83
Alfa-fetoprotein, μg/L	—	2.9 (1.9-4.7)	—	2.8 (1.8-4.3)	3.8 (3.2-9.2)	.17
Medications						
Diuretics	—	15 (37)	—	9 (31)	6 (55)	.17
Beta-blocker	—	12 (29)	—	6 (21)	6 (55)	**.04**
Renin-angiotensin-aldosteron drugs	—	5 (12)	—	4 (14)	1 (9)	.69
Mineralocorticoid receptor antagonist	—	14 (34)	—	7 (24)	7 (64)	**.02**
Acetylsalicylic acid	—	22 (54)	—	17 (59)	4 (36)	.21
Antiarrhythmic drugs	-	3 (7)	—	1 (3)	2 (18)	.11
Oral anticoagulation	—	19 (46)	—	12 (41)	7 (64)	.21
Pulmonary arterial hypertension drugs	—	4 (10)	—	2 (7)	2 (18)	.29
Echocardiography at rest						
Ejection fraction, %	59.0 (55.0-64.0)	50.0 (33.0-60.0)	**.02**	48.2 ± 6.3	49.6 ± 4.2	.421
SV, mL	76.9 (61.4-91.3)	64.2 (55.0-91.3)	.61	79.2 (56.7-98.4)	57.8 (52.2-63.2)	**.048**
SV index, mL/m^2	37.8 ± 12.3	42.7 ± 16.5	.16	45.8 ± 17.6	34.5 ± 10.8	**.02**
CO, L/min	4.7 (3.0-5.8)	4.6 (3.8-6.8)	.70	5.7 (4.4-7.0)	3.8 (3.2-4.3)	**.001**
Cardiac index, L/min/m^2	2.6 (2.3-3.1)	2.7 (2.1-4.1)	.56	3.1 (2.4-4.1)	2.1 (2.0-2.4)	**.002**
>Mild AV valve regurgitation	0 (0)	15 (37)	**<.001**	9 (31)	6 (55)	.17
>Mild ventriculoarterial valve regurgitation	0 (0)	4 (10)	.12	3 (10)	1 (9)	.91
Spirometry						
Percentage predicted FEV_1	91 (81-102)	66 (58-81)	<.001	68 (58-84)	65 (57-71)	.25
Tiffeneau index	0.82 (0.79-0.89)	0.80 (0.75-0.85)	.15	0.80 (0.75-0.85)	0.79 (0.74-0.85)	.68

Data are presented as *n* (%), median (IQR), or mean ± SD. Significant differences are marked with bold font.
**P* value calculated for controls vs Fontan group.
†*P* value calculated for Fontan patients with normal vs elevated PVP/CO slope.

