

A Four-Quadrant Phenotyping Model Based on Partitioned Exercise Pressure–Flow Slopes in Adolescent

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Abstract

Background

In Fontan circulation, an elevated exercise mean pulmonary arterial pressure–to–flow slope ($\Delta mPAP/\Delta Q_p$ slope > 3.0 mmHg/L per min) indicates impaired pulmonary vascular reserve. However, because mPAP represents the sum of transpulmonary gradient (TPG) and pulmonary artery wedge pressure (PAWP), an elevated slope can stem from pre-capillary, post-capillary, or combined components. This exploratory study aimed to dissect $\Delta mPAP/\Delta Q_p$ slope into pre-capillary ($\Delta TPG/\Delta Q_p$) and post-capillary ($\Delta PAWP/\Delta Q_s$) slope components using a four-quadrant model to characterize Fontan phenotypes and their association with exercise capacity.

Methods

Invasive exercise stress catheterization was performed in 14 stable adolescent Fontan patients (median age 14.0 years). Patients were categorized into four dynamic quadrants using pre-capillary ($\Delta TPG/\Delta Q_p > 1.2$ mmHg/L per min) and post-capillary ($\Delta PAWP/\Delta Q_s > 2.0$ mmHg/L per min) thresholds.

Results

The quadrant model dissected $\Delta mPAP/\Delta Q_p$ slope into post-capillary (50%, $n = 7$), pre-capillary (14%, $n = 2$), combined (14%, $n = 2$), and non-limited (21%, $n = 3$) phenotypes. Peak %predicted VO_2 varied across phenotypes: patients with post-capillary or combined phenotypes showed reduced exercise capacity (peak %predicted VO_2 : 63%–84%), whereas those with pre-capillary or non-limited phenotypes maintained preserved capacity (90%–136%). Conventional resting hemodynamics showed no correlation with exercise capacity.

Conclusions

Dissecting the overall $\Delta mPAP/\Delta Q_p$ slope into pre- and post-capillary components refines the pathophysiological evaluation of Fontan exercise hemodynamics. Dynamic post-capillary restriction was frequently observed in adolescent Fontan patients with reduced exercise capacity. Furthermore, identifying specific pre- or post-capillary dynamic restrictions may help guide phenotype-targeted therapeutic strategies.

Introduction

Exercise intolerance is a characteristic complication and crucial prognostic marker in the Fontan circulation [1–3]. During adolescence, exercise capacity frequently declines despite stable resting

hemodynamics and normal natriuretic peptide levels [4,5]. Solely relying on resting parameters can lead to a false sense of security, masking latent circulatory attrition before transitioning to adult care [6].

An elevated exercise mean pulmonary arterial pressure–to–flow slope ($\Delta\text{mPAP}/\Delta\text{Qp}$ slope > 3.0 mmHg/L per min) is an established diagnostic marker for exercise induced pulmonary hypertension in biventricular circulations [7,8] and serves as an indicator of impaired pulmonary vascular reserve in the Fontan circulation [9,10]. However, because mPAP is physiologically dictated by the sum of transpulmonary gradient (TPG) and pulmonary artery wedge pressure (PAWP)—expressed as $\text{mPAP} = \text{TPG} + \text{PAWP}$ —an elevated $\Delta\text{mPAP}/\Delta\text{Qp}$ slope can stem from pre-capillary restriction (pulmonary vascular disease), post-capillary restriction (impaired ventricular compliance), or both [11]. Thus, evaluating the integrated $\Delta\text{mPAP}/\Delta\text{Qp}$ slope alone fails to pinpoint the primary bottleneck.

To overcome this limitation, we hypothesized that dissecting the overall exercise pressure response into dynamic pre-capillary ($\Delta\text{TPG}/\Delta\text{Qp}$) and post-capillary ($\Delta\text{PAWP}/\Delta\text{Qs}$) slope components would identify the primary hemodynamic bottleneck. Accordingly, this exploratory pilot study aimed to partition exercise-induced hemodynamic responses into dynamic pre- and post-capillary slope components using a four-quadrant phenotype model in stable adolescent Fontan patients. Furthermore, we evaluated their relationship with exercise capacity to establish a physiological foundation for targeted therapy during the transition to adult care.

