Exercise catheterization in adults post-Fontan with normal and abnormal hemodynamic criteria: insights into normal Fontan physiology

William R. Miranda MD[1]; C. Charles Jain, MD[1], Barry A. Borlaug, MD[1]; Heidi M. Connolly MD[1], Luke J. Burchill, MBBS, PhD[1]; Alexander Van De Bruaene, MD[2;] Alexander C. Egbe, MBBS[1]

[1]Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN

[2]Division of Structural and Congenital Cardiology, Department of Cardiovascular Sciences, KU Leuven, Leuven, Belgium

Word count: 3,498

Running title: Normal resting and exercise Fontan hemodynamics

Conflict of Interest: None

Funding: Dr. Egbe is supported by National Heart, Lung, and Blood Institute (NHLBI) grants (K23 HL141448, R01 HL158517 and R01 160761).

Corresponding author:

William R. Miranda, MD

Phone: (507)284-1446

Email: miranda.william@mayo.edu

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ejhf.3119

Abstract

Background: The normal (i.e., expected) hemodynamics in adults post-Fontan remain poorly delineated. Moreover, the definitions of elevated exercise pulmonary artery (PA) and PA wedge pressure (PAWP) for this population have not been described.

Methods and Results: Seventy-two adults post-Fontan undergoing exercise catheterization were categorized into abnormal (Group I, n=59; defined as resting mean PA ≥14 mmHg and/or PAWP ≥12 mmHg, ΔPAWP/Δsystemic flow >2 mmHg/l/min, and/or ΔPA/Δpulmonary flow >3 mmHg/l/min) and normal (Group II, n=13) hemodynamics. Thirty-nine patients with non-cardiac dyspnea (NCD) were included as controls. There was no difference in exercise arterial O_2 saturation (87% [81;92] vs 89% [85;93], p=0.29), while exercise PA pressure (27 [23;31] vs 16 [14.5;19.5] mmHg, p<0.001) and PAWP were higher (21 [18;28] vs 12 [8;14] mmHg, p<0.001) in Group I. At peak exercise, Group I had lower heart rate (97 [81;120] vs 133 [112.5; 147.5] bpm, p<0.001) and Qs response (67.3 [43.8;93.1] vs 105.9 (82;118.5) % predicted, p<0.001) than Group II. Exercise SVC pressures were higher (16 [14;22.5] vs 5.5 [3;7.3] mmHg, p<0.001) and arterial O_2 saturation lower (89% [85;93] vs 97% [96;98], p<0.001) in Group II compared to NCD, while no differences in PAWP, stroke volume index, heart rate, or Qs response were seen. If defined as 2 standard deviations above mean values for Group II, elevated PAWP and mean PA pressure post-Fontan would correspond to 20.6 and 25.8 mmHg, respectively.

Conclusion: PAWP >20 mmHg and mean PA pressure >25 mmHg could be used to define elevated values during exercise in adults post-Fontan. The major discrepancy in exercise hemodynamics among Group II compared to controls appears to be the degree of systemic venous hypertension and arterial desaturation.

Key words: Fontan palliation; exercise; hemodynamics; normal

Introduction

Despite >50 years since the description of the procedure[1], the normal (i.e., expected) resting hemodynamics post-Fontan remain poorly defined. Ohuchi et al demonstrated that a central venous pressure ≥14 mmHg was associated with worse survival post-Fontan[2], and this cut-off has been used by some to determine elevated Fontan pressures. A recent expert consensus document did not define increased Fontan pressures but proposed a pulmonary artery wedge pressure (PAWP) ≥12 mmHg post-palliation as abnormal[3]. However, those demonstrating excellent natural history were found to have significantly lower central venous and ventricular filling pressures than these proposed values[4].

We demonstrated that adults post-Fontan had lower resting and exercise PAWP than patients with heart failure with preserved ejection fraction despite having similar systemic ventricular and atrial compliance (ΔPAWP/Δcardiac output ratio)[5]. Therefore, it would be intuitive to expect lower cut-offs for abnormal exercise PAWP post-Fontan than those used in biventricular circulation. However, the PAWP and systemic venous pressures in adults post-Fontan with normal ventricular and pulmonary vascular compliance/reserve during exercise have not been described. Moreover, how their exercise hemodynamics compare to normal individuals is unknown.

To address this knowledge gap, our aims were: 1) describe exercise hemodynamics in adults with normal resting Fontan hemodynamics, ventricular and pulmonary vascular reserve during exercise; 2) compare these to adults post-Fontan with abnormal hemodynamic criteria and individuals with noncardiac dyspnea (NCD).

Methods

Seventy-two adults (age ≥18 years) post-Fontan undergoing exercise venous cardiac catheterization at Mayo Clinic, Rochester, MN between January 2019 and May 2023 were retrospectively identified and categorized into 2 groups according to the presence or absence of abnormal resting and/or

exercise hemodynamics (Groups I and II, respectively). Abnormal resting mean pulmonary artery (PA) and PAWP were defined as ≥14 mmHg[2,6] and ≥12 mmHg[3], respectively. Given the lack of proposed definitions for elevated exercise PA and PAWP post-Fontan, abnormal exercise hemodynamics were defined as ΔPAWP/Δsystemic flow (Qs) ratio >2 mmHg/l/min[7] and/or ΔPA/Δpulmonary flow (Qp) ratio >3 mmHg/l/min[8]. The Institutional Review Board approved the study; only patients authorizing the use of the medical records for research were selected.

Consecutive individuals (3:1 ratio to Group II) diagnosed with NCD during the study period were included as controls. NCD was defined as: 1) absence of a cardiac etiology for exertional dyspnea and exercise intolerance despite extensive noninvasive and invasive cardiopulmonary testing; 2) no prior cardiac surgery, congenital heart disease, or cardiomyopathy; 3) left ventricular ejection fraction >50%, no valvular stenosis and ≤mild regurgitation on echocardiography; 4) no intracardiac shunting by oximetry; 5) resting and exercise PAWP <15 and 25 mmHg, respectively; 6) resting and exercise mean PA ≤20 mmHg at rest and ≤30 mmHg, respectively[8]; 7) ΔPAWP/Δcardiac output ratio ≤2 mmHg/l/min[7] and/or ΔPA/Δcardiac output ratio ≤3 mmHg/l/min[8].

