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Exercise Capacity, NT-proBNP, and Exercise Hemodynamics in Adults Post-Fontan

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ABSTRACT

BACKGROUND Cardiopulmonary exercise testing (CPET) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) measurement are frequently performed in adults post-Fontan, but their correlations with exercise invasive hemodynamics are poorly understood. Moreover, whether exercise cardiac catheterization provides incremental prognostic information is unknown.

OBJECTIVES The authors sought to correlate resting and exercise Fontan pressures (FP) and pulmonary artery wedge pressure (PAWP) with peak oxygen consumption (VO_2) on CPET, NT-proBNP, and clinical outcomes.

METHODS This was a retrospective cohort of 50 adults (age ≥18 years) post-Fontan undergoing supine exercise venous catheterization between 2018 and 2022.

RESULTS Median age was 31.5 years (IQR: 23.7-36.5 years). Ventricular ejection fraction was 48.5% ± 13.0%. Exercise FP and PAWP were related to peak VO_2 and ln NT-proBNP levels. Patients with peak VO_2 <50% predicted had higher exercise FP (30.0 ± 6.8 mm Hg vs 19 mm Hg [IQR: 16-24 mm Hg]; $P < 0.001$) and PAWP (25.9 ± 6.3 mm Hg vs 15.1 ± 7.0 mm Hg; $P < 0.001$) compared with those with more preserved exercise capacity. Exercise FP (30.0 ± 7.1 mm Hg vs 23.2 ± 7.2 mm Hg; $P = 0.003$) and PAWP (25.1 ± 6.7 mm Hg vs 18.8 ± 7.9 mm Hg; $P = 0.006$) were higher in those with NT-proBNP levels ≥300 pg/mL. During a follow-up of 0.9 years (IQR: 0.6-2.9 years), exercise FP and PAWP remained independently associated with a composite of death, cardiac transplantation, or hospitalization due to heart failure/refractory arrhythmias after adjusting for confounders.

CONCLUSIONS In adults post-Fontan, resting and exercise FP and PAWP were inversely related to exercise capacity on noninvasive CPET, and exercise hemodynamics were directly related to NT-proBNP levels. Exercise FP and PAWP were independently associated with clinical outcomes and might be more sensitive than resting values to predict clinical outcomes. (J Am Coll Cardiol 2023;81:1590–1600) © 2023 by the American College of Cardiology Foundation.

Individuals post-Fontan palliation are at risk for progressive diastolic dysfunction due to worsening ventricular compliance, valvular disease, and, in a subset of patients, systolic dysfunction. Thus, adults post-Fontan share similarities with patients who have acquired heart failure with preserved (HFpEF) and reduced (HFrEF) ejection fraction. Exercise capacity during cardiopulmonary exercise testing (CPET) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels are 2 widely used, well-validated diagnostic and prognostic tools in heart failure secondary to acquired pathologies. In HFpEF, increases in pulmonary artery wedge pressure (PAWP) with exercise are independently associated with poorer exercise capacity,[1,2] whereas in HFrEF, these relationships are less consistent.[3,4] Conversely,

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data suggest that natriuretic peptides may be more robustly associated with increased filling pressures in HFrEF compared with HFpEF.[5,6] In both instances, they correlate with increased filling pressures in chronic heart failure patients but only modestly.[7]

Peak oxygen consumption (VO_2) during noninvasive CPET and NT-proBNP levels are frequently measured during the care of post-Fontan patients. However, compared with acquired heart disease, data on invasive hemodynamics correlates are limited, and the associations between peak VO_2 and NT-proBNP levels with PAWP during exercise have not been studied. This is particularly important in Fontan patients because functional capacity limitation is universal, and other potential reasons for exercise intolerance (such as ventilatory and/or skeletal muscle abnormalities) are frequently present. The challenges and lack of standardization in the echo-Doppler assessment of filling pressures in these patients further complicate the determination of the etiology of exercise intolerance post-Fontan. Last, whether exercise invasive Fontan hemodynamics provide incremental prognostic information compared with resting hemodynamics is unknown.

Accordingly, the aim of the present study is to correlate resting and exercise Fontan pressures (FP) and PAWP with: 1) exercise capacity on noninvasive CPET; 2) neurohormonal activation, as reflected by NT-proBNP levels; and 3) clinical outcomes.

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METHODS

The present cohort included 50 consecutive adults (age ≥18 years) post-Fontan palliation undergoing exercise venous catheterization at Mayo Clinic, Minnesota, between November 2018 and May 2022. Indications for cardiac catheterization were worsening clinical condition/exercise intolerance in 29 patients (58%), arrhythmia in 7 (14%), liver disease in 6 (12%), transplant evaluation in 6 (12%), and pulmonary artery branch and Fontan conduit stenosis in 1 each. The Institutional Review Board approved the study, and only patients providing prior authorization to use their medical records were included.

As previously reported,[8,9] exercise venous cardiac catheterization was performed via internal jugular approach using a supine cycle protocol. Exercise was maintained until maximal tolerated effort (Borg perceived effort score >16 and/or dyspnea score >6). Resting and exercise systemic (Qs) and pulmonary (Qp) flows were calculated by the direct Fick principle.[10] Expected exercise-induced changes in flow were calculated as ($\Delta VO_2 \times 0.006$).[11] FP reported herein represent mean pulmonary artery pressures. Pressure measurements represent computer-generated averages of ≥5 consecutive cardiac cycles under spontaneous breathing.

Baseline and follow-up clinical data were abstracted from the electronic medical records. CPET was performed in a standard, symptom-limited fashion using a treadmill (n = 36) or cycle (n = 3) protocol, as previously described.[12-14] The most recent cardiopulmonary exercise data (time difference between catheterization and CPET studies 48 days [IQR: 2-177 days]) and NT-proBNP levels (time difference between catheterization and laboratory studies 2.5 days [IQR: 1-55 days]) were selected. A minimum of 6 months of follow-up were obtained in all patients.