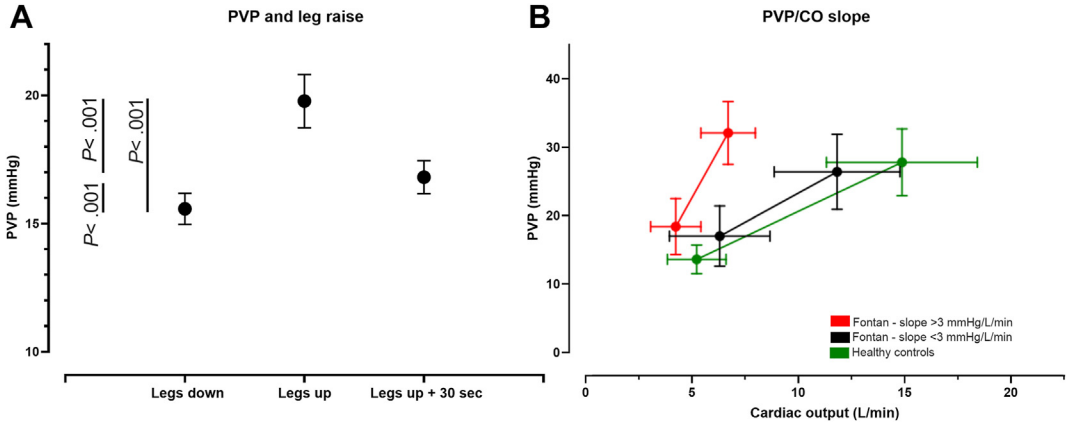

Figure 1 **(A)** There is a significant increase in PVP in patients with a Fontan circulation from legs down to legs up. The PVP then stabilizes to a lower pressure before the start of exercise, which is still slightly higher than the pressure with legs down. The *bars* represent the average ± SEM. **(B)** The slopes of the pressure-flow plots (PVP/CO) of the overall Fontan cohort were steeper than those of healthy controls (1.7 [1.2-3.1] vs 1.4 [1.1-1.8]; *P* = .02), which mainly related to ability of healthy controls to increase CO to a larger extent for a similar increase in pulmonary artery pressure. *Black* indicates Fontan patients with a PVP/CO slope ≤3 mm Hg/L/min, *red* indicates Fontan patients with a PVP/CO slope >3 mm Hg/L/min, and *green* indicates healthy controls. The *cross bars* show the average ± SD at rest and peak exercise for the different groups.

Table 3 Exercise data

Exercise variable	Control group $n = 41$	Fontan group $n = 41$	P value*	PVP/CO slope ≤3 mm Hg/L/min $n = 29$	PVP/CO slope >3 mm Hg/L/min $n = 11$	P value†
Cardiopulmonary variables						
Peak workload, W	171 (140-217)	108 (90-133)	**<.001**	110 (93-137)	86 (72-93)	**.002**
Peak VO_2,mL/kg/min	30.5 ± 9.5	20.6 ± 5.1	**<.001**	22.0 ± 5.0	17.1 ± 4.1	**.004**
Percentage predicted peakVO_2	96.3 ± 21.2	60.7 ± 16.2	**<.001**	65.2 ± 15.3	48.7 ± 13.3	**.003**
Ventilatory efficiency/VCO_2 slope	26.5 (23.8-29.4)	31.8 (26.4-35.8)	**<.001**	31.6 (25.9-34.6)	33.9 (29.8-38.1)	.07
Respiratory exchange ratio	1.10 ± 0.11	1.09 ± 0.08	.55	1.09 ± 0.08	1.09 ± 0.07	.8
HR rest, bpm	68 (58-81)	71 (65-80)	.49	74 (66-82)	65 (60-72)	.06
HR peak, bpm	160 (150-173)	136 (112-153)	**<.001**	137 (124-157)	112 (83-124)	**.004**
HRR, %	136 (123-142)	93 (58-119)	**<.001**	100 (75-127)	65 (42-105)	**.01**
SpO_2 rest, %	97.8 ± 7.4	95.7 ± 3.2	.18	96.2 ± 2.6	94.5 ± 4.3	.24
SpO_2 peak, %	97.9 ± 2.1	89.8 ± 5.1	**<.001**	89.7 ± 5.1	90.3 ± 5.8	.76
PVP (mPAP) rest, mm Hg	13.0 (11.8-15.4)†	17.1 (14.3-19.0)	**<.001**	16.2 (14.1-18.5)	17.5 (15.6-20.5)	.32
PVP (mPAP) peak, mm Hg	27.8 ± 4.9†	28.2 ± 5.5	.89	26.4 ± 5.5	32.1 ± 4.6	**.003**
PVP leg raise delta, mm Hg	—	3.4 (2.3-5.0)	—	3.5 (2.2-4.3)	3.3 (2.8-8.8)	.46
PVP/CO (mPAP/CO) slope, mm Hg/L/min	1.4 (1.1-1.8)	1.7 (1.2-3.1)	**.02**	1.4 (1.1-2.0)	4.1 (3.5-5.3)	<.001

Significant differences are marked with bold font.
*P value calculated for controls vs Fontan group.
†P value calculated for Fontan patients with normal vs elevated PVP/CO slope.

using independent t test analysis. Proportions were evaluated between subgroups using χ^2 analysis. Intra- and interobserver variability was assessed by repeated analysis of the CO at rest and at 40 W of 20 patients at least 2 months after the initial analysis and blinded to the initial results. Interobserver variability was assessed by a second observer (A.V.D.B.). The agreement between the 2 measurements was expressed using the 95% CI and determined as the mean bias ± 1.96 SD. Inter- and intraobserver variability was also assessed using the intraclass correlation coefficient (ICC).[30,31] Univariable regression analysis with percentage predicted peak oxygen consumption as the dependent variable was performed. All tests were 2-sided, and $P < .05$ was considered statistically significant. Data analysis was performed using SPSS for Windows (ver. 24, IBM).