Exploratory analyses were subsequently performed categorizing patients post-Fontan according to clinical status to identify those clinically doing well with expected functional capacity. Patients were included in Group III if they lacked: 1) reported dyspnea, fatigue, or edema; 2) prior atrial arrhythmias or pacemaker implantation, protein-losing enteropathy, or creatine clearance <60 ml/min; 3) ventricular ejection fraction <40% by echocardiography[3]; 4) % predicted VO_2 <50% on outpatient cardiopulmonary exercise testing (CPET)[3]. These were compared to the remainder of the Fontan cohort with available CPET and to the NCD group.

Exercise catheterization was performed using a supine cycle protocol[9]. Resting and exercise Qs and Qp were calculated similarly using direct Fick principle. Qs was calculated using arterial (or pulse oximetry if radial access was not obtained) and PA oximetry data. For Qp calculation, an estimated pulmonary venous O_2 saturation of 95% or the arterial O_2 saturation (if >95%) were used. If bilateral

resting PA O_2 samples were available, the one sampled during exercise was selected for flow calculation. Expected increases in flow correspond to 6 ml per increase in unit (ml/min) of VO_2[10]. Pressure measurements represent a computer-generated mean of ≥5 consecutive cardiac cycles, measured under spontaneous breathing throughout the entire respiratory cycle. In the absence of established definitions, Fontan obstruction was defined as a resting transconduit/pathway gradient ≥3 mmHg and ≥5 mmHg during exercise[11]. Elevated exercise PA and PAWP cut-offs were defined as two standard deviations above the mean for Group II[12,13].

Clinical and laboratory data were retrieved from the medical records and represent the most recent values prior to catheterization. Similarly, if available (n=54), the most recent outpatient CPET (time interval to cardiac catheterization 83.5 [12.8;254] days) were abstracted.

Statistical analyses

Nominal data are presented as counts (%) and continuous data as medians (25^{th};75^{th} percentile) unless stated otherwise. Between-group comparisons were performed using the Fisher's exact and the Wilcoxon tests. N-terminal pro-B-type natriuretic peptide (NT pro-BNP) data were analyzed as log transformed (ln). Statistical analysis was performed using JMP for SAS V.14.1.0; p values <0.05 were considered statistically significant.

Results

Demographic and clinical data for Fontan patients are depicted in Table 1. Double inlet left ventricle was present in 17 patients (23.6%), tricuspid atresia in 14 (19.4%), double outlet right ventricle in 13 (18.1%), hypoplastic left heart syndrome in 12 (16.7%), pulmonary atresia with intact ventricular septum in 11 (15.3%), and other in 5 (6.9%). Fontan connections were: extracardiac conduit in 31

(43.1%), lateral tunnel in 24 (33.3%), atriopulmonary in 9 (12.5%), intra-atrial in 5 (6.9%), and other in 3 (4.1%). Fontan revision had been performed in 22 patients (30.6%). Ten patients had undergone Fontan stenting (13.9%), 6 PA stenting, and 2 coarctation of the aorta stenting (2.8%). Fontan conduit/pathway conduit obstruction was present in 10 patients (14.1%); 10 (14.1%) had patent fenestrations. Indications for cardiac catheterization were: worsening clinical status/exercise intolerance in 37 (51.4%), Fontan-associated liver disease in 10 (13.8%), arrhythmias in 7 (9.7%), transplant evaluation in 6 (8.3%), arterial desaturation in 5 (6.9%), conduit obstruction in 2 (2.8%), and other in 5 (6.9%). Four (5.6%) patients had protein-losing enteropathy.

Comparisons between Groups I and II

Fifty-nine and 13 patients were deemed to have abnormal (Group I) and normal (Group II) hemodynamics, respectively. Compared to Group II, Group I patients were older at the time of catheterization (33.9 [27.2;38.7] vs 23.7 [22.8;27.5] years, p=0.003) and at Fontan palliation (4 [3;7.3] vs 2 [2;3.5] years, p=0.01). The prevalence of New York Heart Association (NYHA) functional class III-IV, cardiac symptoms, and medication use (diuretics, beta blockers, and aldosterone antagonists) was higher in Group I. These also had lower peak % predicted VO_2 on outpatient CPET (44% [36;55.5] vs 58% [52;61], p=0.004) and higher NT pro-BNP levels (329 [166;641] vs 88.5 [70.8;160] pg/ml, p=0.003). Ventricular ejection fraction (52.5% [42.5;57.5] vs 55% [52.5;58.5], p=0.08) or prevalence of ≥moderate atrioventricular valve (AVV) regurgitation (18.6% vs 23.1%, p=0.71) did not differ between groups. Evidence of conduit obstruction was less common in (8.5%) in Group I than Group II (8.5% vs 38.5%, p=0.03); no difference was seen in the prevalence of patent fenestration (Group I 15.5% vs Group II 7.7%, p=0.67).

Resting hemodynamics are presented in Table 2 and Figure 1, while exercise data are depicted in Table 3 and Supplemental Table 1. At rest, Group I had lower arterial O_2 saturation (92% [89;95] vs 94%

(93;95), p=0.02). As expected, Group I had higher SVC (16 [13;18] vs 11 [9;11] mmHg, p<0.001), PA (15 [12;17] vs 10 [9.5;11] mmHg, p<0.001) pressures, and PAWP (10 [8;12] vs 6 [5.5;7] mmHg, p<0.001). Among Group I patients, a PAWP <12 mmHg was seen in 49 (68.1%) and a PA pressure <14 mmHg in 35 (48.6%); additional clinical and hemodynamic data for Group I according to resting filling pressures is shown in Supplemental Table 2.