Methods

Study Population and Ethical Considerations

We retrospectively analyzed 14 consecutive, clinically stable adolescent Fontan patients who underwent invasive exercise stress catheterization (Ex-Cath) at Chiba Children's Hospital between 2023 and 2025. Inclusion criteria required the physical and cognitive ability to perform cycle ergometry testing. To minimize flow estimation errors during pressure–flow analysis, patients with significant atrioventricular valve regurgitation ($\geq$ moderate) or hemodynamically significant aortopulmonary collateral arteries (APCAs)—confirmed by the absence of major collateral flow on routine aortography—were excluded. The study protocol was approved by the Institutional Review Board of Chiba Children's Hospital (Approval No. 2024-024). Due to the retrospective nature of the study, the requirement for written informed consent was waived, and an opt-out approach was utilized in accordance with the institutional guidelines, providing patients and their legal guardians the opportunity to decline participation.

Ex-Cath Protocol and Measurements

Ex-Cath was conducted using a supine cycle ergometer with continuous breath-by-breath gas analysis for oxygen consumption (VO_2) monitoring [9]. Workload was individualized based on preliminary cardiopulmonary exercise testing (CPX) performed within one week prior to catheterization, initiating at 20 watts and increasing incrementally to peak effort (defined by a respiratory exchange ratio > 1.10 or a Modified Borg Scale score > 7). Mean pulmonary arterial pressure (mPAP) and pulmonary artery wedge

pressure (PAWP) were measured at end-expiration and averaged over five consecutive cardiac cycles. Systemic (Qs) and pulmonary (Qp) blood flows were calculated at rest and peak exercise using the direct Fick principle.

Hemodynamic Slope Analysis and Partitioning Framework

To evaluate dynamic circulatory reserve, we prioritized pressure–flow slope analysis ($\Delta\text{Pressure}/\Delta\text{Flow}$) over resting or peak absolute pressure values [12,13], maximizing sensitivity for subtle impairment in adolescents. Hemodynamic responses during exercise were evaluated using pressure–flow relationships (slopes), and abnormal exercise thresholds were defined according to the validated criteria reported by Zeder et al. [14]: an integrated exercise $\Delta\text{mPAP}/\Delta\text{Qp}$ slope > 3.0 mmHg/L per min ($\text{mPAP}/\text{CO} > 3.0$ Wood units, WU) was defined as an abnormal overall hemodynamic response. Because mPAP represents the physiological sum of transpulmonary gradient (TPG) and PAWP ($\text{mPAP} = \text{TPG} + \text{PAWP}$), we dissected the overall exercise pressure response into pre- and post-capillary slope components using physiologically specific flow denominators:

Pre-capillary Component (Pulmonary Vascular Reserve): Calculated as the $\Delta\text{TPG}/\Delta\text{Qp}$ slope, where $\text{TPG} = \text{mPAP} - \text{PAWP}$. Qp was selected as the denominator to precisely reflect flow traversing the pulmonary vascular bed. Corresponding to the pre-capillary pulmonary vascular disease threshold proposed by Zeder et al. ($\text{TPG}/\text{CO} > 1.2\text{WU}$), an abnormal threshold was set at $> 1.2\text{mmHg/L per min}$.

Post-capillary Component (Ventricular Compliance/Distensibility): Calculated as the $\Delta\text{PAWP}/\Delta\text{Qs}$ slope. Qs was deliberately chosen as the denominator to capture the total effective volumetric return to the single ventricle, directly reflecting dynamic ventricular compliance. Corresponding to the exaggerated post-capillary response threshold ($\text{PAWP}/\text{CO} > 2.0\text{WU}$), an abnormal threshold was set at $> 2.0\text{mmHg/L per min}$ [10].

These specific thresholds ($\Delta\text{TPG}/\Delta\text{Qp} > 1.2$ and $\Delta\text{PAWP}/\Delta\text{Qs} > 2.0$) mathematically and physiologically anchored to sum to the benchmark total load threshold ($3.2\text{mmHg/L per min} \approx 3.0\text{mmHg/L per min}$), allowing for a balanced, pathophysiological dissection of overall exercise congestion.