ABBREVIATIONS AND ACRONYMS

CPET = cardiopulmonary exercise testing

FP = Fontan pressures

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

NYHA = New York Heart Association

NT-proBNP = N-terminal pro-B-type natriuretic peptide

PAWP = pulmonary artery wedge pressure

Qp = pulmonary flow

Qs = systemic flow

VO_2 = oxygen consumption

STATISTICAL ANALYSIS. Nominal variables are present as counts (%), and continuous variables are reported as mean ± SD or median (IQR). Patients were classified as having a decreased peak VO_2 on noninvasive CPET (<50% predicted) based on published expert consensus statement definitions.[15] Given the lack of Fontan-specific recommendations, individuals were categorized according to their NT-proBNP levels using a cutoff of 300 pg/mL, which has been reported as optimal for excluding heart failure in acquired heart disease.[16] Groups were compared using unpaired Student's *t*-test or Wilcoxon test, whichever most appropriate. Comparisons between continuous variables were performed using simple linear regression. Noteworthy, *P* values and 95% CIs presented in this report have not been adjusted for multiplicity, and therefore, inferences drawn from these statistics may not be reproducible. Due to the skewed distribution of NT-proBNP levels, ln NT-proBNP was used in the analyses. Similarly, log-transformed ΔPAWP/ΔQs and ΔPA/ΔQp values were used. Regression analyses were used to assess the association between hemodynamics and ln NT-proBNP levels while adjusting for age, body mass, presence of atriopulmonary Fontan connection, ≥moderate atrioventricular regurgitation, ventricular ejection fraction, and renal insufficiency (creatinine clearance <60 mL/min) with results presented as β coefficients ± standard error.

Cox proportional regression analyses were used to assess the association between hemodynamic data

TABLE 1 Demographic and Clinical Data (N = 50)

Age, y	31.5 (23.7-36.5)
Body mass index, m^2	26.2 ± 6.2
Female	18 (36)
Age at time of Fontan, y	3 (2.0-5.3)
Heterotaxy	2 (4)
Right ventricular predominance	19 (38)
Patent fenestration	7 (14)
Protein-losing enteropathy	1 (2)
Hypertension	5 (10)
Diabetes	3 (6)
Pacemaker	20 (40)
Cirrhosis	17 (34)
Prior atrial arrhythmias	24 (48)
Creatinine clearance <60 mL/min	3 (6)
Atrioventricular valve prosthesis/repair	6 (12)
NT-proBNP, pg/mL, n = 45	322 (100-927)
Symptoms	
NYHA functional class III-IV	23 (46)
Dyspnea	31 (62)
Fatigue	21 (42)
Edema	18 (36)
Medications	
Diuretic agent	25 (50)
Beta-blocker	19 (38)
ACE inhibitor/ARB	29 (58)
Aldosterone antagonist	16 (32)
Digitalis	7 (14)
Antiarrhythmic agent	16 (32)
Pulmonary vasomodulator therapy	13 (26)
Echocardiography	
Ejection fraction, %	48.5 ± 13.0
≥Moderate ventriculoarterial regurgitation	1 (2)
≥Moderate atrioventricular regurgitation	10 (20)
Cardiopulmonary exercise test, n = 39	
Peak VO_2, mL/kg/min	17.9 ± 5.1
Peak VO_2, % of predicted	45.3 ± 13.3

Values are median (IQR), mean ± SD, or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; VO_2 = oxygen consumption.

and clinical outcomes (a composite of death, cardiac transplantation, or hospitalization due to heart failure/refractory arrhythmias). Univariable analyses included resting and exercise FP and PAWP as well as clinical variables selected a priori based on reported markers of poor prognosis in post-Fontan patients.[17,18] Bivariable Cox models were then built adjusting for variables significantly associated with clinical outcomes on univariable analyses. Statistical analysis was conducted with JMP for SAS version 14.1.0 (SAS Institute); *P* values <0.05 were considered statistically significant.

RESULTS

Clinical characteristics of the cohort are presented in Table 1. Median age was 31.5 years (IQR: 23.7-36.5 years), and 18 patients were female (36%). Fontan palliation was performed at 3 years (IQR: 2.0-5.3 years). Underlying congenital heart defects were: double inlet left ventricle in 14 patients (28%), double outlet right ventricle in 12 (24%), pulmonary atresia with intact ventricular septum in 9 (18%), tricuspid atresia in 7 (14%), hypoplastic left heart syndrome in 6 (12%), and other in 2 (4%). Types of Fontan connection were: extracardiac conduit in 20 patients (40%), lateral tunnel in 17 (34%), atriopulmonary anastomosis in 7 (14%), intra-atrial tunnel/conduit and atriopulmonary anastomosis in 4 (8%), right atrial appendage-right ventricular anastomosis and Kawashima in 1 each (2%). Five patients (10%) had undergone Fontan stenting and 1 (1%) had undergoing pulmonary artery stenting.

Exertional dyspnea was the most common symptom, present in 31 patients (62%); 23 patients (46%) had New York Heart Association (NYHA) functional class III-IV. Ventricular ejection fraction by transthoracic echocardiography was 48.5% ± 13.0%, with 10 patients (20%) having ≥moderate atrioventricular regurgitation. Peak VO_2 on outpatient CPET was 17.9 ± 5.1 mL/kg/min, corresponding to 45.3% ± 13.3% predicted based on our institution's normative values.

Hemodynamic data are presented in Table 2. At rest, FP was 14.0 ± 4.0 mm Hg, whereas PAWP was 10.0 ± 4.0 mm Hg. Arterial O_2 saturation was 93% (IQR: 89%-95%). Cardiac index was 2.7 L/min/m^2 (IQR: 2.0-3.5 L/min/m^2) with a pulmonary vascular resistance index of 1.8 ± 0.9 U • m^2. At peak exercise (66.4 ± 26.9 W), Borg perceived effort and dyspnea scores were 16.5 ± 2.2 and 6.9 ± 2.2, respectively, whereas respiratory exchange ratio was 1.02 ± 0.1. FP increased to 26.3 ± 7.7 mm Hg, whereas PAWP rose to 21.7 ± 7.9 mm Hg. Pulmonary vascular resistance index decreased to 1.3 ± 0.8 U • m^2.

CORRELATION BETWEEN INVASIVE HEMODYNAMICS AND EXERCISE CAPACITY. There was no difference in resting FP (14.7 ± 4.3 mm Hg vs 13.4 ± 3.8 mm Hg; *P* = 0.29) or PAWP (10.2 ± 4.5 mm Hg vs 9.8 ± 3.6 mm Hg; *P* = 0.70) among patients with NYHA functional class III-IV compared with the rest of the cohort. Patients with higher NYHA functional class tended to display higher exercise FP (28.3 ± 7.9 mm Hg vs 24.7 ± 7.2 mm Hg; *P* = 0.10)