At peak exercise, Group I achieved a lower load (60 [60;80] vs 100 [60;110] W, p=0.02) than Group II. There was no difference in arterial O_2 saturation (87% [81;92] vs 89% [85;93], p=0.29). SVC pressure (27 [23.5;32.5] vs 16 [14;22.5] mmHg, p<0.001), PA pressure (27 [23;31] vs 16 [14.5;19.5] mmHg, p<0.001), and PAWP were higher (21 [18;28] vs 12 [8;14] mmHg, p<0.001) in Group I. If defined as 2 standard deviations above mean values for Group II (PAWP 11.8±4.4, range 7-21 mmHg; PA 17.4±4.2, range 12-27 mmHg), elevated PAWP and PA pressure post-Fontan would correspond to 20.6 and 25.8 mmHg, respectively. There was no difference in stroke volume index (SVi) (43.6 [37.6;53.4] vs 48.1 [39.6;54] ml/m^2, p=0.44) between groups, but Group I patients had lower heart rate (97 [81;120] vs 133 [112.5;147.5] bpm, p<0.001), and, consequently, Qs response (67.3% [43.8;93.1] vs 105.9% [82;118.5] predicted, p<0.001). Qp response (63.1% [44;80.7] vs 88.5% [69.7;108.3] predicted, p<0.002) was also lower in Group I patients. There was no difference in pulmonary vascular resistance index (PVRi) (1.2 [0.8;2.2] vs 1.2 (0.6;1.4) U.m^2, p=0.34).

Comparisons between Group II and NCD

Thirty-nine individuals were included in the NCD group. Their diagnoses at catheterization were: normal resting and exercise hemodynamics in 29 individuals (74.3%), peripheral impairment to exercise in 5 (12.8%), preload failure in 4 (10.3%), and volitional hyperventilation in 1 (2.6%).

Individuals in Group II were younger than NCD patients (23.7 [22.8;27.5] vs 47.1 [36.3;64.9] years, p<0.001) and had lower body mass index (25.2 [21.9;27.6] vs 27 [24.6;32.2] kg/m^2, p=0.04). Group

II had a lower prevalence of NYHA class III-IV functional status, dyspnea, and leg edema, but higher NT pro-BNP levels (88.5 [70.8;160] vs 43 [25;100.3] pg/ml, p=0.01). There was no difference in peak % predicted VO_2 on outpatient CPET (58% [52;61] vs 69% [53;74], p=0.28). Ventricular ejection fraction was lower (55% [52.5;58.5] vs 62% [59;64.3], p=0.001) and ≥moderate AVV regurgitation more prevalent (23.1% vs 0%, p=0.01) in Group II.

Resting cardiac catheterization data demonstrated higher hemoglobin levels (14.5 [13.5;15.3] vs 12.9 [12;13.9] mg/dl, p=0.007) and lower arterial O_2 saturation (94% [93;95] vs 97% [96;99], p<.0001) in Group II compared to NCD. Group II had higher SVC (11 [9;11] vs 5 [2;7] mmHg, p<.0001) but lower PA pressures (10 [9.5;11] vs 14.5 [11.8;18] mmHg, p<0.001). There was no difference in PAWP (6 [5.5;7] vs 8 [5;11] mmHg, p=0.16) or cardiac index (2.5 [2.1;3.0] vs 2.9 (2.4;3.3) l/min/m^2, p=0.11) but Qp (4.1 [3.9;5.0] vs 5.4 [4.7;6.5] l/min, p=0.02) and Qs (4.5 [4.0;5.8] vs 5.4 [4.7;6.5], p=0.03) was lower in Group II.

At peak exercise, SVC pressures were higher (16 [14;22.5] vs 5.5 [3;7.3] mmHg, p<0.001) and PA pressures lower (16 [14.5;19.5] vs 23 [20;25] mmHg, p<0.001) in Group II than in NCD patients. There was no difference in PAWP (12 [8;14] vs 10 [8;13] mmHg, p=0.53) but ΔPAWP/ΔQs was higher in Group II (0.8 [0.4;1.1] vs 0.4 [0.3;0.8] mmHg/l/min, p=0.04). SVi (48.1 [39.6;54] vs 51.6 [45.1;57.4] ml/m^2, p=0.23), heart rate (133 [112.5;147.5] vs 127 [115;148] bpm, p=0.78), and Qs response (105.9 [82;118.5] vs 112.7 (104.3;131.1) % predicted, p=0.07) did not differ between groups. Arterial O_2 saturation was lower in Group II (89% [85;93] vs 97% [96;98], p<0.001).

Exploratory analyses - hemodynamics in Group III and comparisons to NCD

Seven Fontan patients were included in Group III, and their clinical characteristics are presented in Supplemental Table 3. Conduit obstruction was present in 5 (71.4%) and patent fenestration in 1 (14.2%). At rest, Group III patients had lower arterial O_2 saturation (94% [93;96] vs 97% [96;98];

p=0.01), higher SVC (11 [9;11] vs 5 [2;7] mmHg; p<0.001), and lower PA (10 [10;11] vs 14.5 [11.8;18] mmHg; p<0.001) pressures than NCD patients. No differences were seen in PAWP or cardiac index.

Like the findings at rest, Group III had lower exercise arterial O_2 saturation (92% [87;93] vs 97% [96;98]; p<0.001), higher SVC (14 [13;22] vs 5.5 [3;7.3] mmHg; p<0.001), and lower PA (10 [10; 11] vs 14.5 [11.8; 18] mmHg; p=0.004) pressures than NCD patients. The highest exercise PA pressure and PAWP in Group III were 22 and 14 mmHg, respectively. Exercise Svi, Qs response, ΔPA/ΔQp and ΔPAWP/ΔQs ratios did not differ between groups. Group III patients had a lower Qp response than controls (91 [56.6;111.2] vs 112.7 [104.3;131.1] % predicted; p=0.02).

Discussion

To the best of our knowledge, this is the first attempt to establish normal invasive exercise Fontan hemodynamics. The main findings of our study are: 1) PAWP >20 mmHg and mean PA pressure >25 mmHg could be used to define elevated exercise values in adults post-Fontan (Graphical Abstract), although exercise PAWP might be lower in asymptomatic patients; 2) Qs and chronotropic responses were markedly reduced in Group I; 3) there was no difference in exercise PVRi between Groups I and II; 4) systemic venous hypertension and systemic arterial desaturation appear to be the major differences in exercise hemodynamics between Group II and NCD; 5) the characteristics of Group II parallel those associated with an "excellent" natural history post-Fontan.

Normal Fontan hemodynamics

Nonpulsatile systemic venous return to the pulmonary vasculature and venous hypertension are the hallmarks of the Fontan procedure. Additional hemodynamic abnormalities include reduced cardiac output and ventricular preload, varying degrees of systemic arterial desaturation, increased pulmonary

vascular resistance, and chronotropic incompetence[14]. These findings are unequivocally *abnormal* (i.e., pathological) compared to individuals without cardiac disease. However, given their prevalence, these might represent *normal* (i.e., mathematically expected) findings in adults post-Fontan. The heterogeneous anatomy and Fontan connections deepen the conundrum in defining normal Fontan hemodynamics. Although this struggle might be perceived as semantical, determining expected Fontan hemodynamics is paramount as we strive to optimize their delicate circulation and minimize the inevitable long-term complications.

