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Novel techniques for quantifying oxygen pulse curve characteristics during cardiopulmonary exercise testing in tetralogy of fallot

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Abstract

Background: Cardiopulmonary exercise testing (CPET) is used in evaluation of repaired tetralogy of Fallot (rTOF), particularly for pulmonary valve replacement need. Oxygen pulse (O_2P) is the CPET surrogate for stroke volume and peripheral oxygen extraction.

Objectives: This study assessed O_2P curve properties against non-invasive cardiac output monitoring (NICOM) and clinical testing.

Methods: This cross-sectional study included 44 rTOF patients and 10 controls. Three new evaluations for O_2P curve analysis during CPET were developed. Best fit early and late regression slopes of the O_2P curve were used to calculate: 1) the early to late ratio, or "O_2 pulse response ratio" (O_2PRR); 2) the portion of exercise until slope inflection, or "flattening fraction" (FF); 3) the area under the O_2P response curve, or "O_2P curve area".

Results: rTOF patients (median age 35.2 (27.6–39.4); 61% female) had a lower VO_2 max (23.4 vs 45.6 ml/kg/min; $p < 0.001$) and O_2P max (11.5 vs 19.1 ml/beat; $p < 0.001$) compared to

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CRediT authorship contribution statement

David M. Leone: Writing – review & editing, Writing – original draft, Visualization, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Matthew J. Magoon:** Writing – review & editing, Visualization, Validation, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Neha Arunkumar:** Formal analysis, Data curation. **Laurie A. Soine:** Writing – review & editing, Supervision, Project administration, Data curation, Conceptualization. **Elizabeth C. Bayley:** Writing – review & editing, Supervision, Project administration, Data curation. **Patrick M. Boyle:** Writing – review & editing, Visualization, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jonathan Buber:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used Copilot (Microsoft) to reword and rephrase text. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcchd.2024.100539.

controls. Those with a FF occurring <50% through exercise had a lower peak cardiac index and stroke volume, but not VO_2 max, compared to those >50%. FF and O_2P curve area significantly correlated with peak cardiac index, stroke volume, left and right ventricular ejection fraction, and right ventricular systolic pressure.

Conclusion: CPET remains an integral part in the evaluation of rTOF. We introduce three non-invasive methods to assess exercise hemodynamics using the O_2P curve data. These evaluations demonstrated significant correlations with stroke volume, cardiac output, and right ventricular pressure.

Keywords

Oxygen pulse; Exercise physiology; Cardiopulmonary exercise testing; Non-invasive cardiac output monitoring; Stroke volume; Structural heart disease

1. Introduction

Patients with repaired tetralogy of Fallot (rTOF) face lifelong cardiac risks with research focusing on the timing of pulmonary valve replacement and heart failure prevention. Cardiopulmonary exercise testing (CPET) is recommended for evaluating this condition, providing prognostic insights and cardiovascular health assessments [1,2].

Oxygen pulse (O_2P), a standard CPET parameter, is a surrogate for stroke volume (SV) augmentation and oxygen extraction during exercise. It's derived from the Fick principle and is the relationship of the volume of oxygen consumption (VO_2) with the heart rate; reported in units mL/beat [3,4]:

$$V_{O_2} = CO \times (\Delta a - v_{O_2}) \tag{1}$$

where cardiac output (CO) can also be expressed as stroke volume (SV) x heart rate (HR):

$$V_{O_2} = (SV \times HR) \times (\Delta a - v_{O_2}) \tag{2}$$

and the oxygen extraction (change in arterial and venous oxygen content) is typically augmented at a constant rate:

$$\frac{V_{O_2}}{HR} \propto SV = O_2P \propto SV \tag{3}$$

Therefore, O_2P is determined as the quotient of VO_2 with heart rate. Based on this rearrangement, in the absence of significant myopathy, O_2P is proportional to the stroke volume.

O_2P increases linearly with exercise effort as VO_2 and heart rate rise together. However, an inability to augment SV can cause a "flattening" of the O_2P curve [4,5]. This has been shown to occur in ischemic coronary heart disease [6–8], hypertrophic cardiomyopathy [9] and heart failure [10,11], but has only been minimally evaluated in adults with congenital heart disease (ACHD) [12].

Belardinelli et al. first quantified the O_2P response curve's flattening using linear regression, reflecting myocardial ischemia onset and associated stroke volume loss. Subsequent attempts to quantify this pattern haven't seen widespread use or validation [6,7,13,14]. Rossi de Almeida et al. and De Lorenzo et al. assessed clinical outcomes by using expert interpretation of CPET to identify abnormal O_2 pulse (O_2P) curve patterns—normal, low, flat, or descending—based on prior work by Klainman et al. [15–17].

This study was designed to create and assess new methods for automated quantification of O_2P curve changes during CPET. We hypothesized that rTOF patients would show early, abnormal O_2P flattening during maximal exercise due to limited SV augmentation. The study aimed to understand the O_2P and SV relationship in rTOF and generate new CPET measurements. These tools were evaluated against a healthy control group with non-invasive cardiac output measurement (NICOM) helping to identify causes of O_2P flattening.

2. Methods

2.1. Study population

This study was a cross-sectional observational study occurring at a large, regional, quaternary referral center and included rTOF patients referred for CPET between 1/9/2022 and 12/31/2023 ($n = 44$). Inclusion criteria comprised of a history of rTOF, including those with double outlet right ventricle variants and pulmonary atresia with an intact main pulmonary artery.

Exclusion criteria included unrepaired tetralogy of Fallot (TOF), TOF with absent pulmonary valve syndrome, pulmonary stenosis with ventricular septal defect without septal malalignment, and poor-quality NICOM or CPET tracings.

The study also included a control group of healthy individuals (n = 10) with equal sex representation. Demographics were collected for all participants. For the rTOF group, clinical information was abstracted from the electronic health record that included surgical history, echocardiogram (echo), cardiac magnetic resonance (MRI), and electrocardiogram (ECG) results. All imaging data was collected within a year of the CPET. The testing, performed based on clinical indications, was retrospectively assessed.