TABLE 2 Resting and Exercise Hemodynamics

Rest		
Hemoglobin, g/dL	50	14.1 ± 2.2
Arterial O_2 saturation, %	50	93 (89-95)
SVC, mm Hg	50	14.7 ± 5.5
PA, mm Hg	49	14.0 ± 4.0
PAWP, mm Hg	48	10.0 ± 4.0
Arterial systolic pressure, mm Hg	39	118.6 ± 18.6
Arterial diastolic pressure, mm Hg	39	64.5 ± 13.9
Arterial mean pressure, mm Hg	37	81.3 ± 14.5
Cardiac index, L/min/m^2	49	2.7 (2.0-3.5)
PVRi, U • m^2	48	1.8 ± 0.9
Feet-up		
SVC, mm Hg	43	16 (13-20)
PAWP, mm Hg	47	13 (10-15)
Exercise		
Arterial O_2 saturation, %	50	87 (82.8-92)
SVC, mm Hg	43	26.3 ± 8.2
PA, mm Hg	49	26.3 ± 7.7
PAWP, mm Hg	48	21.7 ± 7.9
Arterial systolic pressure, mm Hg	34	153.6 ± 31.3
Arterial diastolic pressure, mm Hg	34	75.7 ± 13.5
Arterial mean pressure, mm Hg	33	10.9 ± 17.3
PVRi, U • m^2	46	1.3 ± 0.8
ΔPAWP/ΔQs	46	4.3 (1.2-7.3)
ΔPA/ΔQp	47	4.8 (2.6-7.9)
ΔPAWP/ΔQs >2 mm Hg/L/min	46	32 (69.6)
ΔPA/ΔQp >3 mm Hg/L/min	47	33 (70.2)
VO_2, mL/kg/min	50	917.2 ± 330.1
Load, W	50	66.4 ± 26.9

Values are n, mean ± SD, or median (IQR).

PA = pulmonary artery; PAWP = pulmonary artery wedge pressure; PVRi = pulmonary vascular resistance index; O_2 = oxygen; Qp = pulmonary flow; Qs = systemic flow; SVC = superior vena cava; VO_2 = oxygen consumption.

and PAWP (23.9 ± 7.4 mm Hg vs 19.8 ± 8.0 mm Hg; $P = 0.07$) compared with those with NYHA functional class I-II.

Thirty-nine patients (78%) underwent outpatient CPET. Scatterplots and linear regression lines for peak VO_2 according to different hemodynamic parameters are presented in **Figure 1**. Resting FP and PAWP correlated with peak VO_2 ($r = -0.43$, slope −0.36; $P = 0.008$ and $r = -0.44$, slope −0.36; $P = 0.006$, respectively); similarly, % predicted peak VO_2 correlated with resting FP and with PAWP ($r = -0.49$, slope −0.16; $P = 0.002$ and $r = -0.57$, slope −0.18; $P < 0.001$, respectively). Peak VO_2 correlated with exercise FP ($r = -0.48$, slope −0.76; $P = 0.002$) and exercise PAWP ($r = -0.52$, slope −0.83; $P < 0.001$), with % predicted peak VO_2 being associated with exercise FP and PAWP ($r = -0.54$, slope −0.33 and $r = -0.60$, slope −0.37, respectively; $P < 0.001$ for both). Peak VO_2 and % predicted VO_2 were associated with exercise Qs ($r = 0.43$, slope 0.23; $P = 0.009$ and $r = 0.50$, slope 0.10; $P = 0.002$, respectively). Similar to absolute pressure measurements at peak exercise, log ΔPAWP/ΔQs ($r = -0.64$, slope −0.08; $P < 0.001$) and log ΔPA/ΔQp ($r = -0.70$, slope −0.06; $P < 0.001$) were also associated with % predicted VO_2 (Supplemental Figure 1).

A peak VO_2 <50% predicted was documented in 24 patients (61.5%). Compared with those with more preserved peak VO_2, there was no statistically significant difference in resting FP (15.0 ± 4.2 mm Hg vs 12.6 ± 4.4 mm Hg; $P = 0.09$), whereas resting PAWP was higher in those with peak VO_2 <50% predicted (11.3 ± 4.3 mm Hg vs 7 mm Hg [IQR: 5-12 mm Hg]; $P = 0.02$). These patients had higher exercise FP (30.0 ± 6.8 mm Hg vs 19 mm Hg [IQR: 16-24 mm Hg]; $P < 0.001$) and PAWP (25.9 ± 6.3 mm Hg vs 15.1 ± 7.0 mm Hg; $P < 0.001$) compared with the rest of the cohort.

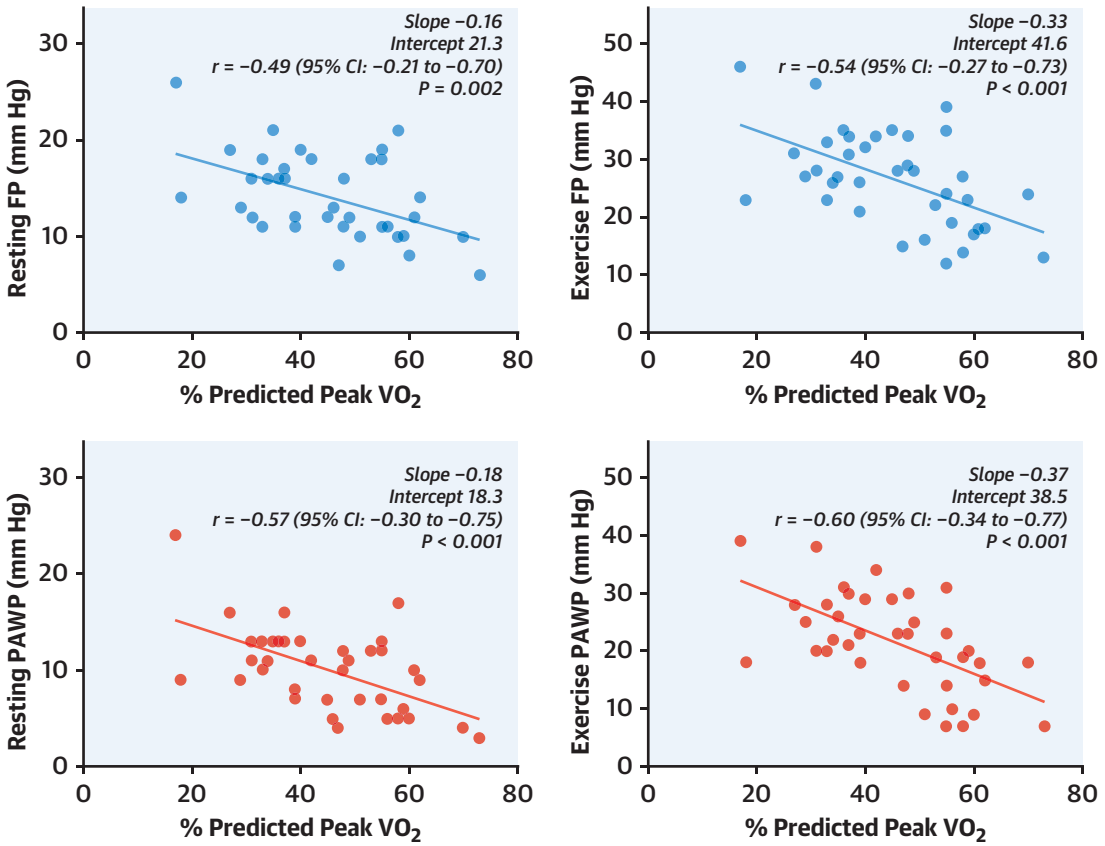
CORRELATION BETWEEN INVASIVE HEMODYNAMICS AND NT-proBNP LEVELS. Forty-five patients (90%) had available NT-proBNP measurements with a median value of 322 pg/mL (IQR: 100-927 pg/mL). Scatterplots and linear regression lines for ln NT-proBNP data are presented in **Figure 2**, whereas scatterplots for hemodynamic data and NT-proBNP values are shown in Supplemental Figure 2. There was no correlation between resting FP and ln NT-proBNP levels ($r = 0.19$,

