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Impact of peak respiratory exchange ratio on the prognostic power of symptoms-limited exercise testing using Bruce protocol in patients with Fontan physiology

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Abstract

Objectives: We evaluated the impact of peak respiratory exchange ratio on the prognostic values of cardiopulmonary exercise variables during symptoms-limited incremental exercise tests in patients with Fontan physiology. *Methods:* Retrospective single-centre chart review study of Fontan patients who underwent exercise testing using the Bruce protocol between 2014 and 2018 and follow-up. *Results:* A total of 34 patients (age > 18 years) had a Borg score of ≥7 on the Borg 10-point scale, but only 50% of patients achieved a peak respiratory exchange ratio of ≥ 1.10 (maximal test). Peak oxygen consumption, percent-predicted peak oxygen consumption, and peak oxygen consumption at the ventilatory threshold was reduced significantly in patients with a peak respiratory exchange ratio of < 1.10. Peak oxygen consumption and percent-predicted peak oxygen consumption was positively correlated with peak respiratory exchange ratio values ($r = 0.356$, $p = 0.039$). After a median follow-up of 21 months, cardiac-related events occurred in 16 (47%) patients, with no proportional differences in patients due to their respiratory exchange ratio (odds ratio, 0.62; 95% CI: 0.18–2.58; $p = 0.492$). Multivariate Cox proportional hazard analysis showed percent-predicted peak oxygen consumption, peak heart rate, and the oxygen uptake efficient slope were highly related to the occurrence of events in patients only with a peak respiratory exchange ratio of ≥ 1.10. *Conclusions:* The value of peak cardiopulmonary exercise variables is limited for the determination of prognosis and assessment of interventions in Fontan patients with sub-maximal effort. Our findings deserve further research and clinical application.

Cardiopulmonary exercise testing provides reproducible, and quantifiable data on cardiac and respiratory performance in patients with congenital heart disease (CHD). The measurement of exercise capacity using peak oxygen consumption has been considered as an important metric predicting cardiac-related events in a variety of cardiovascular conditions including heart failure[1] and pulmonary hypertension.[2] However, the main issue of peak oxygen consumption measure is that it requires a maximal exercise for its interpretation. Age, sex, and body mass index are known factors determining peak oxygen consumption in a healthy population.[3,4] Previous studies have shown that many adults with CHD terminated exercise before reaching their cardiovascular limit, which may be a serious shortcoming to the evaluation of the prognostic value of peak oxygen consumption.[5,6] Fontan circulation is a unique palliation procedure for CHD with single-ventricle physiology, and a decrease in peak oxygen consumption has been demonstrated in most Fontan patients.[7–10] However, a uniform relationship between peak oxygen consumption and mortality or transplantation could not be established in Fontan patients.[10] This inconsistency may be due to differences in exercise efforts.[8,10,11] The peak respiratory exchange ratio, a ratio of carbon dioxide production and oxygen consumption measured via respiratory gas analysis, has been used as an objective criterion of effort during exercise testing.[12] Based on the American College of Cardiology/American Heart Association guidelines, cut-off values of peak respiratory exchange ratio of ≥1.10 is generally accepted as maximal effort, whereas a peak respiratory exchange ratio of <1.10 is considered sub-maximal effort in adults.[13] The impact of peak respiratory exchange ratio on the prognostic power of peak oxygen consumption has been previously assessed in adults with acquired heart failure,[11,14,15] but the implication in patients with Fontan circulation remains uncertain.

The primary objective of this study was to compare the cardiopulmonary exercise testing parameters in Fontan patients with sub-maximal (peak respiratory exchange ratio of < 1.10) versus maximal effort (peak respiratory exchange ratio of ≥ 1.10). The secondary aim was to determine the correlation of cardiopulmonary exercise variables at different peak respiratory

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exchange ratios for increased risk of cardiac-related events in Fontan patients over short-term follow-up.

Methods

Ethical approval

The study protocol was approved by the Memorial Healthcare System's Institutional Review Board. Given the anonymised nature of the data, the requirement for informed consent was waived in this study.