Four-Quadrant Dynamic Phenotype Model

Patients were categorized into four distinct hemodynamic phenotypes by plotting the post-capillary slope ($\Delta\text{PAWP}/\Delta\text{Qs}$, x-axis) against the pre-capillary slope ($\Delta\text{TPG}/\Delta\text{Qp}$, y-axis) using the predefined thresholds:

- Post-capillary phenotype: $\Delta\text{PAWP}/\Delta\text{Qs} > 2.0$ and $\Delta\text{TPG}/\Delta\text{Qp} \leq 1.2$ mmHg/L per min
- Pre-capillary phenotype: $\Delta\text{PAWP}/\Delta\text{Qs} \leq 2.0$ and $\Delta\text{TPG}/\Delta\text{Qp} > 1.2$ mmHg/L per min
- Combined phenotype: $\Delta\text{PAWP}/\Delta\text{Qs} > 2.0$ and $\Delta\text{TPG}/\Delta\text{Qp} > 1.2$ mmHg/L per min
- Non-limited phenotype (Normal Reserve): $\Delta\text{PAWP}/\Delta\text{Qs} \leq 2.0$ and $\Delta\text{TPG}/\Delta\text{Qp} \leq 1.2$ mmHg/L per min

Statistical Analysis

Continuous variables are presented as mean $\pm$ standard deviation (SD) or median with interquartile range (IQR), as appropriate. Paired baseline and peak exercise hemodynamic values were compared using the Wilcoxon signed-rank test. To explore the physiological correlates of exercise capacity, bivariate associations between functional capacity (peak %predicted VO_2 from CPX) and hemodynamic variables (resting, peak, and slope parameters) were evaluated using Pearson's correlation coefficient or Spearman's rank correlation depending on data distribution. Statistical analyses were performed using JMP 16.0 (SAS Institute Inc., Cary, NC, USA), with two-tailed $P < 0.05$ considered statistically significant.

Results

Patient Characteristics and Baseline Findings

The clinical characteristics of the 14 adolescent Fontan patients are summarized in Table 1. The median age at the time of cardiac catheterization was 14.0 years. The cohort exhibited diverse anatomical backgrounds, with heterotaxy present in 29% ($N = 4$) and right ventricular predominance in 43% ($N = 6$) of patients. All participants were clinically stable, as evidenced by baseline laboratory and imaging parameters (Table 2). Notably, the mean BNP level was 7.0 ± 1.9 pg/mL and the mean main ventricular ejection fraction by CMR was $55 \pm 9\%$, both within normal limits. Cardiopulmonary exercise testing showed a mean peak % predicted VO_2 of $78 \pm 8\%$, indicating a relatively preserved baseline functional capacity. At the time of the study, none were receiving pulmonary vasodilators (Table 1).

Hemodynamic Response to Exercise

Invasive exercise stress testing induced significant hemodynamic shifts in all participants (Table 3). Upon reaching peak exercise, mPAP increased significantly from 10.1 ± 1.6 to 17.9 ± 3.0 mmHg and PAWP rose from 6.6 ± 1.5 to 12.9 ± 3.8 mmHg (both $P < 0.001$). Accompanying these pressure changes, Qp increased from 3.5 ± 0.8 to 5.7 ± 0.9 L/min and Qs rose from 4.1 ± 1.0 to 6.4 ± 1.1 L/min (both $P < 0.001$). Notably, while pressures and flows increased, pulmonary vascular resistance index (PVRI) remained relatively unchanged (1.4 ± 0.4 vs. 1.2 ± 0.5 $\text{WU}\cdot\text{m}^2$, $P = 0.26$).

Exercise Hemodynamics and Exaggerated Pressure-Flow Responses

Despite the modest resting pressures, the exaggerated pressure-flow relationship during exercise revealed latent abnormalities. As shown in Fig. 1, the mean $\Delta\text{mPAP}/\Delta\text{Qp}$ slope was 3.9 ± 2.0 mmHg/L per min, exceeding the abnormal threshold of 3.0. An abnormal overall exercise pressure response ($\Delta\text{mPAP}/\Delta\text{Qp}$ slope > 3.0 mmHg/L per min) was identified in 64% (9/14) of the cohort, highlighting the high prevalence of latent hemodynamic impairment even in clinically stable adolescents.

Hemodynamic Phenotyping via Quadrant Analysis

Using the four-quadrant phenotyping model (Fig. 2), we delineated the distinct physiological mechanisms underlying these exaggerated pressure responses. Half of the patients (50%, $n = 7$) were classified into Quadrant IV (Post-capillary phenotype), highlighting impaired ventricular distensibility as the predominant hemodynamic burden. Notably, a distinct pre-capillary component was identified in 28% of the cohort ($n = 4$) of patients, comprising 14% ($n = 2$) with an isolated Pre-capillary phenotype (Quadrant I) and 14% ($n = 2$) with a Combined phenotype (Quadrant II). The remaining 21% ($n = 3$) maintained a preserved hemodynamic reserve (Non-limited phenotype, Quadrant III).