Based on survival outcomes, Ohuchi et al proposed a central venous pressure ≥14 mmHg to be abnormal post-Fontan[2]. In the absence of guideline recommendations, some have incorporated this cut-off as the definition for increased Fontan pressures. Due to the central role played by ventricular diastolic dysfunction in a Fontan circuit, defining elevated ventricular filling pressures is equally important. A recent expert consensus document proposed a ventricular end-diastolic pressure or PAWP ≥12 mmHg as abnormal in this population[3]. This proposition agrees with our observation of a worse prognosis in adults post-Fontan with PAWP >12 mmHg compared to those with lower values[15]. Therefore, according to prognostic data, using 14 and 12 mmHg as cut-offs for elevated resting PA and PAWP post-palliation would be reasonable.

We have reported on the incremental diagnostic value of exercise during cardiac catheterization in adults post-Fontan[5,16-19]. Given the challenges in diagnosing diastolic dysfunction in this population, one would expect the use of exercise invasive hemodynamics to rise. As highlighted[20], establishing expected exercise PA and PAWP values post-Fontan is critically needed. Our results suggest that an exercise PAWP >20 mmHg and mean PA pressure >25 mmHg could be defined as abnormal in these individuals. However, data from Group III suggest that, while 20 mmHg might be a specific cut-off for elevated exercise PAWP, this might be insensitive, with those otherwise doing well showing significantly lower values. Lastly, the exercise central venous pressures in Groups II and III deserve attention. The observed values illustrate the degree of venous hypertension the body is repeatedly exposed to, even in

asymptomatic adults post-Fontan, and provide physiologic support for the end-organ abnormalities that appear out of proportion to a seemingly good clinical picture.

Exercise hemodynamics in Group I

The hemodynamic differences between Group I and Group II offer additional insight into the pathophysiology of Fontan failure and severe exercise limitation in these individuals. In addition to having elevated exercise PA and PAWP pressures, Group I had markedly reduced Qs response to exercise, and their chronotropic response was significantly blunted, likely a combination of intrinsic conduction disease and medication effect. Similar observations have been described in patients with heart failure with preserved ejection fraction[21], being an epiphenomenon of the underlying abnormal atrial and ventricular myocardia. The SVi values in Group I must be cautiously interpreted. Fontan failure is associated with worsening right-to-left shunt, typically mediated by venovenous collaterals. This adaptive process allows for maintenance of stroke volume during exercise but decreases O_2 supply. Collectively, these observations demonstrate the etiology of exercise intolerance in failing Fontan patients is complex, and that the yield of a single pharmacological or structural intervention might be limited.

Resting PVRi tended to be higher in Group I than in Group II. However, no difference was seen during exercise. Our results suggest ventricular filling pressures/pulmonary venous hypertension to predominantly determine afterload to systemic venous return as patients post-Fontan exercise. Abnormal pulmonary vascular resistance has been evoked as a contributor to exercise-induced preload failure in this population and coexistent limited exercise performance. This rationale has fueled the use of pulmonary vasodilators in patients post-Fontan. The current findings challenge this theory and align with studies that failed to show a benefit in exercise capacity following initiation of these medications. Our observations support the need to revisit the prevalence and clinical impact of elevated PVRi in current Fontan patients, whose palliation was performed earlier and more judiciously compared to original cohorts.

Clinical profile of Group II patients

Ohuchi et al reported the clinical and hemodynamic features in "excellent" Fontan survivors[4]. "Excellent" status was defined as absence of clinical (e.g., arrhythmias, protein-losing enteropathy) or hemodynamic (e.g., ventricular ejection fraction <40%, ≥moderate AVV regurgitation) features of Fontan failure. Despite inherent biases due to methodology, the findings in Group II were nearly identical to those of Ohuchi's "excellent" patients – PA/central venous pressure 10 vs 10.1 mmHg, ventricular filling pressure 6 vs 5.9 mmHg, arterial O_2 saturation 94% vs 94.0%, cardiac index 2.5 vs 2.6 l/min/m^2, ventricular ejection fraction 55% vs 53.0%, respectively. These values are also similar to those seen in Group III. Ohuchi subsequently proposed these to represent "optimal" Fontan hemodynamics[6]. Importantly, approximately 50% of Group I patients had normal resting PA pressure or PAWP, and their catheterization data at rest shared similarities with Group II. These findings support the role of exercise even in individuals with normal resting values.

Exercise hemodynamics in Group II compared to NCD

Like in Group II, peak VO_2 on CPET was only ~50% predicted among Ohuchi's "excellent" adults post-Fontan[2]. Insufficient augmentation of ventricular stroke volume has been implicated in the universal exercise intolerance post-Fontan. In contrast to that notion, exercise SVi did not significantly differ between Group II and NCD patients. This agrees with the observations in adults post-Fontan undergoing exercise cardiac magnetic resonance imaging[22]. Moreover, Group II demonstrated appropriate Qs response to exercise. Therefore, the most remarkable hemodynamic difference in Groups II patients compared to NCD appeared to be the degree of venous hypertension and arterial desaturation. Similar findings were obtained when comparing Group III to NCD. Venous claudication is a well-described phenomenon and altered skeletal muscle structure and metabolism have been documented in acquired

venous hypertension[23]. In addition to exercise-induced severe venous hypertension, the inherent systemic arterial desaturation might contribute to impaired muscle composition and function post-Fontan[14,24]. We have observed several adults post-Fontan discontinuing exercise during catheterization due to leg discomfort instead of dyspnea. Peripheral impairment to exercise secondary to skeletal muscle dysfunction is a recognized source of dyspnea, even among heart failure patients[25,26]. We hypothesize that peripheral impairment to exercise constitutes a major etiology of exertional intolerance in post-Fontan patients with optimal hemodynamics, and the current findings underscore the importance and potential benefits of exercise training in this population[27].