2.2. Cardiopulmonary exercise testing

Following calibration of the metabolic cart (Ultima Cardio; MGC Diagnostics, St Paul, MN), data was collected for 3 minutes. This was followed by exercise with breath-to-breath respiratory gas measurement. The HR and rhythm were recorded via continuous 12-lead ECG. Blood pressure was obtained every 2 minutes until peak exercise and 5 minutes into recovery.

Resting and peak exercise parameters included HR, VO_2, percent predicted VO_2, respiratory equivalent ratio (RER), O_2P, percent predicted O_2P, and the slope of minute ventilation (L) per liter of expired CO_2 (VE/VCO_2 slope) taken from start to end exercise. Neder et al. was used to determine predicted values [18]. We also determined the VO_2 recovery slope, a linear regression line of the VO_2 curve from the end of exercise for the first 2 min. This has been shown to carry prognostic implications in congenital heart disease, including rTOF [19,20].

2.3. Non-invasive cardiac output monitoring

The NICOM system (Starling; Baxter, Deerfield, IL) measures changes in impedance between the upper and lower torso, synced with ECG depolarization. This data helps estimate SV and CO by tracking changes in thoracic fluid volumes with each heartbeat. The NICOM device, validated by Swan-Ganz catheterization and thermodilution, records SV, CO, and cardiac index (CI) at regular time intervals [21].

2.4. Oxygen Pulse Curve Characteristics

We set out to analyze and identify scenarios where the O_2P response curve flattened during exercise, calling upon prior work and clinical observations [6,7,13,14]. To achieve this, unfiltered breath-by-breath data was exported to a Python version 3.10 data frame. To maintain consistency across different exercise protocols, the x-axis for exercise was converted to a percentage scale (0% = start, 100% = end). An algorithm was used to fit two linear regression lines for O_2P during exercise. This algorithm selected a transition point to fit two curves across the exercise duration, a penalty function was used to slightly favor flattening of the second slope.

The slopes of each linear regression line were recorded as "x" and "y". The intersection point, "δ", was identified. With the x-axis representing exercise as 0–100%, this point was recorded as the "flattening fraction" (FF), indicating the point in exercise where the change occurred. This can also be calculated with time on the x-axis, where the start of exercise until δ is "α" and the duration from δ to the end of exercise is "β". FF is calculated as $FF = \alpha/(\alpha + \beta)$. A second value, the "$O_2$ pulse response ratio" (O_2PRR), was calculated as $O_2PRR = x/y$. The final calculation was the "O_2 pulse curve area", the area under the O_2P curve from the start to end of exercise, determined via the trapezoidal rule. These three features are illustrated in Fig. 1.

2.5. Statistical analysis

Baseline characteristics are displayed as n (%) or median (inter-quartile range) for categorical or continuous data, respectively. Exercise and demographic characteristics were compared using the Wilcoxon rank sum test and the Fisher's exact test. Comparisons were made between the control and rTOF groups, as well as between the top and bottom halves of the rTOF group for FF and O_2PRR. Feature correlation was performed using Pearson correlation with missing data ignored. A p-value <0.05 was considered statistically significant. Data were collected and managed using REDCap, hosted at the University of Washington, and statistical computation was completed in R version 4.2.3.

2.6. Ethical considerations

All subjects provided written informed consent prior to enrollment. The study was approved by the University of Washington internal review board (STUDY00015598) and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

3. Results

3.1. Study population

54 subjects were recruited for participation, of which 44 had rTOF and 10 were in the control group. Due to the broad definition of pulmonary valve disease used in this analysis, patients had mixed pulmonary valve disease. Those with predominantly regurgitation (n = 34) were compared to those with predominantly stenosis (n = 10). The only differences between the groups were specific to the pulmonary valve, including the regurgitation group to be more likely to have a native valve (53%) or homograft (6%). Alternatively, the stenosis group was more likely to have a melody valve (30%). Given there were no other statistical differences in imaging, CPET, or NICOM parameters, these two groups were combined for the purposes of developing our novel CPET parameters. This comparison can be seen in Supplemental Table S1. As shown in Table 1, baseline demographics were overall similar between the two groups, however there was a slight, but not statistically significant higher, female representation in the rTOF group (61% vs 50%). Patients with rTOF had a higher body mass index (BMI; 27.0 vs 22.5 kg/m^2, p = 0.008), yet the body surface area was similar between the groups with an identical median of 1.8 m^2

3.2. Exercise capacity

CPET variables at peak exercise in the two groups are shown in Table 1. Exercise capacity was lower in the rTOF group, with a lower % predicted peak VO_2 (94.5% vs 140.5%, p < 0.001), maximal HR (164 bpm vs 184 bpm, p < 0.001) and maximal O_2P values (11.5 ml/beat vs. 19.1 ml/beat, P < 0.001). The VE/VCO_2 slope was similar between groups.

Patients with rTOF had a lower NICOM-assessed peak exercise CI of 7.1 vs. 8.2 L/min/m^2, but no differences in the peak exercise SV were noted. Of the three novel evaluations of the O_2P curve, only the O_2 pulse curve area was different between the groups at 8.1 for the rTOF group and 10.9 for the control group (p = 0.01). The FF was lower (occurring earlier) in the rTOF group, but did not reach significance (73% vs 51%, p = 0.08). The O_2PRR was not different between the groups 2.1 vs 1.7, respectively (p = 0.21).

3.3. Oxygen pulse curve characteristic comparisons in repaired tetralogy of fallot

To assess exercise differences based on the FF and O_2PRR the rTOF cohort was divided based on the median for each value: 50% and 1.6, respectively. Patients with earlier flattening (FF < 50%) had a higher right ventricular systolic pressure measured by echo (p = 0.003), were older age at initial surgical repair (p = 0.04), had lower peak SV by NICOM (p = 0.009), and lower peak cardiac index by NICOM (p = 0.002). Pulmonary valve regurgitation degree along with right ventricular and left ventricular ejection fraction were similar in both groups. The O_2PRR with values below the median of 1.6 were associated

with a high RVSP of 44 vs 33 mmHg (p = 0.032). No other feature showed a statistical difference. A comprehensive breakdown of these analyses can be seen in Table 2.