Study population and setting

This was a retrospective, single-centre study cohort design evaluating Fontan patients who performed exercise testing using a treadmill according to Bruce protocol between August, 2014 and April, 2018 at the Cardiovascular Institute, Memorial Healthcare System, Hollywood, Florida, United States of America. The commercial gas exchange measurement system (Ultima2, MedGraphics, St Paul, MN, United States of America) was used to calculate respiratory gas exchange: peak oxygen consumption, carbon dioxide output, minute ventilation, ventilatory threshold, and oxygen consumption at the ventilatory threshold on a breath-by-breath basis. The exercise was terminated when the rate of perceived exertion score of ≥7 on the modified Borg 10-point scale. Peak respiratory exchange ratio, peak heart rate, and blood pressure were taken at peak exercise. Cardiopulmonary exercise testing data were calculated as 30-second averages, which were updated every 10 seconds. Peak oxygen consumption was measured as the highest 30-second average during exercise. The ratio of minute ventilation and carbon dioxide output nadir was taken as the lowest 30-second average during exercise. The ventilatory threshold was measured using the V-slope method.[16] The oxygen uptake efficient slope, which is the rate of increase in oxygen consumption in response to the increase of minute ventilation during incremental exercise was recorded.[17] Patients were excluded if they had incomplete exercise data.

Data collection

Demographic and clinical characteristics were obtained via medical record extraction and consisted of age, gender, body mass index, and NYHA functional class. Patients were followed up for a median of 21 months for the incidence of cardiac-related events, including death; listed for or received heart transplant; supraventricular tachycardia requiring hospitalisation, cardioversion, and electrophysiological studies for atrial fibrillation, atrial flutter, intra-atrial reentrant tachycardia, junctional tachycardia, and atrial tachycardia; ventricular tachycardia or fibrillation; cardiac device implantation; thromboembolic events (a stroke or systemic embolic events); and interventional cardiac catheterisation.

Statistical analysis

Results are expressed as mean ± SD for continuous variables or as a number or percentage for categorical variables. Comparisons between subgroups were performed using unpaired t-test or the Chi-square test as appropriate. The relationship between peak respiratory exchange ratio and age, weight, body mass index, and cardiopulmonary exercise testing parameters were assessed using Pearson correlation coefficient tests. The previously reported mean values for peak oxygen consumption of 23 ml/kg/minute and the ratio of minute ventilation and carbon dioxide output slope of 34 in Fontan patients[18] were used to create event-free survival curves using the Kaplan–Meier plots and were compared using log-rank tests. Cardiopulmonary exercise testing variables were first assessed using univariable Cox hazard analysis, and subsequent multivariable Cox was performed to detect independent predictors associated with cardiac-related events. Receiver-operating characteristic curves were constructed for cardiopulmonary exercise variables identified as independent predictors of cardiac-related events. For all analyses, a two-sided, $p < 0.05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS version 26.0 (IBM, Armonk, NY, United States of America) and GraphPad Prism 7.0 (Graph Pad Software Inc., La Jolla, CA, United States of America).

Results

Patient demographic and clinical characteristics

A total of 34 Fontan patients (mean age 44.96 ± 13.8 years) were identified that had complete cardiopulmonary exercise testing and follow-up data available. Of the 34 patients, 17 (50%) patients did not reach peak respiratory exchange ratio of ≥ 1.1 due to subjective symptoms of leg fatigue, dyspnoea, or Borg score of ≥7 on the 10-point scale. The demographic and clinical characteristics based on the peak respiratory exchange ratio were summarised in Table 1. Age, gender, and body mass index were comparable between the two groups. There were 12 (71%) NYHA Class I patients in the peak respiratory exchange ratio of ≥ 1.10 subgroup compared to 4 (12%) in the peak respiratory exchange ratio of < 1.10 group ($p = 0.006$). Tricuspid atresia was the most common diagnosis (35%). No significant differences were found in the distributions of ventricular morphology between the two groups. There was a total of 27 lateral tunnel Fontan and 7 extracardiac Fontan procedures in the entire cohort. The lateral tunnel Fontan procedure had been done in 14 patients with a peak respiratory exchange ratio of < 1.10 and 3 patients with a peak respiratory exchange ratio of ≥ 1.10, while the extracardiac Fontan had been done in 13 patients with a peak respiratory exchange ratio of < 1.10 and 4 patients with a peak respiratory exchange ratio of ≥ 1.10. The time since Fontan procedure for patients with peak respiratory exchange ratio of < 1.1 was 12.6 ± 8.4 years, whereas it was 14.2 ± 9.8 years in patients with peak respiratory exchange ratio of ≥ 1.1 ($p = 0.422$). A total of 16 (47%) cardiac-related events were observed over a median follow-up of 21 months, 7 (41%) in the peak respiratory exchange ratio of < 1.10 group and 9 (53%) in the peak respiratory exchange ratio of ≥ 1.10 group (odds ratio, 0.62; 95% CI: 0.18–2.58; $p = 0.492$). The details of cardiac events were summarised in Table 1 under each group. Patient age ($r = -0.100$, $p = 0.572$), height ($r = 0.178$, $p = 0.315$), body weight ($r = -0.296$, $p = 0.198$), or body mass index ($r = -0.226$, $p = 0.198$) were not significantly correlated with the respiratory exchange ratio (Fig 1(a–d)).