Future directions

Group II was arbitrarily defined by measures of ventricular and pulmonary vascular compliance/reserve instead of representing asymptomatic individuals undergoing routine catheterization. Moreover, ΔPAWP/ΔQs ratios were higher in Group II than in NCD while no differences were seen between the latter and Group III. Although the current data represent a step toward better understanding exercise limitation and expected exercise hemodynamics post-Fontan, subsequent studies in Fontan patients without structural abnormalities or significant exertional intolerance are needed. Noteworthy, Group II patients were younger than Group I and the impact of aging on expected Fontan hemodynamics is unclear. The role of peripheral impairment to exercise post-Fontan and its diagnosis during catheterization also needs to be refined. In addition, the contribution of pericardial function/restraint to exercise Fontan hemodynamics is currently unknown. Lastly, and perhaps more importantly, whether the hemodynamic cut-offs proposed herein can be used to predict clinical outcomes warrants further investigation.

Limitations

Periodic cardiac catheterization is not performed at our institution; therefore, the study population has inherent selection biases. This, for example, contributed to the prevalence of conduit obstruction and ≥moderate AVV regurgitation in Groups II and III. However, the normal Qs response and observed low ΔPAWP/ΔQs and ΔPA/ΔQp ratios (particularly amongst asymptomatic patients) argue against a significant impact of these clinical characteristics on their exercise hemodynamics. Although this is the largest experience in invasive exercise testing post-Fontan, the number of patients in Group II was small, potentially resulting in type II error. Despite the stringent hemodynamic criteria applied to NCD group, these did not represent patients necessarily free of cardiovascular disease. ΔPAWP/ΔQs and ΔPA/ΔQp cut-offs applied herein were derived from patients with acquired heart disease undergoing upright cycling. Qp might have been underestimated in post-Fontan patients with concomitant pulmonary disease. Lastly, we acknowledge the potential issues with multiplicity, but the sample size limited our ability to adjust for that.

Conclusion

PAWP >20 mmHg and mean PA pressure >25 mmHg could be used to define elevated values in adults post-Fontan undergoing exercise catheterization, although exercise PAWP might be lower in asymptomatic patients. The major discrepancy in exercise hemodynamics between Group II and NCD appears to be the degree of systemic venous hypertension and arterial desaturation.

References

1. Fontan F, Baudet E. Surgical repair of tricuspid atresia. *Thorax* 1971;**26**:240-248. doi: 10.1136/thx.26.3.240
2. Ohuchi H, Miyazaki A, Negishi J*, et al.* Hemodynamic determinants of mortality after Fontan operation. *Am Heart J* 2017;**189**:9-18. doi: 10.1016/j.ahj.2017.03.020
3. Alsaied T, Rathod RH, Aboulhosn JA*, et al.* Reaching consensus for unified medical language in Fontan care. *ESC Heart Fail* 2021;**8**:3894-3905. doi: 10.1002/ehf2.13294
4. Ohuchi H, Ono S, Tanabe Y*, et al.* Long-term serial aerobic exercise capacity and hemodynamic properties in clinically and hemodynamically good, "excellent", Fontan survivors. *Circ J* 2012;**76**:195-203. doi: 10.1253/circj.cj-11-0540
5. 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* 2022. doi: 10.1002/ejhf.2706
6. Ohuchi H. Where Is the "Optimal" Fontan Hemodynamics? *Korean Circ J* 2017;**47**:842-857. doi: 10.4070/kcj.2017.0105
7. Eisman AS, Shah RV, Dhakal BP*, et al.* Pulmonary Capillary Wedge Pressure Patterns During Exercise Predict Exercise Capacity and Incident Heart Failure. *Circ Heart Fail* 2018;**11**:e004750. doi: 10.1161/CIRCHEARTFAILURE.117.004750
8. Kovacs G, Herve P, Barbera JA*, et al.* An official European Respiratory Society statement: pulmonary haemodynamics during exercise. *Eur Respir J* 2017;**50**. doi: 10.1183/13993003.00578-2017
9. Jain CC, Borlaug BA. Performance and Interpretation of Invasive Hemodynamic Exercise Testing. *Chest* 2020;**158**:2119-2129. doi: 10.1016/j.chest.2020.05.552
10. 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. doi: 10.1161/01.cir.35.6.1049
11. Miranda WR, Jain CC, Burchill LJ*, et al.* Correlation Between Fontan Pathway Diameter and Inferior-Superior Vena Cava Gradients in Adults Undergoing Exercise Catheterization. *Circ Cardiovasc Interv* 2023;**16**:e012493. doi: 10.1161/CIRCINTERVENTIONS.122.012493
12. Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. *Eur Respir J* 2009;**34**:888-894. doi: 10.1183/09031936.00145608
13. Simonneau G, Montani D, Celermajer DS*, et al.* Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J* 2019;**53**. doi: 10.1183/13993003.01913-2018
14. Tran DL, Gibson H, Maiorana AJ*, et al.* Exercise Intolerance, Benefits, and Prescription for People Living With a Fontan Circulation: The Fontan Fitness Intervention Trial (F-FIT)-Rationale and Design. *Front Pediatr* 2021;**9**:799125. doi: 10.3389/fped.2021.799125
15. Miranda WR, Hagler DJ, Taggart NW*, et al.* Elevated ventricular filling pressures and long-term survival in adults post-Fontan. *Catheter Cardiovasc Interv* 2020;**95**:803-809. doi: 10.1002/ccd.28340
16. 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. doi: 10.1016/j.jacc.2020.10.003
17. Miranda WR, Jain CC, Borlaug BA, Connolly HM, Egbe AC. Exercise invasive hemodynamics in adults post-Fontan: A novel tool in understanding functional limitation and liver disease. *J Heart Lung Transplant* 2022;**41**:704-707. doi: 10.1016/j.healun.2022.02.023
18. Miranda WR, Jain CC, Borlaug BA*, et al.* Exercise Capacity, NT-proBNP, and Exercise Hemodynamics in Adults Post-Fontan. *J Am Coll Cardiol* 2023;**81**:1590-1600. doi: 10.1016/j.jacc.2023.02.031
19. Miranda WR, Jain CC, Cabalka AK*, et al.* Exercise Catheterisation to Unmask Fontan Pathway Obstruction. *Can J Cardiol* 2022;**38**:1125-1126. doi: 10.1016/j.cjca.2022.04.027