To integrate functional capacity into this physiological framework, patients were stratified in Fig. 2 by CPX-derived peak % predicted VO_2 (open circles: $\geq 85\%$; filled circles: $< 85\%$). Patients with reduced exercise capacity ($< 85\%$, filled circles) clustered almost exclusively within the post-capillary-impaired profiles (Quadrants II and IV). Conversely, those with isolated pre-capillary restriction or non-limited reserve consistently demonstrated preserved exercise capacity.

Correlations with Functional Capacity

To evaluate clinical relevance, we analyzed the relationship between exercise hemodynamic parameters and functional capacity. As summarized in Table 2, exercise capacity parameters—including peak % predicted VO_2 —were derived from independent CPX performed within one week prior to catheterization. Among resting parameters, conventional indices such as BNP and EF failed to predict CPX-derived exercise loads (Table 4). Regarding exercise-induced parameters, while peak Qs index showed a moderate positive correlation with the peak % predicted VO_2 ($R = 0.51$, $P = 0.06$), whereas the absolute peak PAWP during exercise exhibited no such relationship ($R = -0.20$, $P = 0.50$). Notably, the $\Delta\text{PAWP}/\Delta\text{Qs}$ slope showed a more consistent negative correlation with this CPX-derived functional marker ($R = -0.46$, $P = 0.09$), suggesting that exercise tolerance is more closely linked to dynamic ventricular distensibility than to absolute pressure levels.

Discussion

This study demonstrates that clinically stable adolescent Fontan patients exhibit latent impairment in dynamic hemodynamic reserve that remains undetected by conventional resting parameters. Utilizing a quadrant phenotyping model based on exercise-induced pressure–flow slopes, we revealed that exercise intolerance in this cohort is pathophysiologically heterogeneous.

Pathophysiological Importance of Pre- versus Post-Capillary Partitioning

The finding and strength of this study lies in the pathophysiological necessity of partitioning the overall exercise pressure slope ($\Delta\text{mPAP}/\Delta\text{Qp}$) into discrete pre-capillary ($\Delta\text{TPG}/\Delta\text{Qp}$) and post-capillary ($\Delta\text{PAWP}/\Delta\text{Qs}$) slope components.

The $\Delta\text{mPAP}/\Delta\text{Qp}$ slope reflects global pressure elevation without identifying the primary site of resistance. In our cohort, half of the patients (50%, $n = 7$) presented with isolated post-capillary

phenotype, and an additional 14% ($n = 2$) demonstrated combined phenotype. Crucially, integrating functional capacity into Fig. 2 revealed that patients with reduced exercise capacity (peak % predicted $\text{VO}_2 < 85\%$ filled circles) were almost exclusively clustered in these post-capillary impaired quadrants. This proves that the impairment of ventricular compliance—where filling pressures rise precipitously even with modest flow augmentation—serves as the primary component on exercise capacity in adolescent Fontan patients. Furthermore, this classification highlights the diagnostic limitations of static resting PVRI. In healthy circulations, exercise triggers pulmonary vascular recruitment and vasodilation, resulting in a steep drop in PVRI. In our cohort, average PVRI remained static from rest to peak exercise (1.4 ± 0.4 vs. $1.2 \pm 0.5 \text{ WU}\cdot\text{m}^2$, $P = 0.26$), confirming a global loss of dynamic pulmonary vascular recruitment capacity. However, relying solely on resting PVRI conceals 28% of patients (Quadrants I and II) who are losing pulmonary vascular reserve. $\Delta\text{TPG}/\Delta\text{Qp}$ slope provides a sensitive diagnostic window to unmask early pre-capillary disease before resting PVRI becomes abnormal.

Hemodynamic Assessment via Pressure–Flow Slopes in Submaximal Exercise

Our findings also suggest potential physiological advantages of pressure–flow slope analysis over absolute peak pressure measurements during supine exercise catheterization. In adolescent cohorts, achieving true maximal exercise effort during invasive supine ergometry is variable and technically challenging. Absolute peak filling pressures, such as the peak PAWP diagnostic threshold proposed by Miranda et al. [12], are heavily confounded by the absolute workload achieved and peak volumetric output. In contrast, pressure–flow slope analysis evaluates the intrinsic stiffness of the single ventricle and pulmonary vascular bed across incremental flow states, providing an index that is independent of exercise effort or submaximal workload. This explains why absolute peak pressures failed to correlate with exercise capacity in our study (Table 4), whereas the $\Delta\text{PAWP}/\Delta\text{Qs}$ slope demonstrated a consistent trend toward an inverse correlation ($R = -0.46$, $P = 0.09$), capturing the compliance bottleneck of the single ventricle.