3.4. Correlations

Pearson correlation analysis between the novel O_2P curve evaluations and clinical or exercise features was conducted using data from both the rTOF and control groups. Correlations can be viewed in the correlogram matrix depicted in Fig. 2. Comparisons with selected clinical features can be seen in Fig. 3. These clinical features included those between FF and echo right ventricular systolic pressure ($r = -0.56$, $p = 0.001$), FF and NICOM max CI ($r = 0.42$, $p = 0.002$), O_2P curve area and MRI right ventricular SV ($r = 0.54$, $p = 0.01$), O_2P curve area and MRI left ventricular SV ($r = 0.46$, $p = 0.02$), O_2P curve area and NICOM max SV ($r = 0.55$, $p < 0.001$), and O_2P curve area and NICOM max CI ($r = 0.46$, $p < 0.001$).

4. Discussion

We have developed a tool that can take CPET data and calculate the O_2P slope producing three new measurements: O_2PRR, FF, and O_2P curve area. These novel O_2P slope measurements, especially FF and O_2P curve area, correlate with stroke volume as determined by MRI and NICOM at peak exercise (Fig. 4). FF tended to be lower in those with higher right ventricular systolic pressures, often seen in rTOF. While initially tested on rTOF individuals, this assessment can be applied to any demographic. Our cohort enrolled rTOF patients who did not have significant exercise limitations (given the high percent predicted peak VO_2) and represent a higher-functioning population of patients with rTOF. Caution should be used in applying the exercise findings of this pilot study to the larger population of rTOF.

4.1. Flattening fraction

We picked the point where the O_2P curve slope changes due to prior observations that patients with worse performance on CPET often have premature flattening of the O_2P. This O_2P curve difference has been described in several scenarios including heart failure where a flattened, or even down-sloping, phenotype has been described [10]. Belardinelli et al. found that this inflection was observed in subjects who had a positive nuclear stress test, suggesting an ischemia-related drop in cardiac output not mediated by heart rate [6]. They also showed that earlier flattening had a higher burden of perfusion abnormalities on nuclear testing [7]. This abnormal exercise response has been evaluated in hypertrophic cardiomyopathy. A recent study categorized O_2P curves into normal, flattened, or down-sloping if it occurred <65% through exercise. Participants with the latter two characteristics had lower VO_2 max, work rate, and O_2P [9]. However, our cohort did not replicate these findings. Notably, the functional class of our study was higher, and the cutoff point we employed, set at 50% of exercise duration (which corresponds to the median for our group), occurred earlier in the exercise protocol.

Based on the Fick principle, an earlier flattening of the O_2P indicates impaired SV augmentation during exercise. This phenotype was more pronounced in the patients in our

cohort who had a fixed pulmonary outflow obstruction, rather than pulmonary regurgitation (Fig. 3 and Table 2). This is consistent with work done by Steinmetz et al. who used cardiac MRI during recumbent cycle ergometry in repaired rTOF subjects. Compared to age matched healthy controls, the rTOF group had a significantly decreased cardiac output through the pulmonary valve at increasing work of exercise, further suggesting rTOF patients have abnormalities in exercise driven SV alteration [22].

NICOM helped differentiate between impaired SV augmentation and impaired oxygen extraction, two potential causes of O_2P flattening. The latter has been shown to occur in heart failure patients with preserved ejection fraction [23]. While 50% of exercise was the FF cutoff in this pilot study, future studies should establish clinically meaningful cutoffs. In our small control group with above-average exercise capacity, the median time for flattening was later than in rTOF patients (73% vs 51% of exercise). Although not statistically significant, a larger study might be powered to detect a difference.

4.2. Oxygen pulse response ratio

In conjunction with the timing of flattening, the ratio of the early to late slopes was thought to be important in quantifying the O_2P dynamics during exercise. O_2P typically increases linearly during exercise as SV rises due to inotropic effects on the ventricle. This is matched with increasing heart rates once SV can't be further increased to further increase VO_2 [4,5,24]. However, during maximal exercise, symptoms like leg fatigue and heavy breathing occur at cardiovascular limits, often associated with VO_2 and O_2P curve flattening. This late peaking and flattening is a normal response [5]. Our O_2PRR calculation suggests that the ratio in healthy individuals could resemble that in individuals with early flattening, as it merely shows a relationship between the two slopes. This may explain why this parameter did not reveal as many significant clinical associations as FF and the area under the O_2P curve. It is possible that there exists a clinical correlation between exercise-related stroke volume and both FF and O_2PRR, when considered together, which surpasses the insights gained by examining either factor in isolation.

4.3. Oxygen pulse curve area

We measured the O_2P curve area to simplify the assessment of changes in the O_2P curve over the course of the CPET and avoid limitations that occur when only looking at the peak O_2P. The measurement is agnostic to the type of exercise (i.e. treadmill or cycle ergometer). To remove the duration of exercise as a significant contribution in the x-axis, we standardized all studies on a 0–100% scale of completion with 0% being the beginning of the exercise protocol, and 100% when the subject reached maximal effort. We hypothesized that this would account for flattening of the O_2P as the area would be less than if there was a continued linear increase. The O_2P curve area significantly correlated with several estimates of stroke volume, both at rest by MRI, and peak exercise, as measured by NICOM (Fig. 2). One limitation is in the occurrence of chronotropic incompetence where the relatively low heart rate in the denominator causes an elevation in the absolute value of the O_2P, often higher than cohort predicted maximums, despite a low VO_2.