RESULTS

Patient Population

Baseline characteristics are shown in Tables 1 and 2. Thirty-two (78%) had a dominant left ventricle (tricuspid atresia [$n = 19$], double-inlet left ventricle [$n = 8$], pulmonary atresia with intact ventricular septum [$n = 4$], and ventricular septal defect [$n = 1$]). Among individuals with nondominant left ventricle anatomy, there were 5 patients with double-outlet right ventricle, 2 with hypoplastic left heart syndrome, 1 with mitral atresia, and 1 with congenitally corrected transposition of the great arteries. Twenty-nine had an extracardiac conduit (of whom 8 had prior conversion from atriopulmonary connection); in 7 patients an intra-atrial connection was created; atriopulmonary connection was present in 3 individuals; and 2 patients had the right atrial appendage connected to the pulmonary artery in combination with a bidirectional Glenn. Six patients underwent prior conduit stenting, and none had a measured pressure gradient over the Fontan pathway.

Fontan patients had lower ventricular ejection fraction, higher hemoglobin, and higher NT-pro-BNP levels compared to controls. The NT-pro-BNP level was normal in 11 (27%) individuals after Fontan repair. A PVP/CO slope >3 mm Hg/L/min was present in 11 patients (27.5%), and these patients were more likely to have worse functional class (New York Heart Association III-IV) and higher NT-pro-BNP. Additionally, they were more likely to have a cardioverter-defibrillator, a history of atrial arrhythmia or thromboembolism, and mental health issues and abnormal lung function when compared to those with a slope <3 mm Hg/L/min (Table 1).

EXERCISE HEMODYNAMICS

Peripheral Venous Pressures at Rest and During Exercise

In patients who performed a leg raise maneuver ($n = 27$), PVP increased from 15.6 ± 3.5 mm Hg to 19.8 ± 5.4 ($P < .001$). Subsequently, after 30 seconds PVP decreased to 16.8 ± 4.1 mm Hg ($P < .001$), although it remained significantly higher compared to the baseline level with legs down ($P < .001$; Figure 1).

Measurements of resting PVP just before the beginning of exercise were available for 40 patients, with a median value of 17.1 (14.3-19.0) mm Hg. During exercise, PVP increased from 17.9 ± 4.0 mm Hg at rest to 28.2 ± 5.5 mm Hg at peak exercise.

In the control group mPAP at rest was lower than resting PVP in Fontan patients ($P < .001$), whereas peak mPAP and peak PVP were similar in both cohorts ($P = .889$).

Patients with the slope >3 mm Hg/L/min did not differ with regard to resting PVP (17.5 [15.6-20.5] vs 16.2 [14.1-18.5] mm Hg; $P = .323$) but reached significantly higher PVP values at peak exercise when compared to those with normal slope (32.1 ± 4.6 vs 26.4 ± 5.5 mm Hg, $P = .003$; Figure 1 and Table 3).

Cardiopulmonary Exercise Test and Exercise Echocardiography

Detailed characteristics of exercise physiology of the study group are shown in Table 2. In Fontan patients, mean peak VO_2 was