Diagnostic Gap with Resting Parameters

These dynamic findings expose a critical diagnostic gap in routine clinical follow-up. As shown in Table 4, resting parameters—including mPAP, PAWP, main ventricular ejection fraction, and resting BNP—failed to predict objective functional exercise capacity or the magnitude of exercise-induced pressure rises. Even among adolescents maintaining good resting hemodynamics, the mean $\Delta\text{mPAP}/\Delta\text{Qp}$ slope was $3.9 \pm 2.0 \text{ mmHg/L per min}$, exceeding the abnormal threshold ($> 3.0 \text{ mmHg/L per min}$) validated in adult Fontan cohorts. This confirms that adolescent patients operate with a narrow dynamic circulatory reserve despite clinical stability. Relying solely on resting data creates a "false sense of security"; invasive exercise stress catheterization is indispensable to unmask dynamic abnormalities at an early stage.

Comparison with Adult Cohorts and Neurohormonal Discrepancy

Our finding that resting BNP levels do not correlate with exercise hemodynamics contrasts with the findings of Miranda et al. in adult Fontan cohorts, where resting NT-proBNP significantly correlated with exercise-induced PAWP elevation [12]. This discrepancy underscores a physiological "time lag" between dynamic ventricular stiffness and neurohormonal activation. Miranda's adult cohort (median age 31.5 years) likely represents an advanced disease spectrum with established neurohormonal upregulation due to chronic systemic congestion. Conversely, our adolescent patients (median age 14.0 years) are in an earlier phase of compensated attrition. At this stage, while resting hemodynamics and neurohormonal biomarkers remain normal, the underlying physical stiffness and reserve exhaustion are unmasked during exercise.

Clinical Implications: Phenotype-Targeted Therapy

Differentiating pre- from post-capillary components may help tailor therapeutic strategies in Fontan patients, offering a plausible explanation for the inconsistent outcomes of previous pulmonary vasodilator trials [15]. In patients with post-capillary phenotype, pulmonary vasodilators may yield limited functional benefit and could inadvertently elevate ventricular filling pressures; therefore, therapeutic management in this subgroup might be better directed toward improving ventricular compliance and reducing systemic afterload. Conversely, patients with isolated pre-capillary phenotype may represent more suitable candidates for targeted pulmonary vasodilator therapy, as reducing pulmonary resistance could optimize ventricular preload without overloading post-capillary filling pressures. Consequently, this quadrant framework may provide a practical screening approach for patient selection in future phenotype-targeted clinical trials [16].

Limitations and Position as an Exploratory Pilot Study

Several limitations must be noted. First, this study was conducted as an exploratory pilot study with a small sample size ($n = 14$), which limited statistical power (Type II error) and caused clinically relevant associations—such as that between the $\Delta\text{PAWP}/\Delta\text{Qs}$ slope and peak % predicted VO_2 ($R = -0.46$, $P = 0.09$)—to remain at the trend level. Second, the partitioned threshold for pre-capillary phenotype ($\Delta\text{TPG}/\Delta\text{Qp} > 1.2$ mmHg/L per min) was adapted de novo within this single-ventricle framework based on adult biventricular benchmarks [14], requiring further prospective calibration. Third, given the single-center, cross-sectional design and the pulmonary vasodilator-naïve status of our cohort, longitudinal phenotype transitions and direct drug responses were not evaluated.

Nevertheless, as a proof-of-concept pilot study, these findings provide a novel, hypothesis-generating framework. Future multi-center, prospective longitudinal studies are warranted to validate these partitioned thresholds and investigate whether phenotype-targeted therapy preserves long-term hemodynamic reserve in Fontan patients.

Conclusion

In clinically stable adolescent Fontan patients, partitioning the overall exercise pressure response ($\Delta mPAP/\Delta Q_p$ slope) into dynamic pre-capillary ($\Delta TPG/\Delta Q_p$) and post-capillary ($\Delta PAWP/\Delta Q_s$) components provides a clearer pathophysiological evaluation of exercise hemodynamics. Using a four-quadrant phenotype model, this exploratory pilot study revealed phenotypic variability that was undetectable by conventional resting parameters.