TABLE 3 Univariable and Bivariable Cox Model Adjusting for Age, Arterial O_2 Saturation, and History of Atrial Arrhythmias

	Univariable		Model 1 Age		Model 2 Arterial O_2 Saturation		Model 3 Atrial Arrhythmias	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Rest								
Fontan pressure, per 1 mm Hg	1.18 (1.03-1.37)	0.02	1.06 (0.99-1.14)	0.02	1.13 (0.97-1.31)	0.12	1.17 (1.00-1.37)	0.047
PAWP, per 1 mm Hg	1.21 (1.06-1.40)	0.005	1.28 (1.10-1.52)	0.003	1.15 (0.98-1.35)	0.07	1.24 (1.06-1.48)	0.008
Exercise								
Fontan pressure, per 1 mm Hg	1.15 (1.05-1.26)	0.001	1.18 (1.07-1.32)	0.002	1.13 (1.03-1.25)	0.009	1.14 (1.04-1.25)	0.007
PAWP, per 1 mm Hg	1.15 (1.06-1.27)	0.002	1.17 (1.06-1.33)	0.001	1.13 (1.03-1.25)	0.009	1.14 (1.04-1.25)	0.006

Abbreviations as in Table 2.

FIGURE 1 Peak VO_2 Data and Invasive Exercise Hemodynamics



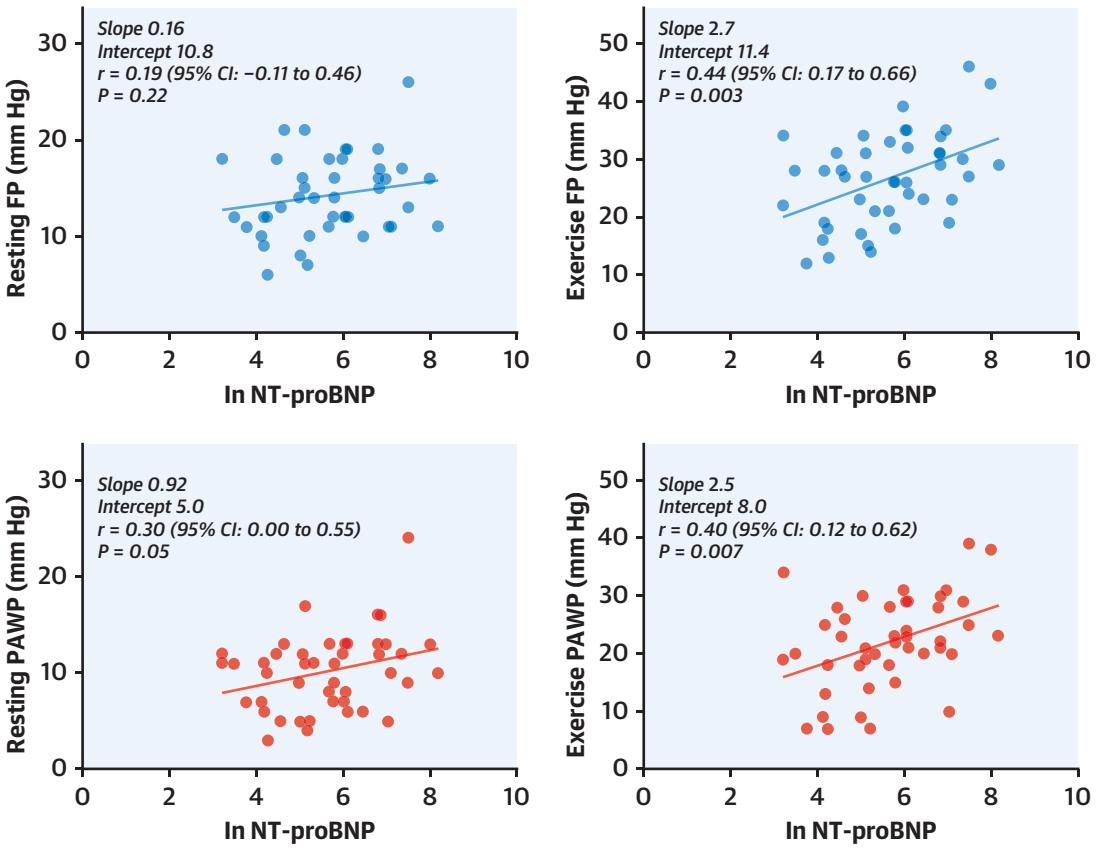
Individual graphs show linear regression results for the associations between resting and exercise Fontan pressures (FP) and pulmonary artery wedge pressure (PAWP) with % predicted peak oxygen consumption (VO_2) on noninvasive cardiopulmonary exercise testing. No corrections for multiple testing were applied.

slope 0.61; $P = 0.22$), whereas a trend was seen toward a direct correlation between the latter and resting PAWP ($r = 0.30$, slope 0.92; $P = 0.05$). There was a correlation between exercise FP ($r = 0.44$, slope 2.7; $P = 0.003$) and PAWP ($r = 0.40$, slope 2.5; $P = 0.007$) with ln NT-proBNP levels. These associations remained present after adjusting for comorbidities/confounders (Supplemental Table 1). Ventricular ejection fraction and ≥moderate atrioventricular regurgitation were also independently associated with ln NT-proBNP levels. Like FP and PAWP at peak exercise, log ΔPA/ΔQp ($r = 0.49$, slope 0.42; $P = 0.001$) and log ΔPAWP/ΔQs ($r = 0.32$, slope 0.43; $P = 0.04$) and were also associated with ln NT-proBNP values (Supplemental Figure 2).