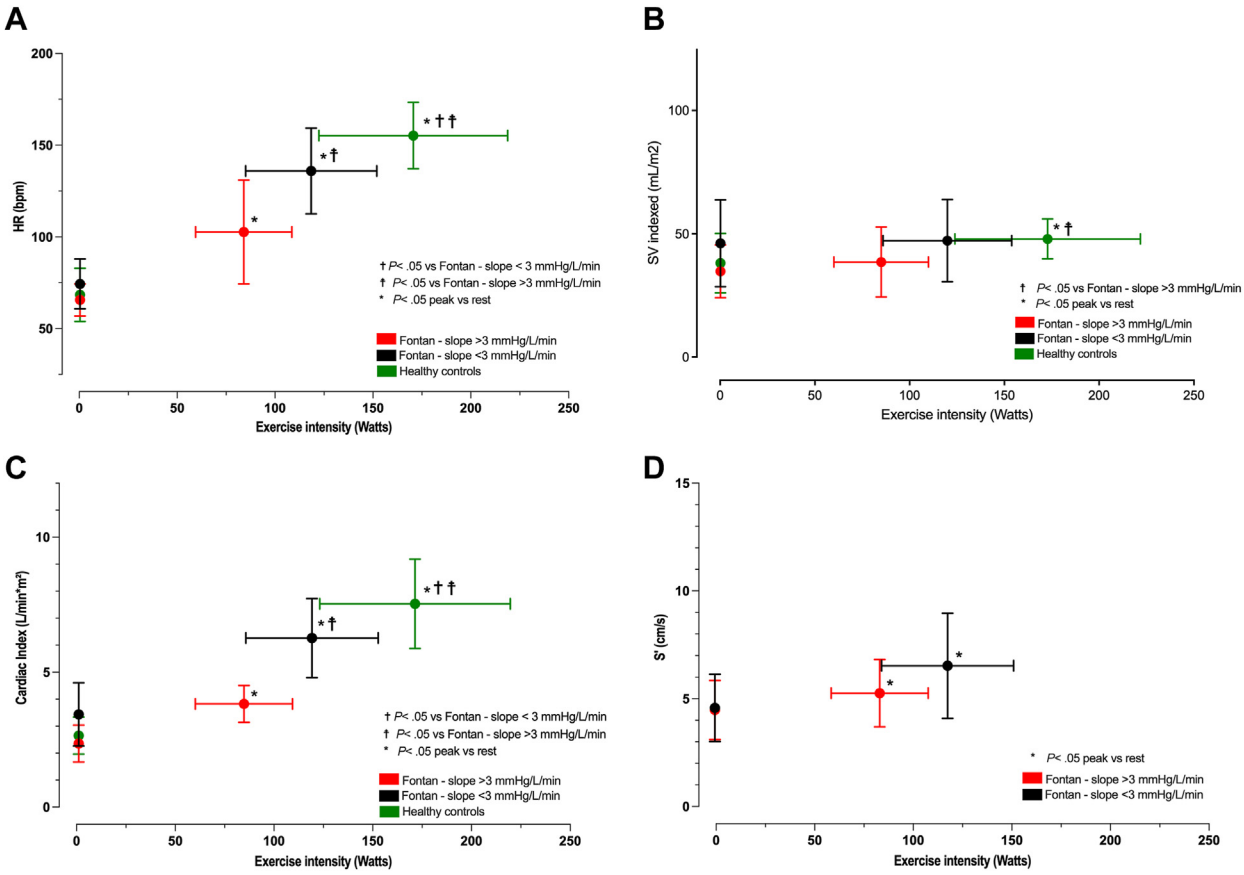

Figure 2 Change in HR **(A)**, SVi **(B)**, cardiac index **(C)**, and peak systolic velocity of the lateral annulus of the dominant ventricle **(D)** throughout exercise. Heart rate reserve and peak cardiac index are lower in Fontan patients with a steeper PVP/CO slope and lower for all Fontan patients when compared to controls. *Black* indicates Fontan patients with a PVP/CO slope <3 mm Hg/L/min, *red* indicates Fontan patients with a PVP/CO slope ≥3 mm Hg/L/min, and *green* indicates healthy controls. The *cross bars* display the average ± SD at rest and peak exercise for the different groups.

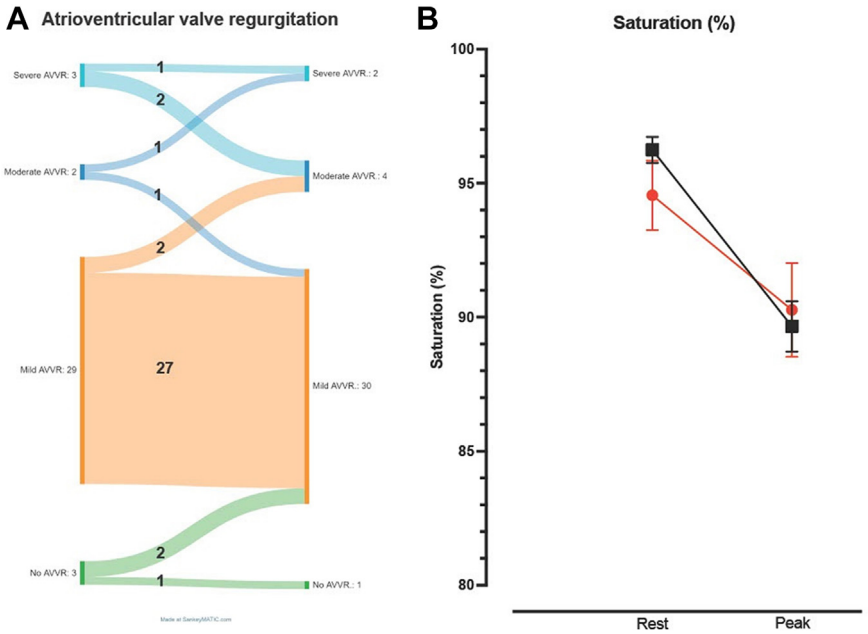

Figure 3 Changes in degree of atrioventricular valve regurgitation **(A)** and oxygen saturation **(B)** from rest *(left)* to peak *(right)* exercise. The degree of desaturation is similar between Fontan patients with a steeper PVP/CO slope (indicated in *red color*) when compared to the subgroup with normal slope *(black color)*.