20. Hager A. Invasive Cardiopulmonary Exercise Testing in Patients With Fontan Circulation. *J Am Coll Cardiol* 2023;**81**:1601-1604. doi: 10.1016/j.jacc.2023.03.380
21. Wolsk E, Kaye DM, Komtebedde J*, et al.* Determinants and consequences of heart rate and stroke volume response to exercise in patients with heart failure and preserved ejection fraction. *Eur J Heart Fail* 2021;**23**:754-764. doi: 10.1002/ejhf.2146
22. Latus H, Hofmann L, Gummel K*, et al.* Exercise-dependent changes in ventricular-arterial coupling and aortopulmonary collateral flow in Fontan patients: a real-time CMR study. *Eur Heart J Cardiovasc Imaging* 2022;**24**:88-97. doi: 10.1093/ehjci/jeac001
23. Tsouknidas I, Charisis N, Eklof B, Labropoulos N. Venous Claudication: a Scoping Review of the Pathophysiology and Clinical Importance. *Eur J Vasc Endovasc Surg* 2022;**64**:535-543. doi: 10.1016/j.ejvs.2022.08.006
24. Cordina R, O'Meagher S, Gould H*, et al.* Skeletal muscle abnormalities and exercise capacity in adults with a Fontan circulation. *Heart* 2013;**99**:1530-1534. doi: 10.1136/heartjnl-2013-304249
25. Dhakal BP, Malhotra R, Murphy RM*, et al.* Mechanisms of exercise intolerance in heart failure with preserved ejection fraction: the role of abnormal peripheral oxygen extraction. *Circ Heart Fail* 2015;**8**:286-294. doi: 10.1161/CIRCHEARTFAILURE.114.001825
26. Nayor M, Houstis NE, Namasivayam M*, et al.* Impaired Exercise Tolerance in Heart Failure With Preserved Ejection Fraction: Quantification of Multiorgan System Reserve Capacity. *JACC Heart Fail* 2020;**8**:605-617. doi: 10.1016/j.jchf.2020.03.008
27. Khoury M, Cordina R. Exercise Training for People Living With Fontan Circulation: An Underutilized Intervention. *Can J Cardiol* 2022;**38**:1012-1023. doi: 10.1016/j.cjca.2022.01.008

Figure Legends

Figure 1. Resting hemodynamic data

(CI – cardiac index; HR – heart rate; NCD – noncardiac dyspnea; PA – PAWP – pulmonary artery wedge pressure; SVC – superior vena cava; SVi – stroke volume index)

Figure 2. Exercise hemodynamic data

(HR – heart rate; NCD – noncardiac dyspnea; PA – PAWP – pulmonary artery wedge pressure; Qs – systemic flow; SVC – superior vena cava; SVi – stroke volume index)

Graphical Abstract. Proposed cut-offs for abnormal resting and exercise hemodynamics in adults post-Fontan

(PAWP – pulmonary artery wedge pressure)

Table 1. Clinical characteristics					
	Group I (n=59)	**Group II (n=13)**	**NCD (n=39)**	**p-value I x II**	**p-value II x NCD**
Age, years	33.9 (27.2;38.7)	23.7 (22.8;27.5)	47.1 (36.3;64.9)	0.003	<0.001
Body mass index, kg/m^2	26.5 (22.5;33)	25.2 (21.9;27.6)	27 (24.6;32.2)	0.26	0.04
Female sex	24 (40.7%)	7 (53.9%)	27 (69.2%)	0.54	0.33
NYHA functional class III-IV	25 (42.3%)	1 (7.7%)	19 (50%)	0.02	0.008
Predominant RV morphology	24 (40.7%)	4 (30.8%)	-	0.75	-
Hypertension	4 (6.8%)	2 (15.4%)	12 (30.7%)	0.26	0.47
Diabetes	4 (6.8%)	0	0	0.99	-
Pacemaker	28 (47.5%)	2 (15.4%)	0	0.06	0.06
History of atrial arrhythmias	34 (57.6%)	1 (7.7%)	0	0.001	0.25
Creatinine clearance <60 ml/min	4 (6.8%)	0	4 (10.5%)	0.99	0.56
NT-pro BNP, pg/ml	329 (166;641)	88.5 (70.8;160)	43 (25;100.3)	0.003	0.01
Symptoms					
Dyspnea	41 (69.5%)	4 (30.1%)	39 (100%)	0.01	<0.001
Fatigue	32 (54.2%)	2 (15.4%)	13 (33%)	0.01	0.30
Edema	28 (47.5%)	0	10 (25.6%)	0.001	0.05
Medications					
Diuretics	37 (62.7%)	0	4 (10.3%)	<0.001	0.56
Betablocker	24 (40.7%)	1 (7.7%)	5 (12.8%)	0.03	0.99
ACEi/ARB	33 (55.9%)	6 (46.2%)	11 (28.2%)	0.55	0.31
Aldosterone antagonist	23 (38.9%)	0	2 (5.2%)	0.007	0.99
Digitalis	7 (11.9%)	2 (15.4%)	0	0.66	0.06
Antiarrhythmic agent	20 (34%)	1 (7.7%)	0	0.09	0.25
Phosphodiesterase type 5 inhibitor	17 (28.8%)	1 (7.7%)	0	0.16	0.25
Echocardiography					
Ejection fraction, %	52.5 (42.5;57.5)	55 (52.5;58.5)	62 (59;64.3)	0.08	0.001
≥moderate AVV regurgitation	11 (18.6%)	3 (23.1%)	0	0.71	0.01
Cardiopulmonary exercise test					
Peak VO_2, ml/kg/min	16.1 (14.1;20.1)	24.9 (21.2;27)	25.5 (18;30.8)	<0.001	0.92
Peak VO_2, % of predicted	44 (36;55.6)	58 (52;61)	69 (53;74)	0.004	0.26

ACEi/ARB – angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; AVV – atrioventricular valve; NT-pro BNP – N-terminal pro-brain natriuretic peptide; NYHA – New York Heart Association.