4.4. Controls

Healthy controls were used for comparison in developing these tools. Despite higher peak VO_2, O_2P, and heart rate in the control group, only O_2P curve area differed between the groups (8.1 vs 10.9). The flattening fraction occurred 20% earlier in the rTOF group, but this did not reach statistical significance (Table 1). The rTOF group, mostly patients in their 4th decade of life, reached a normal exercise capacity, with a median VO_2 of 23.4 ml/kg/min and predicted VO_2 of 94.5%. This is similar to prior reported peak VO_2 in this age group [25]. In comparison, the control group was an above average group of subjects with a median peak VO_2 of 45.6 ml/kg/m^2 and predicted VO_2 of 140.5%. Nonetheless, this helped establish an understanding of exercise physiology among healthy and physically active individuals and was used in the creation and calibration of the O_2P curve analyses.

Interestingly, despite increased peak VO_2, CI, and HR in the control group, there was no peak SV difference between the controls and rTOF (88.5 vs 89.0 ml). The lack of difference in peak SV may account for the lack of difference between the two groups in terms of FF and O_2PRR as these were created to be an estimate of SV during exercise. The change also suggests that there may be a relationship with oxygen extraction in the exercising muscles and O_2P, as outlined by the Fick equation. There is evidence that suggests factors contributing to increasing VO_2 are attributable to enhanced cellular oxygen extraction following training [26–28]. Further studies would be required to better understand this relationship. We aim to refine these tools and apply them to aid in prognostication in rTOF and other forms of congenital heart disease and heart failure.

4.5. Limitations

The study was a prospective pilot study and limited to a single center and subjects were recruited based on clinical practice patterns, introducing potential selection biases. While all patients were born with similar anatomy, their physiology, surgical, and structural heart histories varied significantly. Some patients had severe pulmonary regurgitation, while others had pulmonary valve stenosis leading to a heterogeneous group that may have limited interpretation. Despite these differences, the two pulmonary valve physiology groups had no statically different CPET parameters.

This was a relatively small cohort study of 54 subjects with a 4:1 patient to control ratio. Despite the small sample size, we believe it offers meaningful insights. Future studies should involve a larger patient cohort and validation with multiple centers.

In our statistical analysis, we attempted to explore clinical correlations using new tools. We divided our rTOF based on median levels, which may not be optimal for FF and O_2PRR. We evaluated correlations between these new variables and clinical features like SV and CO. While some features showed statistical correlation, this doesn’t imply causation due to potential unaccounted confounding variables.

Technical issues also arose. On 4 occasions, patients underwent NICOM evaluation, but excessive lead noise made interpretation impossible, leading to their exclusion from all analysis. Early breath-by-breath measurements sometimes contained significant outliers. For accurate linear regression, we used raw, unfiltered data without accounting for these outliers.

In some cases, the fitted curves appeared “suboptimal” due to noise and included a slope not considered in the final CPET interpretation. To ensure reproducibility and externalization of the algorithm, these were kept unaltered. All exercise test results and slopes can be seen in Supplemental Fig. S1.

5. Conclusion

CPET is an important tool in the evaluation of repaired rTOF. The O_2P is a non-invasive evaluation of SV modifications during exercise. Three new tools developed to assess abnormal changes in the O_2P include the FF, O_2PRR, and O_2P curve area. These showed correlations with NICOM derived SV, CO, and SV measured on routine clinical imaging.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

David M. Leone reports financial support was provided by Matthew’s Hearts of Hope. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

ACHD	Adult Congenital Cardiology
CI	Cardiac Index
CO	Cardiac Output
CPET	Cardiopulmonary Exercise Testing
FF	Flattening Fraction
HR	Heart Rate
NICOM	Non-invasive Cardiac Output Monitoring
O_2P	Oxygen Pulse

O_2PRR	O_2 Pulse Response Ratio
RER	Respiratory Equivalent Ratio
rTOF	Repaired Tetralogy of Fallot
SV	Stroke Volume
VO_2	Volume of Oxygen Consumption

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Clinical Perspectives

- Oxygen pulse is used during cardiopulmonary exercise testing as a surrogate marker for stroke volume.
- Early flattening or the oxygen pulse curve during exercise has been described as an abnormal response.
- This study uses new techniques to quantify oxygen pulse in three new ways in healthy controls and patients with tetralogy of Fallot. These findings are then compared these measurements to non-invasive stroke volume measurements.
- While initially evaluated in tetralogy of Fallot, these tools can be used in any demographic and may have importance in other forms of structural heart disease and heart failure.