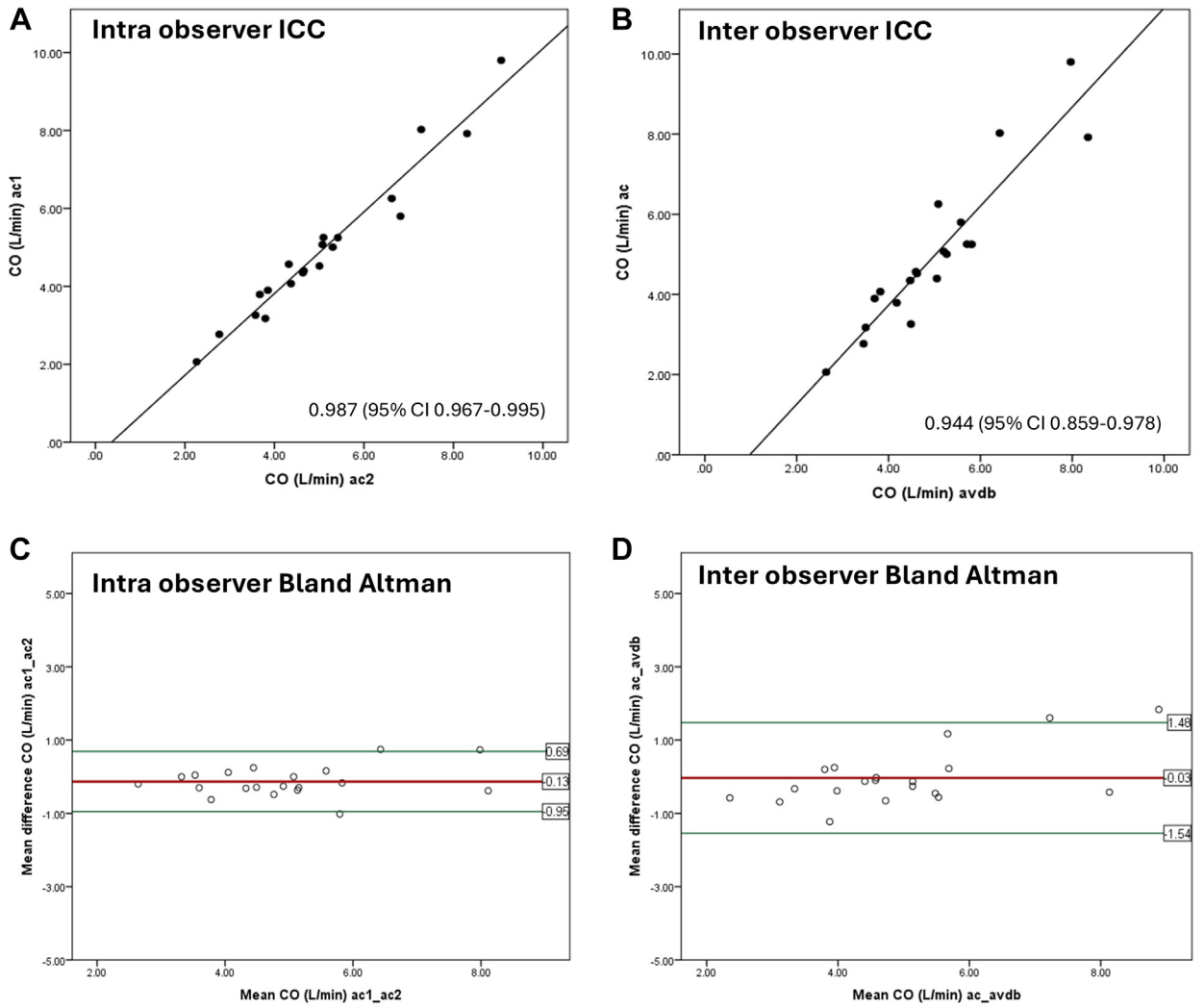

Figure 4 Intra- and interobserver ICC **(A** and **B)** and intra- and interobserver variability using Bland-Altman **(C** and **D)** with regard to CO calculations.