Cardiopulmonary exercise variables according to the respiratory exchange ratio

The cardiopulmonary exercise variables of Fontan patients based on their sub-maximal versus maximal effort were presented in Table 2. There was no significant difference in exercise duration between two groups, 6.5 ± 2.2 minutes versus 8.2 ± 3.6 minutes ($p = 0.142$). Peak oxygen consumption and percentage of predicted peak oxygen consumption values (based on age, sex, and

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Table 1. Baseline demographic and clinical data by pRER status

Variable	Fontan pRER < 1.10 (n = 17)	Fontan pRER ≥ 1.10 (n = 17)	p-value
Age, years	24.1 ± 7.1	26.1 ± 5.5	0.361
Female, n (%)	9 (53)	7 (41)	0.492
BMI, kg/m^2	27.7 ± 10.4	26.1 ± 5.7	0.583
Functional class, n (%)			
NYHA I	4 (24)	12 (71)	0.006
NYHA II	8 (47)	4 (24)	0.151
NYHA III or IV	5 (29)	1 (5)	0.368
Diagnosis, n (%)			
HLHS	6 (35)	5 (29)	0.714
Tricuspid atresia	7 (41)	5 (29)	0.473
Unbalanced AV canal	2 (12)	3 (18)	0.628
Other	2 (12)	4 (24)	0.628
Ventricular morphology, n (%)			
Right	7 (41)	5 (29)	0.473
Left	7 (41)	5 (29)	0.473
Other (ambiguous)	3 (18)	7 (41)	0.199
Type of Fontan surgery			
Lateral tunnel	14 (82)	13 (76)	0.672
Extracardiac conduit	3 (18)	4 (24)	0.672
Time since Fontan, years			
Mean ± SD	12.6 ± 8.4	14.2 ± 9.8	0.422
Cardiac events, n (%)	7 (41)	9 (53)	0.492
Death	2 (12)	1 (6)	0.545
Heart transplant	1 (6)	2 (12)	0.545
Hospitalisation (arrhythmia)	2 (12)	3 (18)	0.628
Surgical intervention	1 (6)	1 (6)	1
Catheter intervention	1 (6)	2 (12)	0.545

body mass index) were significantly lower in patients with peak respiratory exchange ratio of < 1.10 compared to those with a peak respiratory exchange ratio of ≥ 1.10 (p = 0.031 and p = 0.039, respectively). The mean value of oxygen consumption at ventilatory threshold (% of peak oxygen consumption) was lower in patients with a peak respiratory exchange ratio of < 1.10 compared to those with a peak respiratory exchange ratio of ≥ 1.10 (37.0 ± 4.5% versus 44.4 ± 9.4%, p = 0.008). There were no differences in terms of peak heart rate, percent of predicted peak heart rate, the ratio of minute ventilation and carbon dioxide output slope and percent of predicted ratio of minute ventilation and carbon dioxide output slope, and oxygen uptake efficient slope between two subgroups (Table 2).

Figure 2(a–f) shows the relationship of peak respiratory exchange ratio with peak oxygen consumption, percent of predicted peak oxygen consumption, peak heart rate, the ratio of minute ventilation and carbon dioxide output slope, oxygen consumption at the ventilatory threshold, and oxygen uptake efficient slope. Both peak oxygen consumption and percent predicted oxygen consumption was positively correlated with peak respiratory exchange ratio values (r = 0.356, p = 0.039). There was no apparent correlation between peak respiratory exchange ratio and peak heart rate (r = 0.124, p = 0.122), ratio of minute ventilation and carbon dioxide output slope (r = −0.100, p = 0.573), and oxygen consumption at ventilatory threshold (r = 0.162, p = 0.361). There was a trend towards a positive correlation between peak respiratory exchange ratio and oxygen uptake efficient slope (r = 0.223, p = 0.204) in these patients, but not statistically significant.