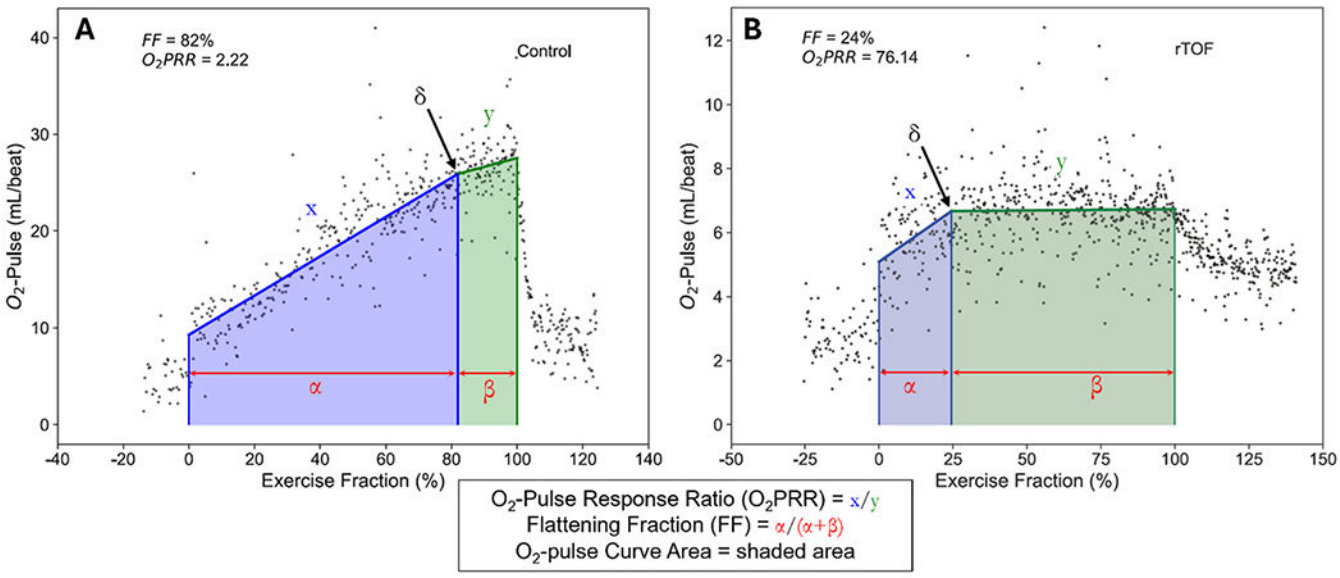

Fig. 1. Oxygen Pulse Curve Characteristics.

An example of two cardiopulmonary exercise test results. **A** is a subject from the control group whereas **B** is from the repaired tetralogy of Fallot group and demonstrated early flattening. The early slope (x), late slope (y), and transition point (δ) are determined by the algorithm for the best fit. Oxygen pulse response ratio (O_2PRR) is calculated as x/y. The fattening fraction (FF) is the point where δ occurs. It also can be characterized as $\alpha(\alpha+\beta)$ or the amount of time during exercise until the slope changes. The area under the curve (entire shaded area) was used to quantify the oxygen pulse curve area (O_2P curve area).

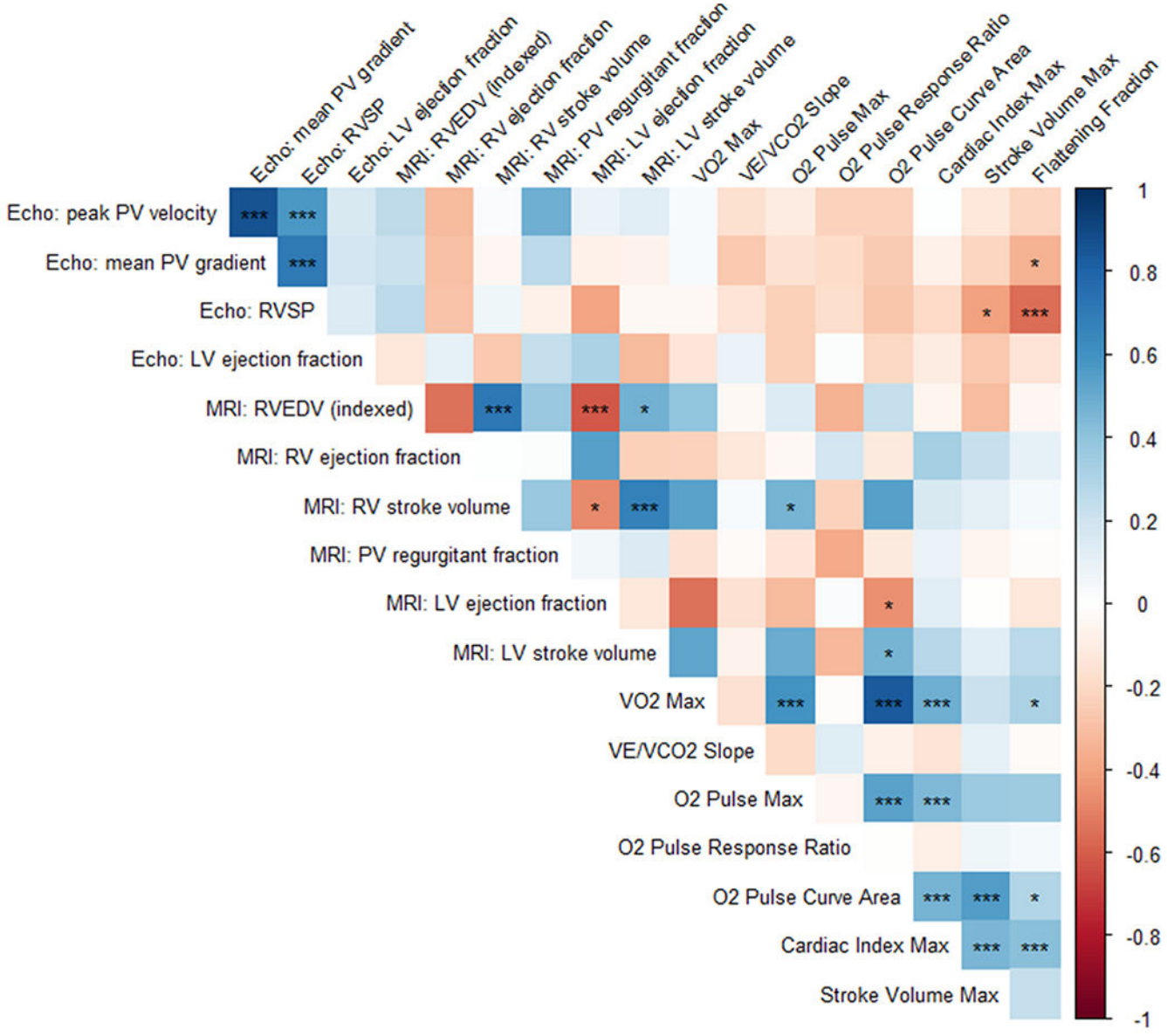

Fig. 2. Correlogram of Oxygen Pulse Curve Characteristics and Clinical Measurements.