Post-capillary phenotype was identified as a potential mechanism associated with reduced exercise capacity. By helping localize individual hemodynamic bottlenecks, this partitioned slope approach offers a useful framework for phenotype-targeted therapeutic strategies during the transition to adult-centered care.

Declarations

Author Contribution

K.H. was responsible for the conceptualization, methodology, formal analysis, data curation, investigation, project administration, and writing of the original draft. T.I. and H.N. contributed to validation and writing – review & editing. H.A. provided supervision and contributed to conceptualization and writing – review & editing. All authors reviewed and approved the final manuscript.

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Disclosures / Conflicts of Interest:

The authors have no conflicts of interest to declare.

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Tables

Table 1 to 4 are available in the Supplementary Files section.

Figures

Figure 1

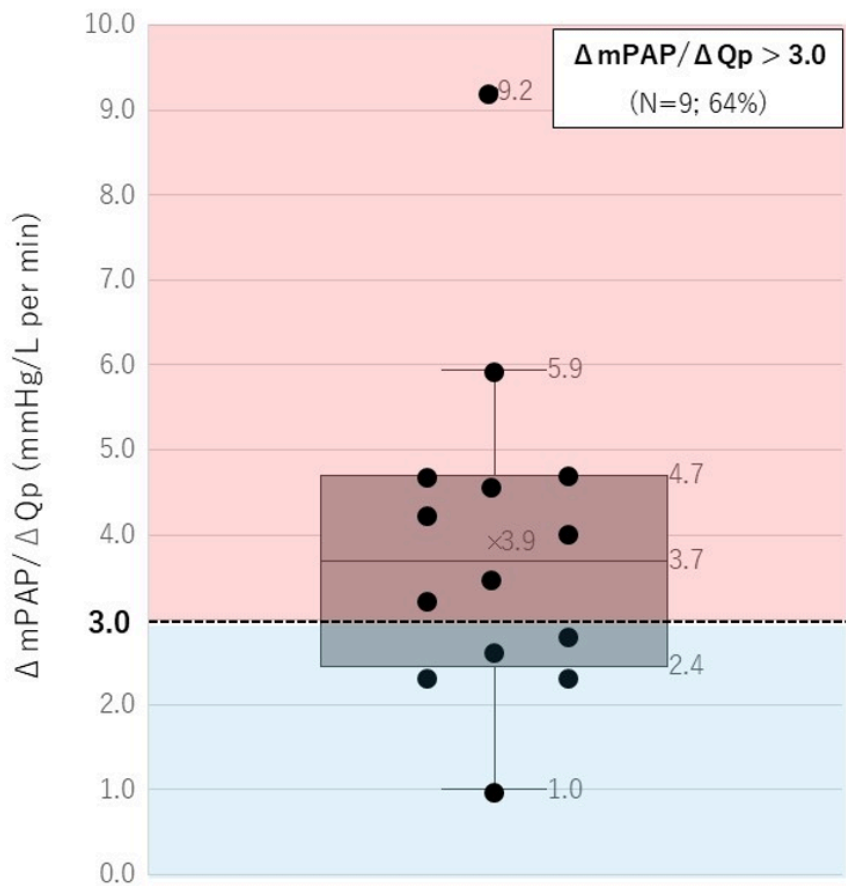


Figure 1

Exaggerated Pulmonary Pressure–Flow Response During Exercise

Distribution of the $\Delta mPAP/\Delta Qp$ slope in adolescent Fontan patients. The horizontal dashed line indicates the established abnormal threshold of 3.0 mmHg/L per min. An exaggerated pulmonary pressure–flow response ($\Delta mPAP/\Delta Qp$ slope > 3.0 mmHg/L per min) was observed in 64% (9/14) of the cohort. The box represents the interquartile range (IQR), the horizontal line within the box indicates the median (3.7 mmHg/L per min), and the cross symbol (×) represents the mean (3.9 ± 2.0 mmHg/L per min). Whiskers extend to $1.5 \times$ IQR.