Impact of respiratory exchange ratio on the predictive power of cardiopulmonary exercise variables

During a median follow-up period of 21 months (interquartile range, 13–28 months), cardiac events occurred in 16 patients (47%). On Kaplan–Meier analysis, there was no significant difference (p = 0.907) in the occurrence of the cardiac events between the patients with a peak respiratory exchange ratio of < 1.10 and the patients with a peak respiratory exchange ratio of ≥ 1.10 (Fig 3(a–c)), although the peak oxygen consumption presented a significant difference (p = 0.031) between the two groups (Table 2). The Kaplan–Meier survival curves grouped according to the mean value of the peak oxygen consumption of ≥ 23 or <23 ml/kg/minute (published normal value in literature)[18] showed no significant difference (p = 0.661) in the occurrence of the cardiac-related events (Fig 3b). The analysis of the survival curve of these patients according to the mean value of the ratio of minute ventilation and carbon dioxide output slope of ≥ 34 or <34 (published normal value in literature)[18] also failed to show any significant difference (p = 0.656) in the occurrence of the cardiac-related events (Fig 3c).

On multivariate Cox proportional hazard analysis, percent-predicted peak oxygen consumption, peak heart rate, and oxygen uptake efficient slope were found to be independent predictors of cardiac events only in the patients with a peak respiratory exchange ratio of ≥ 1.10 (Table 3). None of the cardiopulmonary exercise variables were independent predictors of cardiac-related events in patients with peak respiratory exchange ratio of < 1.1. A hazard ratio of 0.57 (95% CI 0.35–0.94) was observed for each unit (ml O_2/kg/minute) increase in predicted peak oxygen consumption, a hazard ratio of 1.33 (95% CI 1.03–1.71) was observed for each unit decrease in peak heart rate, and a hazard ratio of 1.01 (95% CI 1.00–1.01) was observed for each unit increase in oxygen uptake efficient slope to predict cardiac events to predict cardiac-related events only in patients with peak respiratory exchange ratio of ≥ 1.1.

Receiver-operating characteristics curve analysis was performed to determine optimal cut-off values for percent-predicted peak oxygen consumption, peak heart rate, and oxygen uptake efficient slope predicting cardiac events in Fontan patients with a peak respiratory exchange ratio of ≥ 1.1 during cardiopulmonary exercise testing (Table 4). The area under the receiver-operating curve of 0.36 (95% CI 0.07–0.65, p = 0.336) was observed for predicted peak oxygen consumption, with an associated cut-off point of <57.5% (sensitivity 44%, specificity 50%). The area under the receiver-operating curve for peak heart rate was 0.64 (95% CI 0.35–0.93, p = 0.336), with an associated cut-off point of ≤151 (sensitivity 67%, specificity 50%). The area under the receiver-operating curve for oxygen uptake efficient slope was 0.51 (95% CI 0.23–0.80, p = 0.923), with an associated cut-off point of ≥2266 (sensitivity 67%, specificity 50%).

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Table 2. CPET findings by RER status

Variable	Fontan pRER < 1.10 (n = 17)	Fontan pRER ≥ 1.10 (n = 17)	p-value
Exercise duration, minutes	6.5 ± 2.2	8.2 ± 3.6	0.142
Peak VO_2	19.7 ± 4.1	23.2 ± 4.8	0.031
Predicted peak VO_2 (%)	50.7 ± 8.8	58.6 ± 12.3	0.039
VO_2 at VAT	37.0 ± 4.5	44.4 ± 9.4	0.008
Peak HR	145.6 ± 21.2	156.2 ± 14.9	0.103
Predicted peak HR (%)	73.5 ± 9.6	78.2 ± 9.2	0.155
VE/VCO_2 slope	36.5 ± 8.1	34.9 ± 3.9	0.471
Predicted VE/VCO_2 slope	143.4 ± 49.3	124.1 ± 31.8	0.186
OUES	2032.9 ± 485.7	2330.3 ± 637.6	0.137

Data given as mean ± standard deviation (SD).