Boxes are colored based on r valve for Pearson correlation. LV = left ventricle, MRI = magnetic resonance imaging, PV = pulmonary valve, RV = right ventricle, RVEDV = right ventricular end diastolic volume, RVSP = right ventricular systolic pressures * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

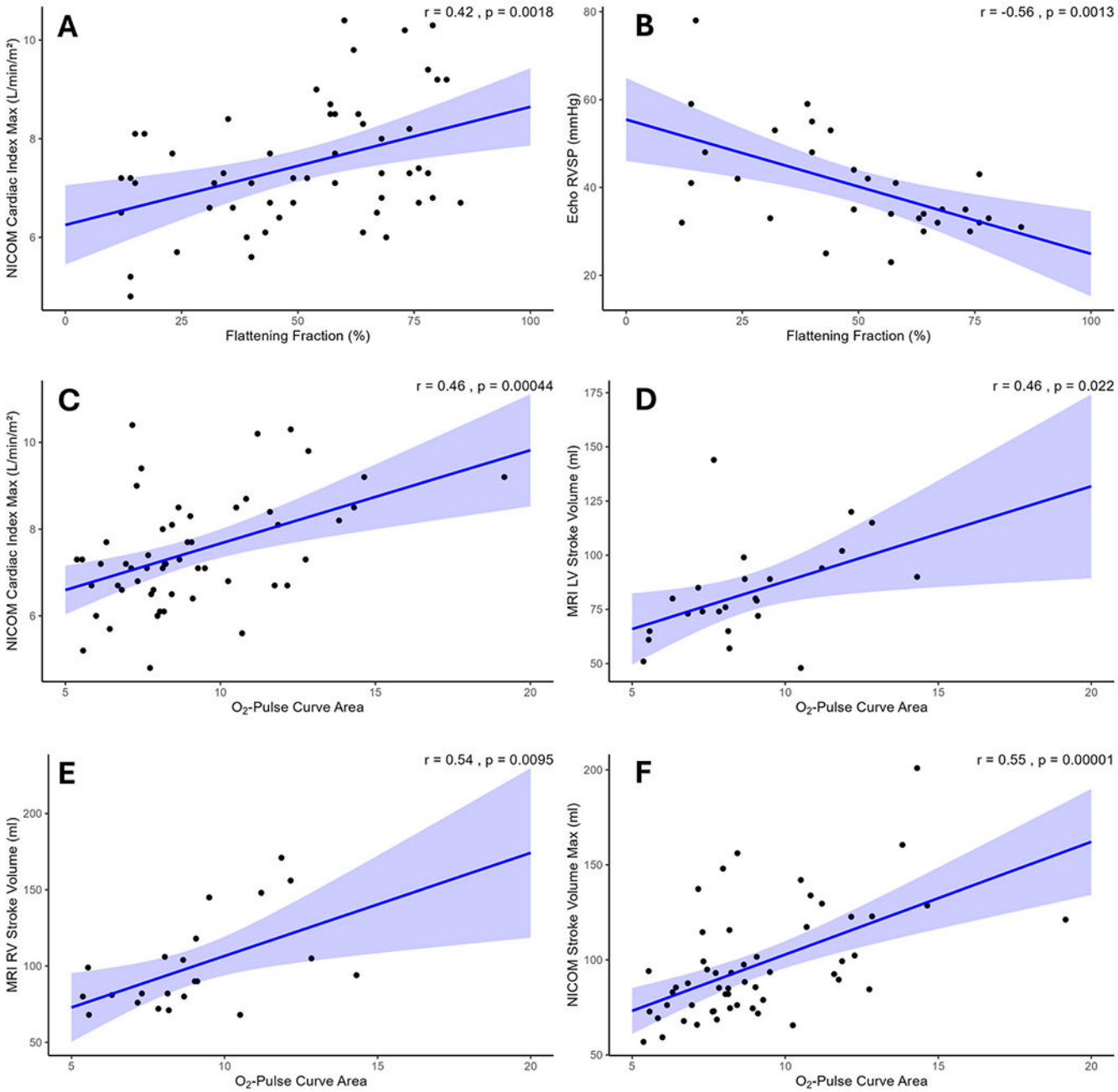

Fig. 3. Correlation Plots of Selected Comparisons.

Shaded areas show 95% confidence intervals. LV = left ventricle, METS = metabolic equivalents, NICOM = non-invasive cardiac output monitor, PV = pulmonary valve, RER = respiratory exchange ratio, RV = right ventricle, RVEDV = right ventricular end diastolic volume, RVSP = right ventricular systolic pressures.