20.6 ± 5.1 mL/kg/min, with a mean predicted VO_2 of 60.7% ± 16.2%. Ten Fontan patients (24%) did not achieve 50% of the predicted peak VO_2, whereas 6 (15%) reached ≥80% predicted peak VO_2. Median peak workload in the whole study group was 108 (range, 49-224; interquartile range, 90-133) W. Resting SV indexed (SVi) by body surface area was <35 mL/m^2 in 18 (44%) patients after Fontan operation. Resting cardiac index was <2.2 L/m^2 in 12 (29%) individuals. All patients were able to augment the CO throughout the exercise. Of interest, although HR and cardiac index at rest were similar between controls and Fontan patients, peak HR and peak cardiac index were significantly lower in Fontan patients when compared to controls. In addition, SVi did not increase in Fontan patients (43 ± 16 to 45 ± 16 mL/m^2; $P = .443$), whereas it did in healthy controls (38 ± 12 to 48 ± 8 mL/m^2; $P < .001$). The resultant pressure-flow slope was on average steeper in Fontan patients when compared to controls (Figures 1 and 2, Table 3).

Patients with a PVP/CO slope >3 mm Hg/L/min had significantly lower exercise capacity when compared to those with a normal slope (peak VO_2, 17.1 ± 4.1 vs 22.0 ± 5.0 mL/kg/min; $P = .004$; percentage predicted peak VO_2, 48.7 ± 13.3 vs 65.2 ± 15.3; $P = .003$; peak workload (86 [72-93] vs 110 [93-137] W; $P = .002$). Patients with PVP/CO slope >3 mm Hg/L/min had lower resting SVi (34.5 ± 10.8 vs 45.8 ± 17.6 mL/m2; $P = .048$) and cardiac index (2.1 [2.0-2.4] vs 3.1 [2.4-4.1] L/min/m^2; $P = .002$), as well as lower peak cardiac index (3.8 ± 0.8 vs 6.3 ± 1.5; $P < .0001$) and peak HR (112 [83-124] vs 137 [124-157]; $P = .004$) when compared to those with normal slope.

Chronotropic response was significantly more blunted in those with PVP/CO slope >3 mm Hg/L/min (peak HR, 112 [83-124] vs 137 [124-157] bpm; $P = .004$; HRR, 65% [42%-105%] vs 100% [75-127]; $P = .01$). There was no significant difference with regards to oxygen saturation decrease during the exercise test between the group with elevated versus normal PVP/CO slope (delta SpO_2 −4.3 ± 2.9 vs −6.6 ± 4.3; $P = .063$).

The evolution of AV valve regurgitation and oxygen saturation during exercise is summarized in Figure 3. The majority of patients had mild AV valve regurgitation (71%), which mostly remained stable during exercise. Oxygen saturation in the study group decreased significantly during exercise in comparison to the healthy controls, although saturation at peak exercise was similar

Table 4 Univariable regression analysis: predictors of percentage predicted peak VO_2

Variable	Unstandardized beta coefficient	Standardized beta coefficient	*P* value
Age	−0.140	−0.085	.96
Body mass index	1.498	0.385	**.013**
S' rest	−0.347	−0.039	.823
S' delta	2.050	0.244	.152
E/e' rest	−0.372	0.058	.735
E/e' delta	0.743	0.113	.506
HR rest	0.102	0.087	.587
HR delta	0.294	0.490	**.001**
SVi rest	−0.132	−0.135	.401
SVi delta	0.060	0.033	.839
Cardiac index rest	−1.333	−0.098	.541
Cardiac index delta	5.815	0.421	**.006**
PVP rest	−0.874	−0.228	.156
PVP delta	−0.203	−0.062	.701
SpO_2 rest	0.922	0.181	.257
SpO_2 delta	0.344	0.086	.595
CO/VO_2	−1.933	−0.282	.074
Peak ventilation/maximum voluntary ventilation	12.855	0.192	.234
Ventilatory efficiency /VCO_2 slope	0.390	−0.161	.328
VO_2/W slope	1.239	0.122	.452
NT-pro-BNP	−0.017	−0.269	.102
Percentage predicted FVC	0.345	0.324	**.044**
Percentage predicted FEV_1	0.337	0.309	.055
Tiffeneau index	12.374	0.058	.728
Leg raise maneuver delta	−0.893	−0.210	.294
PVP/CO slope	−4.418	−0.411	**.009**