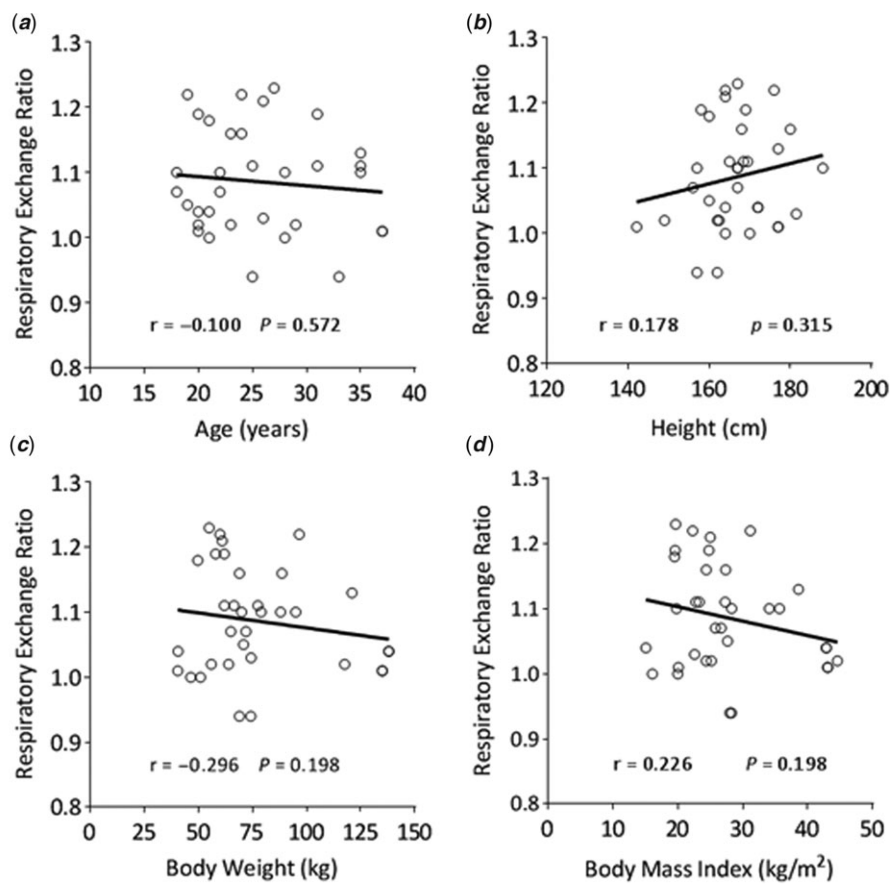

Figure 1. Scatter plots showing the correlation of peak respiratory exchange ratio with age and body size parameters in a population of 34 Fontan patients. (***a***) Correlation of peak respiratory exchange ratio versus age. (***b***) Correlation of peak respiratory exchange ratio versus height. (***c***) Correlation of peak respiratory exchange ratio versus body weight. (***d***) Correlation of peak respiratory exchange ratio versus body mass index.

Discussion

The cardiopulmonary exercise variables are affected by the patients' abilities to perform the exercise with maximum efforts. Previous studies have shown that one-third of the patients with heart failure were unable to reach the peak respiratory exchange ratio of ≥ 1.10 and that the test results are deemed insufficient for predicting prognosis.[19] In this study, we show that 50% of Fontan patients had a peak respiratory exchange ratio of < 1.10 even though they reached a Borg score of ≥7, and their exercise capacity is decreased consistently with published data.[10] There was no difference in the type of ventricle, type of Fontan surgery, time since Fontan completion, exercise duration, and several cardiac-related events between two groups. As the demographic data (age, gender, body mass index, ventricular morphology, and diagnosis) are identical between the two groups, both peak oxygen consumption and percent-predicted peak oxygen consumption was positively correlated with peak respiratory exchange ratio values, indicating that peak respiratory exchange ratio is an important determinant of cardiopulmonary exercise variables