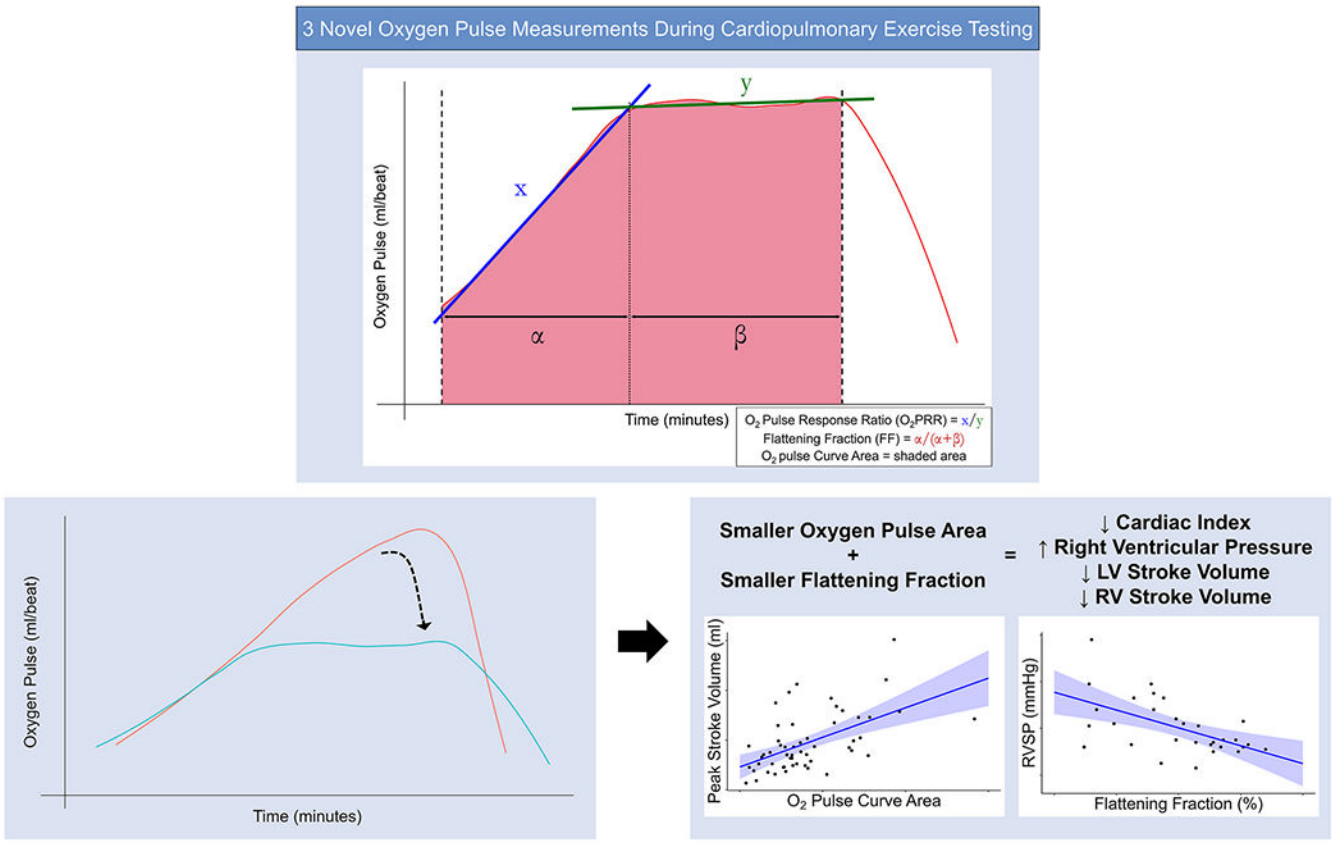

Fig. 4. 3 Novel Oxygen Pulse Measurements During Cardiopulmonary Exercise Testing.

Oxygen pulse curve area and flattening fraction, derived during cardiopulmonary exercise testing correlated with stroke volume, cardiac output, and right ventricular pressure. RVSP = right ventricular systolic pressure. The arrow shows “flattening” of the oxygen pulse curve compared to a normal response.

Table 1
Group Demographics and Maximal Exercise Parameters.

BMI = body mass index, BSA = body surface area, METS = metabolic equivalents, VO_2 = volume of oxygen consumption per minute, VE/VCO_2 Slope = slope of minute ventilation (L) per liter of expired CO_2, RER = respiratory exchange ratio, rTOF = repaired Tetralogy of Fallot.

Demographics			
	Control, N = 10	**rTOF, N = 44**	**p-value[a]**
Age, y	34.1 (32.0, 35.1)	35.2 (27.6, 39.4)	0.96
Sex			0.72
Female	5 (50 %)	27 (61 %)	
Male	5 (50 %)	17 (39 %)	
Ethnicity			0.23
Hispanic or Latino	1 (10 %)	4 (9.1 %)	
Non-Hispanic or Latino	5 (50 %)	32 (73 %)	
Unknown	4 (40 %)	8 (18 %)	
Race			>0.99
Asian	1 (10 %)	6 (14 %)	
Black or African American	0 (0 %)	1 (2.3 %)	
Unknown	2 (20 %)	8 (18 %)	
White	7 (70 %)	29 (66 %)	
BMI, kg/m^2	22.5 (19.8, 24.4)	27.0 (23.9, 32.6)	0.008
BSA, m^2	1.8 (1.7, 1.9)	1.8 (1.7, 2.1)	0.82
Maximal Exercise			
METS	13.1 (10.8, 14.5)	6.7 (5.4, 8.0)	<0.001
VO_2, ml/min	2960.5 (2532.5, 3625.3)	1770.5 (1488.0, 2264.5)	<0.001
VO_2, ml/kg/min	45.6 (37.7, 50.9)	23.4 (18.9, 28.1)	<0.001
VO_2, % Predicted	140.5 (135.3, 150.8)	94.5 (72.0, 104.8)	<0.001
Heart Rate, beats/min	184.0 (171.5, 187.8)	164.5 (148.5, 174.5)	0.004
O_2 Pulse, ml/beat	19.1 (14.2, 22.2)	11.5 (9.8, 14.8)	<0.001
O_2 Pulse, % Predicted	142.0 (133.5, 152.3)	109.0 (84.8, 122.8)	<0.001
RER	1.1 (1.1, 1.2)	1.2 (1.1, 1.2)	0.45
Stroke Volume, ml	88.5 (76.5, 100.5)	89.0 (76.2, 116.1)	0.72
Cardiac Index, $L/min/m^2$	8.2 (7.4, 9.2)	7.1 (6.6, 8.1)	0.011
VO_2 Recovery Slope	−826.2 (−992.1, −693.9)	−508.7 (−622.1, −391.1)	<0.001
VE/VCO^2 Slope	27.4 (25.1, 30.8)	30.7 (27.2, 34.1)	0.070
O_2 Pulse Response Ratio	2.1 (1.9, 2.8)	1.6 (0.8, 2.2)	0.13
Flattening Fraction %	73.0 (40.8, 79.0)	50.5 (35.0, 64.8)	0.080
O_2 Pulse Curve Area	10.9 (8.4, 12.6)	8.1 (7.1, 9.3)	0.013

[a] Wilcoxon rank sum test; Fisher's exact test.

Table 2

Novel Oxygen Pulse Curve Measurements in Repaired Tetralogy of Fallot.

Flattening fraction (FF) and oxygen pulse response ration (O_2PRR) were split for the repaired tetralogy of Fallot group and divided by median. CPET = cardiopulmonary exercise test, ECG = electrocardiogram, LV = left ventricle, METS = metabolic equivalents, NICOM = non-invasive cardiac output monitor, PV = pulmonary valve, RER = respiratory exchange ratio, RV = right ventricle, RVEDV = right ventricular end diastolic volume.