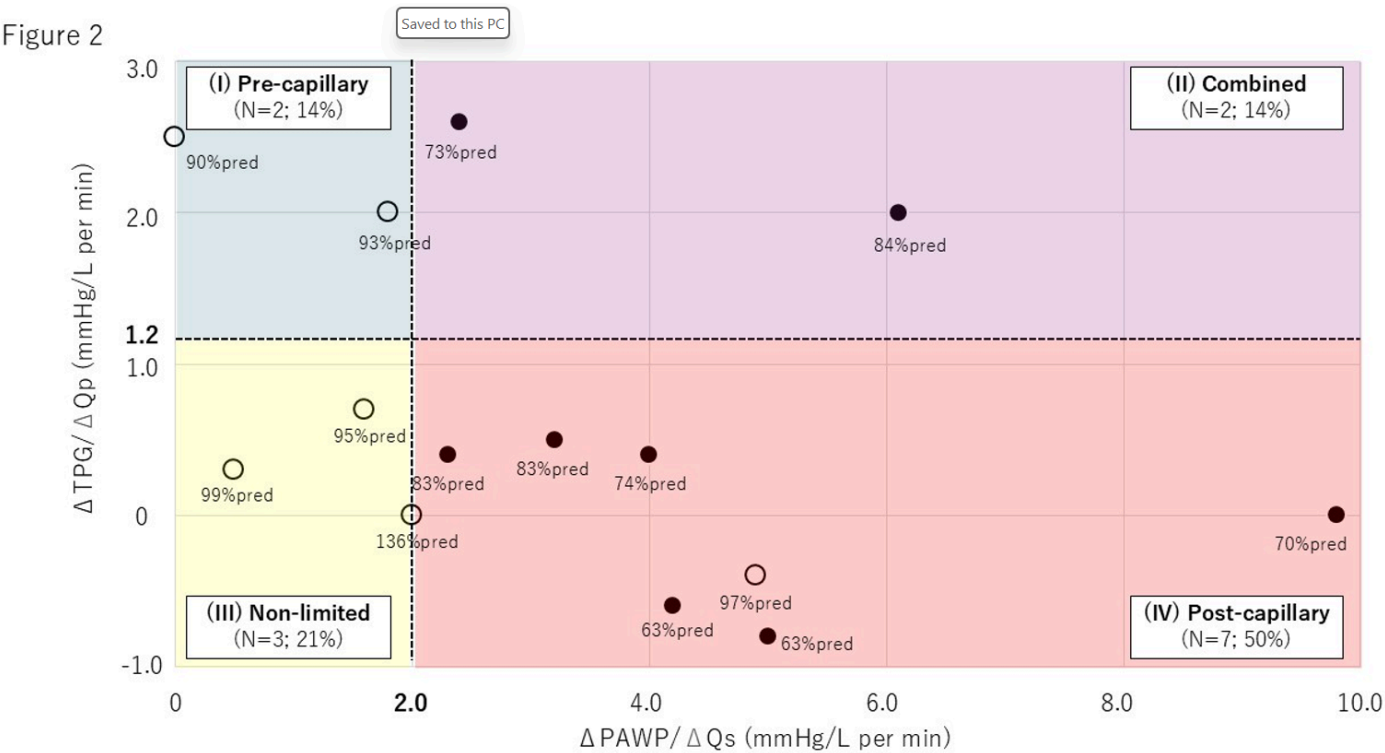


Figure 2

Quadrant Phenotyping Model for Individualized Hemodynamic Assessment

Analysis of hemodynamic phenotypes based on the $\Delta PAWP/\Delta Qs$ slope (representing post-capillary load) and the $\Delta TPG/\Delta Qp$ slope (representing pre-capillary load). Dashed lines indicate the thresholds for post-capillary (2.0 mmHg/L per min) and pre-capillary (1.2 mmHg/L per min) impairment. Notably, ΔQs was utilized as the denominator for the post-capillary component to accurately reflect the total volume load on the systemic ventricle. Individual values for peak % predicted VO_2 are shown alongside each data point (open circles: peak % predicted $VO_2 \geq 85\%$; filled circles: peak % predicted $VO_2 < 85\%$).

Patients are categorized into four distinct profiles: (I) Pre-capillary phenotype (n = 2, 14%), (II) Combined phenotype (n = 2, 14%), (III) Non-limited phenotype (n = 3, 21%), and (IV) Post-capillary phenotype (n = 7,

50%). Although post-capillary impairment was overall most prevalent (64% [9/14], Quadrants II and IV), a distinct pre-capillary component was identified in 28% (4/14) of the cohort (Quadrants I and II). Percentages may not sum to 100 due to rounding.

Supplementary Files

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