Table 2. Resting hemodynamics					
	Group I (n=59)	**Group II (n=13)**	**NCD (n=39)**	**p-value I x II**	**p-value II x NCD**
Rest					
Hemoglobin, g/dl	14 (12.8;15.9)	14.5 (13.5;15.3)	12.9 (12;13.9)	0.66	0.007
Arterial O_2 saturation, %	92 (89;95)	94 (93;95)	97 (96;99)	0.02	<0.001
PA O_2 saturation, %	69 (66;73)	71 (68;74)	74 (71;78)	0.11	0.080
SVC, mmHg	16 (13;18)	11 (9;11)	5 (2;7)	<0.001	<0.001
PA, mmHg	15 (12;17)	10 (9.5;11)	14.5 (11.8;18)	<0.001	<0.001
PAWP, mmHg	10 (8;12)	6 (5.5;7)	8 (5;11)	<0.001	0.16
Arterial systolic pressure, mmHg	119 (109;133)	121 (114; 149.5)	141 (128;161)	0.22	0.04
Arterial diastolic pressure, mmHg	61 (53.8;72.8)	73 (56.5;75)	73 (67;82)	0.32	0.09
Arterial mean pressure, mmHg	79 (73;92)	84 (75;97.5)	97 (89;110)	0.29	0.04
Qp, l/min	4.3 (3.4;5.5)	4.1 (3.9;5.0)	5.4 (4.7;6.5)	0.81	0.004
Qs, l/min	5.1 (3.9;6.9)	4.5 (4.0;5.8)	5.4 (4.7;6.5)	0.27	0.03
Cardiac index, l/min/m^2	2.8 (2.2;3.5)	2.5 (2.1;3.0)	2.9 (2.4;3.3)	0.27	0.11
Stroke volume, ml	71.5 (60;94.0)	59.2 (48.9;82.5)	75 (60.2;83.0)	0.36	0.20
Stroke volume index, ml/m^2	39.7 (31.7;47.1)	32.8 (27.3;47.7)	37.2 (31.9;45.7)	0.36	0.49
Heart rate, bpm	69 (66;78)	80 (57.5;84)	78 (66;85)	0.75	0.51
PVRi, U.m^2	2.0 (1.2;2.6)	1.3 (1.2;1.9)	2.3 (1.8;2.8)	0.08	0.001
PVR, WU	1.0 (0.7;1.5)	0.8 (0.6;1.1)	1.2 (0.9;1.5)	0.11	0.003
SVR, dynes/seconds/cm^{-5}	1081 (689;1442)	1215 (899;1434)	1254 (1088; 1624)	0.43	0.26
PA – pulmonary artery; PAWP – pulmonary artery wedge pressure; PVRi – pulmonary vascular resistance index; SVC – superior vena cava; SVR – systemic vascular resistance.					

Table 3. Hemodynamics during feet-up and peak exercise					
	Group I (n=59)	**Group II (n=13)**	**NCD (n=39)**	**p-value I x II**	**p-value II x NCD**
Feet-up					
SVC, mmHg	18.5 (14.8;21)	14.5 (11.3;16)	6 (4.5;8)	0.02	<0.001
PAWP, mmHg	13 (11;16)	9 (7.3;9.8)	11 (8; 13)	<0.001	0.05
Exercise					
Arterial O_2 saturation, %	87 (81;92)	89 (85;93)	97 (96;98)	0.29	<0.001
PA O_2 saturation, %	27 (21;34)	31 (27;41)	43 (33; 48)	0.047	0.002
SVC, mmHg	27 (23.5;32.5)	16 (14;22.5)	5.5 (3;7.3)	<0.001	<0.001
PA, mmHg	27 (23;31)	16 (14.5;19.5)	23 (20;25)	<0.001	<0.001
PAWP, mmHg	21 (18;28)	12 (8;14)	10 (8;13)	<0.001	0.53
Arterial systolic pressure, mmHg	150 (137.5;170.5)	164 (135.5;194.8)	184 (159;202.3)	0.47	0.26
Arterial diastolic pressure, mmHg	70 (64.5;82.5)	82 (75.3;87.5)	79 (72;93.3)	0.76	0.85
Arterial mean pressure, mmHg	102.0±17.2	112.5 (92.8;121.3)	116.5 (103.8;130.3)	0.48	0.34
Qp, l/min	7.1 (5.4;8.9)	10.4 (8.7;11.1)	12.7 (10.8;13.8)	<0.001	0.002
Qs, l/min	8.2 (6.7;10.1)	11.7 (9.2;12.6)	12.7 (10.8;13.8)	<0.001	0.06
Stroke volume, ml	84.6 (66.7;96.0)	88.1 (71.3;98.5)	97.8 (83.3;110.2)	0.58	0.08
Stroke volume index, ml/m^2	43.6 (37.6;53.4)	48.1 (39.6;54)	51.6 (45.1;57.4)	0.44	0.23
Heart rate, bpm	97 (81;120)	133 (112.5;147.5)	127 (115;148)	<0.001	0.78
Qs response, % predicted	67.3 (43.8;93.1)	105.9 (82;118.5)	112.7 (104.3;131.1)	<0.001	0.07
Qp response, % predicted	63.1 (44;80.7)	88.5 (69.7;108.3)	112.7 (104.3;131.1)	0.002	<0.001
PVRi, U/m^2	1.2 (0.8;2.2)	1.2 (0.6;1.4)	1.8 (1.3;2.4)	0.34	<0.001
PVR, WU	0.6 (0.4;1.2)	0.6 (0.4;0.8)	0.9 (0.7;1.2)	0.50	0.003
SVR, dynes/seconds/cm^{-5}	1081 (689;1442)	669 (526;710)	763 (571;838)	0.25	0.31
ΔPAWP/ΔQs, mmHg/l/min[1]	4.3 (2.4;8.2)	0.8 (0.4;1.1)	0.4 (0.3;0.8)	<0.001	0.04
ΔPA/ΔQp, mmHg/l/min[1]	4.8 (2.8;8.4)	1.1 (0.9;1.9)	1.2 (0.6;1.7)	<0.001	0.51
VO_2, ml/min	11.8 (9.3;13.1)	17.2 (14.1;19.2)	14.2 (11.2;19.8)	<0.001	0.40
Load, W	60 (60;80)	100 (60;110)	80 (80;120)	0.02	0.15
Respiratory exchange ratio	1.03 (0.94;1.07)	1.02 (0.99;1.08)	1.05 (1.0;1.13)	0.97	0.13

[1]reported as absolute values. PA – pulmonary artery; PAWP – pulmonary artery wedge pressure; PVR – pulmonary vascular resistance; PVRi – pulmonary vascular resistance index; SVC – superior vena cava; SVR – systemic vascular resistance.