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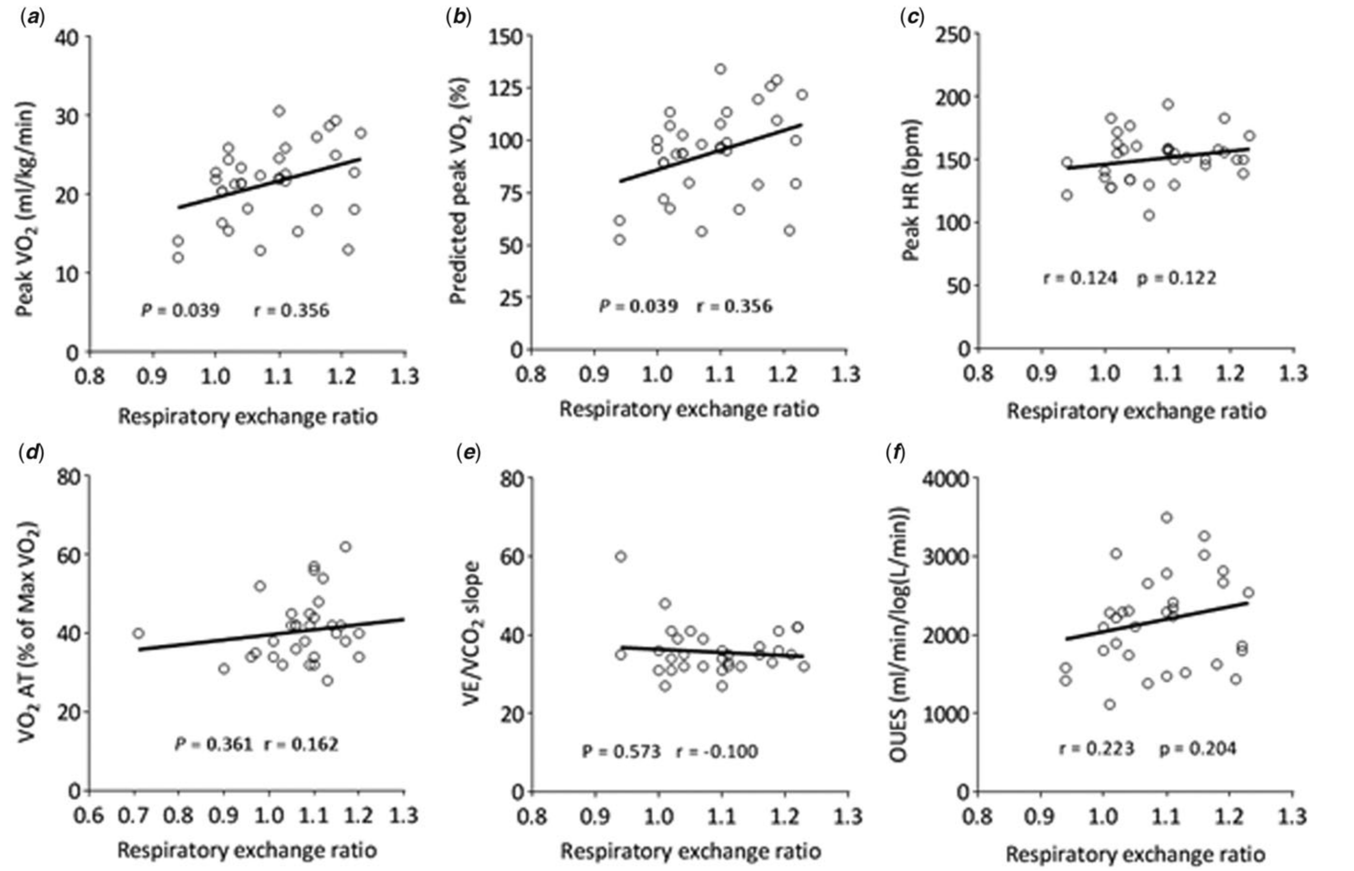

Figure 2. Scatter plots showing the correlation between different parameters of exercise capacity and peak respiratory exchange ratio in a population of 34 Fontan patients. (***a***) Correlation of peak oxygen consumption versus peak respiratory exchange ratio, (***b***) Correlation of percent-predicted peak oxygen consumption versus peak respiratory exchange ratio. (***c***) Correlation of peak heart rate versus peak respiratory exchange ratio. (***d***) Correlation of oxygen consumption at the ventilator threshold versus peak respiratory exchange ratio. (***e***) Correlation of the ratio of minute ventilation and carbon dioxide output slope versus peak respiratory exchange ratio, (***f***) Correlation of oxygen uptake efficiency slope versus peak respiratory exchange ratio.