An NT-proBNP level ≥300 pg/mL was seen in 23 patients (51%). There was no difference in resting FP (15.1 ± 3.8 mm Hg vs 13.4 ± 4.4 mm Hg; $P = 0.17$) or PAWP (11.1 ± 4.2 mm Hg vs 9.3 ± 3.6 mm Hg; $P = 0.11$) between those with NT-proBNP levels ≥300 pg/mL and the remainder of the cohort. However, exercise FP (30.0 ± 7.1 mm Hg vs 23.2 ± 7.2 mm Hg; $P = 0.003$) and PAWP (25.1 ± 6.7 mm Hg vs 18.8 ± 7.9 mm Hg; $P = 0.006$) were higher in those with NT-proBNP levels ≥300 pg/mL compared with patients with lower NT-proBNP levels.

Figure 3 presents FP and PAWP data according to % predicted peak VO_2 and NT-proBNP levels. When analyzing those with a % predicted peak VO_2 ≥50%, there was no difference in resting FP (14.4 ± 4.0 mm Hg vs 12.0 ± 5.0 mm Hg; $P = 0.34$) or PAWP (9.0 ± 3.5 mm Hg vs 8.3 ± 4.6 mm Hg; $P = 0.66$) values in those with NT-proBNP level ≥300 pg/mL compared with the rest of the cohort, but the former had higher

FIGURE 2 **NT-proBNP and Invasive Exercise Hemodynamics**



Individual panels show linear regression results for the associations between resting and exercise FP and PAWP with ln N-terminal pro-B-type natriuretic peptide (NT-proBNP) values. No corrections for multiple testing were applied. Abbreviations as in Figure 1.

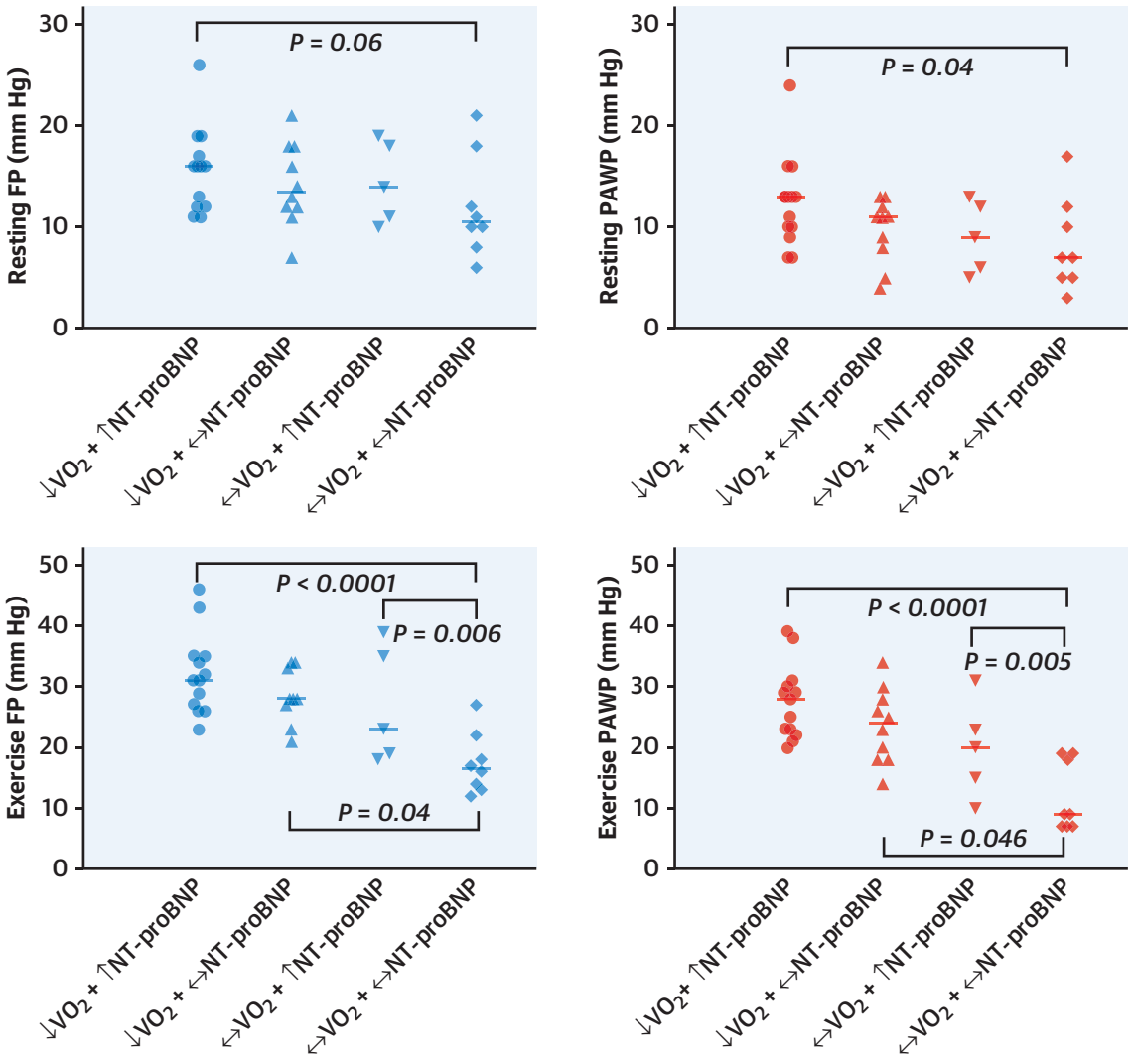
exercise FP (26.8 ± 9.6 mm Hg vs 17.4 ± 5.0 mm Hg; $P = 0.04$) and PAWP (19.8 ± 8.0 mm Hg vs 11.9 ± 5.7 mm Hg; $P = 0.046$). Among those with % predicted peak VO_2 <50%, those with NT-proBNP level ≥300 pg/mL had numerically higher FP and PAWP at rest and during exercise, but these differences did not achieve statistical significance.

CORRELATION BETWEEN INVASIVE HEMODYNAMICS AND CLINICAL OUTCOMES. During a follow-up of 0.9 years (IQR: 0.6-2.9 years), 15 patients (30%) achieved the composite outcome of death (n = 1), cardiac transplantation (n = 6), or hospitalization due to heart failure/refractory arrhythmias (n = 8). Univariable Cox model analysis is presented in Supplemental Table 2 and multivariable analysis in **Table 3**. FP and PAWP both at rest and during exercise were significantly associated with clinical outcomes on univariable analyses. Age at the time of catheterization, resting arterial O_2 saturation, and prior atrial arrhythmias were also associated with clinical outcomes on univariable analyses. Resting FP and PAWP were significantly associated with outcomes after adjustment for age and history of atrial arrhythmias but not when arterial O_2 saturation was incorporated into the model. Exercise FP and PAWP remained independently associated with clinical outcomes in all bivariate analyses.