Significant differences are marked with bold font.

between Fontan patients with the abnormal versus normal slope ($P = .760$). The change of various echocardiographic parameters in response to exercise is demonstrated in Supplemental Table 1; the relationship between the PVP/CO slope (as a continuous variable) and parameters reflecting exercise tolerance is summarized in Supplemental Table 2.

There was a very good agreement in measurements of CO between 2 blinded observers (A.C. and A.V.D.B.). Mean bias ± limits of agreement for CO measures were −0.13 L/min (−0.95-0.69) and −0.03 L/min (−1.54-1.48) for intra- and interobserver variability, respectively. The CO intraobserver ICC was 0.987 (95% CI, 0.967-0.995), and interobserver ICC was 0.944 (95% CI, 0.859-0.978; Figure 4).

Variables Related to Exercise Capacity

In univariable regression analysis, a larger HRR (HR delta, $P = .001$), a larger increase in cardiac index during exercise (cardiac index delta, $P = .006$), a higher percentage predicted FVC ($P = .044$), and a lower pressure-flow slope (PVP/CO slope, $P = .009$) were related to better percentage predicted peakVO_2 (Table 4).

DISCUSSION

This study explores a novel, noninvasive diagnostic approach by combining exercise echocardiography and cardiopulmonary gas exchange with simultaneous PVP calculations to provide a comprehensive insight into hemodynamic patterns of response to exercise in Fontan patients.

Differences in Exercise Hemodynamics Between Fontan Patients and Controls

Our study confirms prior studies[32-36] that Fontan patients have worse exercise tolerance (on average 60% predicted peak oxygen consumption) when compared to age- and gender-matched healthy controls. Our data also confirm that the absence of a subpulmonary pump limits CO augmentation throughout exercise.[5,12,37] About 30% of Fontan patients had a low resting cardiac index, while on average resting SVi, cardiac index, and HR were similar to controls. In contrast, peak HR, SVi, and cardiac index were significantly lower in Fontan patients and even more reduced in those with a steeper pressure-flow plot. The inability to increase SVi (in contrast to controls) suggests that the increase in cardiac index in Fontan patients is

mainly related to an increase in HR. Fontan patients with an abnormal pressure flow slope had an even lower HRR, potentially related to a higher prevalence of atrial arrhythmias and subsequent use of beta-blockers. Since the failing Fontan circulation shares similarities to heart failure with preserved ejection fraction, beta-blocker withdrawal may improve exercise capacity in selected Fontan patients.[5,8,38] On the other hand, improving the chronotropic response by atrial pacing did not impact exercise capacity in Fontan patients.[39]

Fontan Pressure at Rest and During Exercise

In Fontan patients, elevated systemic venous pressure (Fontan pressures) is the main driving force propelling blood through the pulmonary vasculature but also a main cause of end-organ damage, such as cirrhosis, renal dysfunction, and protein-losing enteropathy.[16] Peripheral venous pressure measurements represent a validated, less invasive, less costly alternative to measure Fontan pressure at rest and during exercise[18] and in combination with echocardiography can be used to further elucidate mechanisms of exercise intolerance in Fontan patients.

Of interest, we noted a transient increase in PVP of 3 mm Hg on average during a leg raise maneuver. Although this did not correlate to exercise capacity, it warrants further investigation as this pressure difference is similar to the differences in pulmonary capillary wedge pressure reported by Miranda *et al.*[8] during a similar maneuver.

During exercise, Fontan pressure increased in all patients, which is consistent with the response to exercise seen in healthy subjects.[40] However, in contrast to healthy subjects who can increase (systolic) pulmonary artery pressure to up to 60 mm Hg,[41] there appears to be a limit to the extent that Fontan pressure can increase during exercise,[5] with only 1 patient exceeding a PVP of 40 mm Hg during exercise in this study.