Clinical Features	Flattening Fraction			O2-Pulse Response Ratio		
	<50 %, N = 22	>50 %, N = 22	p-value[a]	<1.60, N = 22	>1.60, N = 22	p-value[a]
Age at CPET, y	35.9 (29.4, 39.3)	34.0 (27.3, 42.4)	0.58	35.0 (27.3, 39.6)	35.5 (27.8, 39.1)	0.93
Age at Complete Repair, y	2.5 (0.7, 4.0)	1.0 (0.3, 1.9)	0.039	1.7 (0.7, 3.8)	1.1 (0.3, 2.9)	0.29
RVSP (Echo), mmHg	48.0 (38.0, 54.0)	33.0 (31.5, 35.0)	0.003	44.0 (34.5, 53.0)	33.0 (32.0, 38.0)	0.032
PV Regurgitation (Echo)			0.35			>0.99
Mild	6 (30 %)	4 (22 %)		5 (25 %)	5 (28 %)	
Mod	5 (25 %)	9 (50 %)		7 (35 %)	7 (39 %)	
Severe/Free	9 (45 %)	5 (28 %)		8 (40 %)	6 (33 %)	
LV Ejection Fraction (Echo), %	61.5 (58.3, 65.5)	58.5 (56.3, 60.0)	0.069	59.5 (55.8, 64.0)	59.0 (57.0, 62.0)	0.61
RVEDV (MRI), ml/m^2	123.9 (97.4, 145.7)	111.4 (91.6, 123.4)	0.48	122.7 (92.1, 149.5)	111.4 (102.1, 123.7)	0.79
RV Ejection Fraction (MRI), %	46.0 (43.0, 46.0)	46.5 (43.5, 53.8)	0.33	46.0 (37.3, 47.5)	46.5 (43.8, 54.3)	0.24
LV Stroke Volume (MRI), ml	75.0 (72.3, 79.8)	87.0 (64.3, 97.8)	0.38	87.0 (74.0, 91.0)	74.0 (64.0, 84.8)	0.18
PV Regurgitation (MRI), %	21.0 (16.0, 41.0)	22.8 (16.0, 30.5)	0.87	26.0 (19.5, 42.0)	18.0 (13.8, 26.5)	0.17
LV Ejection Fraction (MRI), %	57.0 (54.0, 63.0)	59.0 (55.0, 60.9)	0.81	58.0 (54.5, 60.8)	59.0 (54.0, 62.0)	0.91
METS	6.6 (5.5, 8.0)	6.8 (5.4, 8.0)	0.91	6.2 (5.4, 8.1)	7.1 (5.5, 8.0)	0.47
VO_2, ml/min	1637.0 (1389.5, 1899.8)	1821.0 (1580.8, 2304.0)	0.18	1820.0 (1466.0, 2220.0)	1727.0 (1528.8, 2258.3)	0.94
VO_2, ml/kg/min	22.9 (19.1, 28.0)	23.8 (18.9, 27.9)	0.92	21.5 (18.8, 28.6)	24.7 (19.1, 28.0)	0.45
VO_2, % Predicted	0.9 (0.7, 1.0)	1.0 (0.7, 1.1)	0.79	0.9 (0.7, 1.0)	1.0 (0.8, 1.1)	0.44
Heart Rate, beats/min	167.5 (157.0, 177.5)	160.0 (147.0, 173.0)	0.20	158.5 (147.0, 173.0)	165.5 (157.0, 175.5)	0.24
O_2 Pulse, ml/beat	10.8 (9.4, 12.4)	12.4 (10.5, 16.2)	0.091	11.8 (9.6, 14.9)	10.9 (9.9, 13.1)	0.51
O_2 Pulse, % Predicted	1.1 (0.9, 1.2)	1.1 (0.8, 1.3)	0.41	1.1 (0.9, 1.2)	1.1 (0.8, 1.2)	0.72
RER	1.1 (1.1, 1.2)	1.2 (1.1, 1.2)	0.16	1.2 (1.1, 1.2)	1.2 (1.1, 1.2)	0.73
Stroke Volume (NICOM), ml	84.0 (73.7, 92.2)	106.9 (86.3, 132.8)	0.009	93.4 (77.9, 126.5)	85.6 (73.7, 98.8)	0.30
Cardiac Index (NICOM), L/min/m^2	6.7 (6.2, 7.2)	7.4 (6.9, 8.5)	0.002	7.2 (6.6, 8.1)	7.1 (6.6, 7.6)	0.60

Clinical Features	Flattening Fraction			O2-Pulse Response Ratio		
	<50 %, N = 22	**>50 %, N = 22**	**p-value[a]**	**<1.60, N = 22**	**>1.60, N = 22**	**p-value[a]**
VO_2 Recovery Slope	−446.4 (−592.3, −397.2)	−558.2 (−655.0, −396.4)	0.30	−528.8 (−605.6, −415.9)	−497.0 (−660.1, −378.5)	>0.99
VE/VCO_2 Slope	31.1 (26.7, 34.5)	30.3 (27.7, 33.3)	0.92	31.1 (27.2, 33.9)	30.0 (27.5, 33.9)	0.92
O_2 Pulse Response Ratio	1.3 (0.6, 2.2)	1.8 (1.2, 2.9)	0.13	0.8 (0.3, 1.1)	2.3 (1.9, 3.4)	<0.001
Flattening Fraction, %	34.0 (15.5, 42.3)	65.5 (58.5, 73.8)	<0.001	46.5 (33.0, 63.0)	55.0 (40.8, 67.0)	0.45
O_2 Pulse Curve Area	7.8 (6.7, 9.1)	8.3 (7.4, 10.8)	0.25	7.9 (7.1, 9.3)	8.2 (7.0, 9.2)	0.86

[a]Wilcoxon rank sum test; Fisher’s exact test; Wilcoxon rank sum exact test.