DISCUSSION

The main findings of the study are: 1) resting and exercise FP and PAWP were inversely related to exercise capacity on noninvasive CPET in adults post-Fontan; 2) NT-proBNP levels were directly related to exercise FP and PAWP; 3) peak VO_2 <50% predicted and NT-proBNP ≥300 pg/mL were associated with more abnormal hemodynamics during exercise; and 4) exercise FP and PAWP were independently

FIGURE 3 **Hemodynamics and Phenotypes According to Peak VO_2 and NT-proBNP**

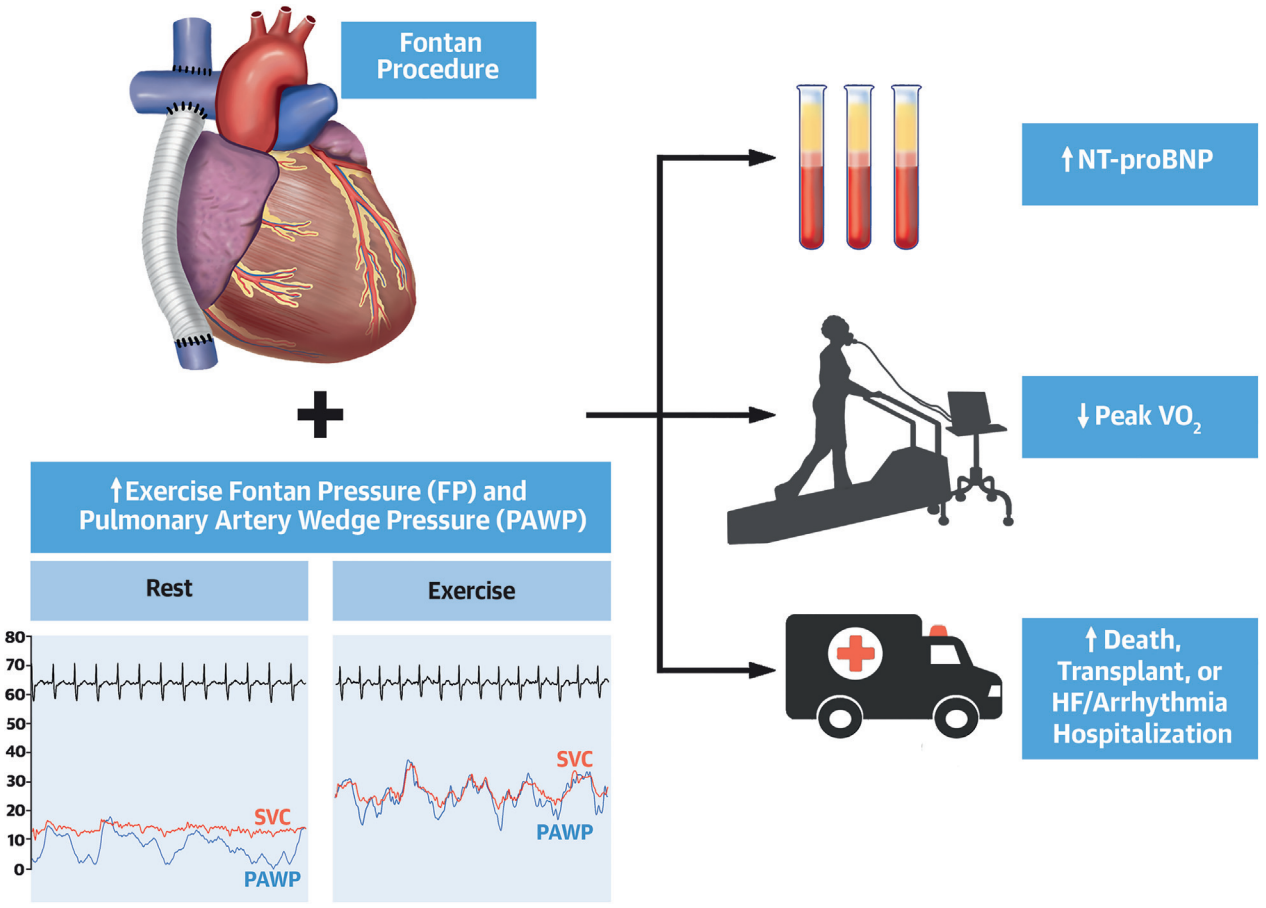


Resting and exercise Fontan and pulmonary artery wedge pressure data according to clinical phenotypes when patients are categorized according to peak VO_2 and NT-proBNP levels. ↓VO_2 = peak VO_2 % predicted <50%; ↔ VO_2 = peak VO_2 % predicted ≥50%; ↔ NT-proBNP = NT-proBNP <300 pg/mL; ↑ NT-proBNP = NT-proBNP ≥300 pg/mL. Abbreviations as in **Figure 1**.

associated with clinical outcomes after adjustments for confounders (**Central Illustration**).

Due to the presence of passive, nonpulsatile systemic venous return, pulmonary venous pressure (ie, PAWP) plays a central role in Fontan physiology. Therefore, normal ventricular (systolic and diastolic) and valvular function is critical. However, diastolic dysfunction is a well-recognized consequence of single ventricle physiology, starting before Fontan palliation.[19] Moreover, valvular insufficiency and ventricular systolic dysfunction can occur in a subset of patients, particularly those with right ventricular morphology. Despite these potential risk factors for elevation in systemic atrial pressure (and inevitably FP), establishing the diagnosis of diastolic dysfunction in adults post-Fontan remains a clinical conundrum, as even standard cardiac catheterization is insensitive for its diagnosis. We have recently reported that, despite lower resting and exercise filling pressures compared with HFpEF, systemic atrium and single ventricle compliance is markedly abnormal in adults post-Fontan.[10] Our findings demonstrate

CENTRAL ILLUSTRATION **Invasive Exercise Hemodynamics, Clinical, and Prognostic Data in Adults Post-Fontan**



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Increased exercise Fontan pressures (FP) and pulmonary artery wedge pressure (PAWP) are associated with N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels, peak oxygen consumption (VO_2) on cardiopulmonary exercise testing (CPET), and clinical outcomes. HF = heart failure; SVC = superior vena cava.

that invasive exercise hemodynamics unmask occult diastolic dysfunction as Qs and preload to the systemic ventricle increase.