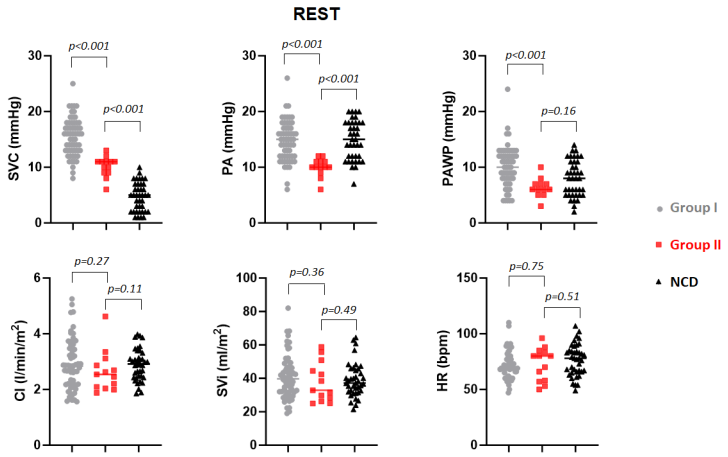


Figure 1 revision final.tif

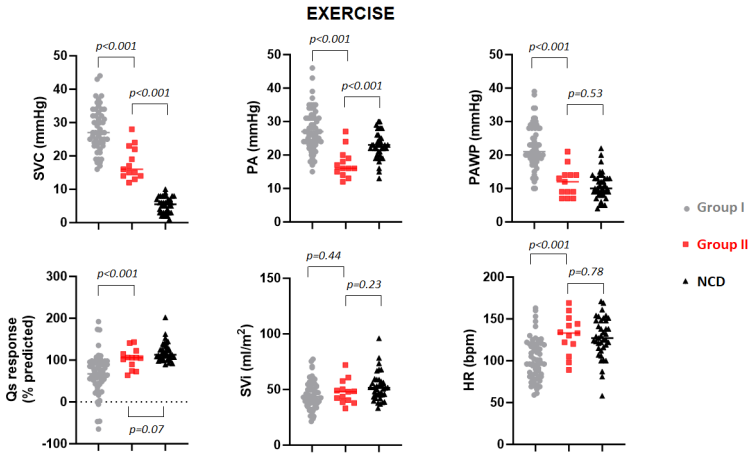
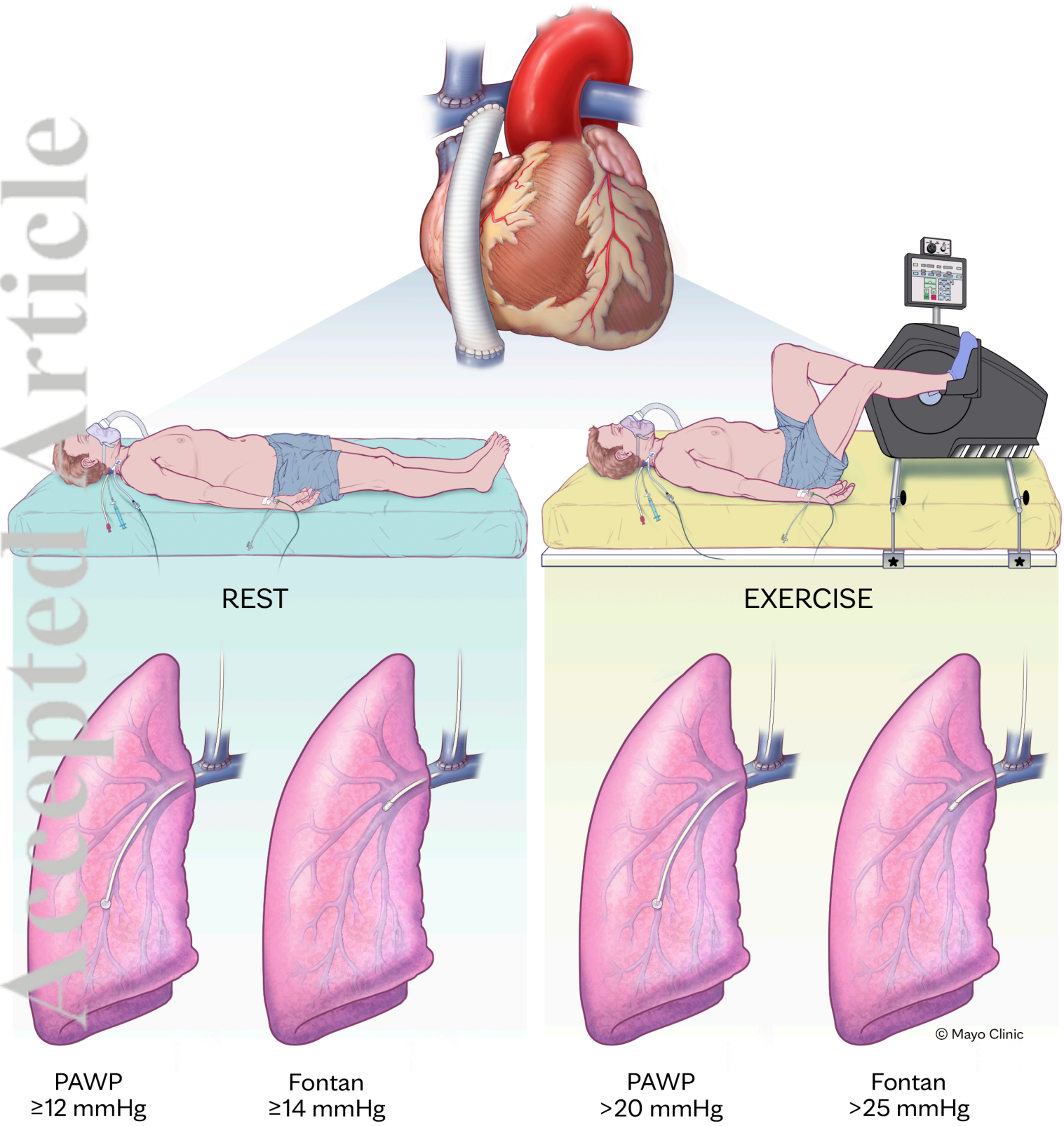


Figure 2 revision final.tif



Graphical abstract.tif