Pressure-Flow Plots in Fontan Patients

Since pulmonary artery pressure is flow dependent, a multipoint relation between pressure and flow rather than a single measurement[19,40,42-45] is more appropriate. A pressure-flow slope steeper than 3 mm Hg/L/min has been related to worse clinical status (including endothelial dysfunction, liver stiffness, renal impairment, and volume overload) and worse outcome in Fontan patients.[16] In our study, 25% of patients had an elevated PVP/CO slope, which is lower than in the cohort assessed by Egbe *et al.*,[16] likely reflecting selection bias, with sicker patients being referred for cardiac catheterization. In this study, patients with a steeper PVP/CO slope (>3 mm Hg/L/min) also had worse New York Heart Association class, worse exercise tolerance, and higher NT-pro-BNP compared to those with a normal PVP/CO slope. This subgroup was also more likely to have lung function abnormalities, a history of thromboembolism, and a history of atrial arrhythmia, to use beta-blockers, and to have a limited HR response during exercise, reflecting the multifactorial origin of exercise intolerance. Finally, a particular concern is that half of patients with a steeper slope reported mental health issues. Overall worse clinical status may indeed have a significant impact on the mental status and overall quality of life of our patients.[46,47] Alternatively, a worse mental health status could lead to unhealthy behaviors such as a sedentary lifestyle, which is known to negatively impact cardiovascular health[46,47]

Determinants of Exercise Capacity

A PVP/CO slope >3 mm Hg/L/min was related to worse exercise tolerance, whereas absolute PVP measurements were not, indicating that combining pressure and flow increases the sensitivity and specificity of detecting abnormalities. However, an elevated PVP/CO slope is not diagnosis specific, and efforts should be made to identify causal pulmonary vascular disease, diastolic or systolic ventricular dysfunction, AV valve regurgitation, or a combination of factors. Still, the close correlation between noninvasive PVP and invasively measured wedge pressure[18] suggests a central role for diastolic dysfunction in the pathophysiology of exercise intolerance in Fontan patients. In this cohort of Fontan patients, worse AV valve regurgitation, impaired systolic function and lower oxygen saturation at rest or during exercise were not related to worse exercise capacity. This could be due to the small number of patients with severe AV valve regurgitation and severely reduced ventricular systolic function.

Limitations

It is important to underline a few limitations of the study. First, the ratio of PVP to CO has not been invasively validated. The method using CO derived from the velocity-time integral may have introduced inaccuracies and requires further validation in Fontan patients. Second, mPAP and PVP were obtained by echocardiography and direct venous pressure measurement, respectively. Although both measure pulmonary artery pressure, differences in acquisition may have introduced error. Third, the threshold of >3 mm Hg/L/min was derived from previous studies assessing various cohorts including Fontan patients.[16] Whether this represents the optimal cutoff for Fontan patients remains to be evaluated as some suggest a wider range of normal up to 3.5 mm Hg/L/min.[48] Also the prognostic value of the PVP/CO slope requires validation. Fourth, the assessment of ejection fraction in Fontan patients is challenging. There are specific anatomical considerations (dominant left or right ventricle, various extents of septal contribution to the systolic movement) and variability between measurements that require caution when interpreting small differences. Fifth, this is a single-center study with a limited number of patients and needs validation in a larger, multicenter cohort of patients. Sixth, although there was good intra- and interobserver agreement, there were a few outliers, especially during exercise. The use of at least 4 measurements during the study and linear regression analysis will limit the measurement errors.

CONCLUSION

Patients with Fontan circulation have worse exercise tolerance and higher NT-pro-BNP when compared to controls. Although similar at rest, the main differences relate to the inability of Fontan patients to increase cardiac index and HR during exercise, resulting in an overall steeper pressure-flow slope in Fontan patients. A steeper PVP/CO plot (>3 mm Hg/L/min) in Fontan patients is associated with worse clinical status, including higher New York Heart Association class, lung function abnormalities, atrial arrhythmia, and higher NT-pro-BNP. Patients with a steeper PVP/CO slope were more likely to have blunted chronotropic response and had higher peak PVP and lower peak cardiac index. Moreover, a steeper PVP/CO slope was related to decreased exercise capacity, whereas absolute PVP values were not. This suggests the value of implementing CPETecho-PVP in the setting of a dedicated Fontan clinic.

REVIEW STATEMENT

Given her role as *JASE* Editor-in-Chief, Patricia A. Pellikka, MD, had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the

editorial process for this article was delegated to guest editor John Simpson, MD.

CONFLICTS OF INTEREST

None.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.echo.2025.05.007.

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