Reduced functional capacity is universal in patients post-Fontan palliation[20] and peak VO_2 is a marker of increased morbidity and mortality in this population.[21] In addition to abnormalities of the single ventricle and atrioventricular or semilunar valves, other concomitant abnormalities (Fontan pathway, pulmonary artery or pulmonary venous obstruction, residual coarctation of the aorta, abnormal pulmonary vascular resistance) might contribute to decreased exercise performance. Given the inherent structural and functional abnormalities of a single ventricle and the Fontan circulation, it would be natural to infer the etiology of exercise limitation post-Fontan is predominantly cardiac. By contrast, several other processes have been implicated in the reduced performance in these patients, including peripheral skeletal musculature, diaphragmatic function, and pulmonary parenchymal and vascular abnormalities.[22] Our results suggest that those with a % predicted peak VO_2 <50% indeed have higher ventricular filling pressures, particularly during exercise. However, the correlation between peak VO_2 and exercise ventricular filling pressures in adults post-Fontan was modest. This observation replicates the observations in heart failure secondary to acquired heart disease[1,3,4] and underscores the complex determinants of peak VO_2, as the pathophysiology of exercise limitation in acquired heart failure has been shown to go well beyond filling pressures.[23] To

identify potential therapeutic targets, further investigation regarding the contributing factors to reduced functional capacity and exertional symptoms in patients post-Fontan is warranted.

Guidelines recommend measurement of NT-proBNP levels for the diagnosis of heart failure in acquired heart disease regardless of ejection fraction,[24] because NT-proBNP levels have also been shown to provide incremental clinical and prognostic information even in those with HFrEF. Although intuitive and commonly performed, supportive evidence for the use of the NT-proBNP and, perhaps more importantly, interpretation of its values in adults post-Fontan are limited. It has been suggested that higher NT-proBNP levels are associated with presence of an atriopulmonary Fontan connection[25] and, similar to our findings, atrioventricular valve regurgitation and ventricular dysfunction.[25] However, the correlation between NT-proBNP and ventricular filling pressures in adults post-Fontan has not been described.

In our cohort, NT-proBNP levels were not associated with resting hemodynamics, and correlated poorly with exercise Fontan pressures and PAWP. These findings are in agreement with the poor correlations between NT-proBNP levels and filling pressures reported in biventricular circulation[26,27] and reflect the intricate nature of NT-proBNP secretion. However, it should be noted that NT-proBNP levels ≥300 pg/mL were associated with higher FP and PAWP during exercise, suggesting that serum biomarkers can be used to identify individuals with adverse underlying Fontan hemodynamics. Noteworthy, despite being similar to the median NT-pro BNP level for the entire cohort, this level is less than the one used to diagnose heart failure per guideline criteria[28] and more compatible with data derived from HFpEF patients.[29]

Several studies have reported the association between elevated Fontan pressures and clinical outcomes postpalliation.[17,30,31] Our group has also demonstrated that elevated PAWP is associated with increased all-cause and cardiovascular mortality in adults post-Fontan.[32] However, resting Fontan and ventricular filling pressures are frequently normal in symptomatic patients or those with Fontan failure,[10,32] thus limiting the usefulness of hemodynamics in their management and risk stratification. We previously showed the utility of exercise catheterization in Fontan patients in identifying impaired pulmonary vascular reserve, though our initial publication did not focus on the etiology underlying this.[8] The results of the present study suggest that exercise at the time of catheterization in adults post-Fontan unmasks underlying diastolic dysfunction but also provides incremental prognostic information. Exercise FP and PAWP were independently associated with a composite of death, heart failure hospitalization, incident arrhythmias, and the need for transplantation even after adjusting for confounders. Despite the inherent differences between single ventricle physiology and acquired heart disease, our findings parallel those of Omote et al,[33] who demonstrated that exercise hemodynamics predicted heart failure hospitalization or death in patients with biventricular circulation and unexplained dyspnea.

FUTURE DIRECTIONS. The current results further support the clinical utility of exercise venous catheterization in adults post-Fontan with exercise intolerance. Our observations suggest that exercise hemodynamics better correlate with exercise capacity and neurohormonal activation than resting measurements, but also that the exercise values might be more sensitive in predicting clinical outcomes. Additional studies assessing if invasive hemodynamics could allow the early recognition of patients with less favorable underlying hemodynamics and perhaps guide therapeutic interventions prior to the development of overt Fontan failure are warranted.

Patients with more preserved exercise capacity and lower NT-proBNP levels had normal resting and exercise PAWP. This suggests other causes as the explanation for functional limitation in these patients. Conversely, those with abnormal VO_2 values and elevated NT-proBNP levels had significantly abnormal hemodynamics. Whether phenotyping adults post-Fontan based on % predicted peak VO_2 and NT-proBNP levels can predict underlying hemodynamics and prognosticate adults post-Fontan deserves subsequent investigation.

STUDY LIMITATIONS. The study population represents a retrospective cohort referred to invasive hemodynamic assessment and, therefore, is subject to inevitable biases. Similar to other studies in adult Fontan patients, the study population was heterogeneous. Given the sample size, type II error could have been introduced. Because CPET and laboratory testing were performed at the discretion of the referring providers, albeit available in most, they were not performed in all subjects. Last, the follow-up period was short due to the recent introduction of exercise at the time of cardiac catheterization in patients post-Fontan at our center. The association between invasive exercise Fontan hemodynamics and long-term clinical outcomes remains to be determined.

CONCLUSIONS

In adults post-Fontan, resting and exercise FP and PAWP were inversely related to exercise capacity on noninvasive CPET, while exercise hemodynamics were directly related to NT-proBNP levels. Our results suggest that combining peak VO_2 and NT-proBNP data might allow us to identify patients with normal PAWP during exercise and those with unfavorable resting and exercise hemodynamics. Lastly, exercise FP and PAWP might be more sensitive than resting values in predicting clinical outcomes in this population, suggesting that invasive exercise hemodynamics could be used not only for the diagnosis of occult diastolic dysfunction but also to prognosticate these patients.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In adults who have undergone Fontan palliation, abnormal invasively measured exercise hemodynamics are associated with impaired exercise capacity and elevated NT-proBNP levels, and may be more sensitive than resting hemodynamic measurements in predicting clinical outcomes.

TRANSLATIONAL OUTLOOK: Additional studies are needed to determine whether invasive hemodynamic measurement could guide therapeutic interventions before the development of overt Fontan failure.

REFERENCES

1. Reddy YNV, Olson TP, Obokata M, Melenovsky V, Borlaug BA. Hemodynamic correlates and diagnostic role of cardiopulmonary exercise testing in heart failure with preserved ejection fraction. *J Am Coll Cardiol HF*. 2018;6:665–675.

2. Obokata M, Olson TP, Reddy YNV, Melenovsky V, Kane GC, Borlaug BA. Haemodynamics, dyspnoea, and pulmonary reserve in heart failure with preserved ejection fraction. *Eur Heart J*. 2018;39:2810–2821.

3. Fink LI, Wilson JR, Ferraro N. Exercise ventilation and pulmonary artery wedge pressure in chronic stable congestive heart failure. *Am J Cardiol*. 1986;57:249–253.

4. Franciosa JA, Ziesche S, Wilen M. Functional capacity of patients with chronic left ventricular failure. Relationship of bicycle exercise performance to clinical and hemodynamic characterization. *Am J Med*. 1979;67:460–466.

5. van Veldhuisen DJ, Linssen GC, Jaarsma T, et al. B-type natriuretic peptide and prognosis in heart failure patients with preserved and reduced ejection fraction. *J Am Coll Cardiol*. 2013;61:1498–1506.

6. Parekh N, Maisel AS. Utility of B-natriuretic peptide in the evaluation of left ventricular diastolic function and diastolic heart failure. *Curr Opin Cardiol*. 2009;24:155–160.

7. Parsonage WA, Galbraith AJ, Koerbin GL, Potter JM. Value of B-type natriuretic peptide for identifying significantly elevated pulmonary artery wedge pressure in patients treated for established chronic heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol*. 2005;95:883–885.

8. Egbe AC, Miranda WR, Anderson JH, Borlaug BA. Hemodynamic and clinical implications of impaired pulmonary vascular reserve in the Fontan circulation. *J Am Coll Cardiol*. 2020;76:2755–2763.

9. Jain CC, Borlaug BA. Performance and interpretation of invasive hemodynamic exercise testing. *Chest*. 2020;158:2119–2129.

10. Miranda WR, Borlaug BA, Jain CC, et al. Exercise-induced changes in pulmonary artery wedge pressure in adults post-Fontan versus heart failure with preserved ejection fraction and non-cardiac dyspnoea. *Eur J Heart Fail*. 2023;25(1):17–25. https://doi.org/10.1002/ejhf.2706

11. Epstein SE, Beiser GD, Stampfer M, Robinson BF, Braunwald E. Characterization of the circulatory response to maximal upright exercise in normal subjects and patients with heart disease. *Circulation*. 1967;35:1049–1062.

12. Kaminsky LA, Imboden MT, Arena R, Myers J. Reference standards for cardiorespiratory fitness measured with cardiopulmonary exercise testing using cycle ergometry: data from the Fitness Registry and the Importance of Exercise National Database (FRIEND) registry. *Mayo Clin Proc*. 2017;92:228–233.

13. Kaminsky LA, Arena R, Myers J. Reference standards for cardiorespiratory fitness measured with cardiopulmonary exercise testing: data from the Fitness Registry and the Importance of Exercise National Database. *Mayo Clin Proc*. 2015;90:1515–1523.

14. Squires RW, Allison TG, Johnson BD, Gau GT. Non-physician supervision of cardiopulmonary exercise testing in chronic heart failure: safety and results of a preliminary investigation. *J Cardiopulm Rehabil*. 1999;19:249–253.

15. Alsaied T, Rathod RH, Aboulhosn JA, et al. Reaching consensus for unified medical language in Fontan care. *ESC Heart Fail*. 2021;8:3894–3905.

16. Januzzi JL, van Kimmenade R, Lainchbury J, et al. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. *Eur Heart J*. 2006;27:330–337.

17. Khairy P, Fernandes SM, Mayer JE Jr, et al. Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery. *Circulation*. 2008;117:85–92.

18. Pundi KN, Johnson JN, Dearani JA, et al. 40-Year follow-up after the Fontan operation: long-term outcomes of 1,052 patients. *J Am Coll Cardiol*. 2015;66:1700–1710.

19. Budts W, Ravekes WJ, Danford DA, Kutty S. Diastolic heart failure in patients with the Fontan circulation: a review. *JAMA Cardiol*. 2020;5:590–597.

20. Diller GP, Giardini A, Dimopoulos K, et al. Predictors of morbidity and mortality in contemporary Fontan patients: results from a multicenter study including cardiopulmonary exercise testing in 321 patients. *Eur Heart J*. 2010;31:3073–3083.

21. Fernandes SM, Alexander ME, Graham DA, et al. Exercise testing identifies patients at increased risk

for morbidity and mortality following Fontan surgery. *Congenit Heart Dis*. 2011;6:294–303.

22. Laohachai K, Ayer J. Impairments in pulmonary function in Fontan patients: their causes and consequences. *Front Pediatr*. 2022;10:825841.

23. Malhotra R, Bakken K, D'Elia E, Lewis GD. Cardiopulmonary exercise testing in heart failure. *J Am Coll Cardiol HF*. 2016;4:607–616.

24. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79(17):e263–e421. https://doi.org/10.1016/j.jacc.2021.12.012

25. Heck PB, Muller J, Weber R, Hager A. Value of N-terminal pro brain natriuretic peptide levels in different types of Fontan circulation. *Eur J Heart Fail*. 2013;15:644–649.

26. Knebel F, Schimke I, Pliet K, et al. NT-ProBNP in acute heart failure: correlation with invasively measured hemodynamic parameters during recompensation. *J Card Fail*. 2005;11(5 suppl):S38–S41. https://doi.org/10.1016/j.cardfail.2005.04.012

27. Verbrugge FH, Omote K, Reddy YNV, Sorimachi H, Obokata M, Borlaug BA. Heart failure with preserved ejection fraction in patients with normal natriuretic peptide levels is associated with increased morbidity and mortality. *Eur Heart J*. 2022;43:1941–1951.

28. Januzzi JL Jr, Chen-Tournoux AA, Christenson RH, et al. N-terminal pro-B-type natriuretic peptide in the emergency department: the ICON-RELOADED study. *J Am Coll Cardiol*. 2018;71:1191–1200.

29. Grewal J, McKelvie RS, Persson H, et al. Usefulness of N-terminal pro-brain natriuretic Peptide and brain natriuretic peptide to predict cardiovascular outcomes in patients with heart failure and preserved left ventricular ejection fraction. *Am J Cardiol*. 2008;102:733–737.

30. Miranda WR, Borlaug BA, Hagler DJ, Connolly HM, Egbe AC. Haemodynamic profiles in adult Fontan patients: associated haemodynamics and prognosis. *Eur J Heart Fail*. 2019;21:803–809.

31. Ohuchi H, Miyazaki A, Negishi J, et al. Hemodynamic determinants of mortality after Fontan operation. *Am Heart J*. 2017;189:9–18.

32. Miranda WR, Hagler DJ, Taggart NW, Borlaug BA, Connolly HM, Egbe AC. Elevated ventricular filling pressures and long-term survival in adults post-Fontan. *Catheter Cardiovasc Interv*. 2020;95:803–809.

33. Omote K, Verbrugge FH, Sorimachi H, et al. Central hemodynamic abnormalities and outcome in patients with unexplained dyspnea. *Eur J Heart Fail*. 2023;25(2):185–196. https://doi.org/10.1002/ejhf.2747

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APPENDIX **For supplemental figures and tables, please see the online version of this paper.**