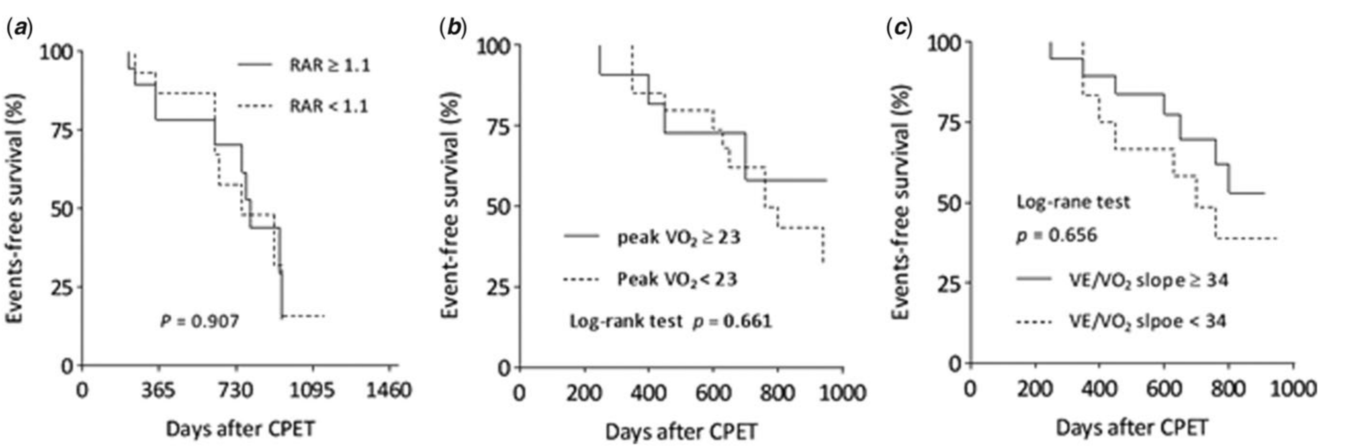

Figure 3. Kaplan–Meier plots showing the combined event-free survival in a population of 34 Fontan patients. Patients were classified into two groups according to peak respiratory exchange ratio (***a***), peak oxygen consumption (***b***), and the ratio of minute ventilation and carbon dioxide output slope (***c***), and log-rank probability values for comparisons between the two groups are shown.

in Fontan patients, similar to previous findings reported by Bongers et al.[20]

The power of peak oxygen consumption as a predictor for cardiac-related events in Fontan patients was inconsistent amongst the previous studies.[10,21,22] The reasons for such inconsistencies could be because of variable efforts (respiratory exchange ratio is not included in the most analysis) or due to different exercise protocols. In our study, multivariate Cox proportional hazard analysis identified that percent-predicted peak oxygen consumption, peak heart rate, and oxygen uptake efficient slope are related to the occurrence of cardiac-related events in patients with a peak respiratory exchange ratio of ≥ 1.10, but not in those with a

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Table 3. Multivariate Cox regression analysis to predict cardiac events in adults with Fontan circulation

	pRER < 1.10			pRER ≥ 1.10		
CPET variables	HR	95% CI	p-value	HR	95% CI	p-value
Peak VO_2	1.39	0.00–0.37	0.965	1.01	1.00–1.01	0.325
Predicted peak VO_2 (%)	0.07	0.00–57.4	0.073	0.57	0.35–0.94	0.027
VO_2 at VT (%)	4.85	0.00–0.50	0.785	1.32	0.89–1.95	0.171
Peak HR	0.97	0.06–15.3	0.981	1.33	1.03–1.71	0.027
Predicted HR (%)	0.82	0.01–56.5	0.925	0.69	0.46–1.04	0.077
VE/VCO_2 slope	0.18	0.00–0.99	0.695	0.90	0.56–1.45	0.664
Predicted VE/VCO_2 slope	1.20	0.67–2.13	0.531	0.98	0.94–1.02	0.376
OUES	1.02	0.93–1.11	0.672	1.01	1.00–1.01	0.023

Abbreviations: CI=confidence interval; HR = hazard ratio; HR = heart rate; VT = ventilatory threshold.

Table 4. ROC curve analysis

	pRER ≥ 1.10		
Variables	Area	95% CI	p-value
Predicted peak VO_2, (%)	0.36	0.07–0.65	0.336
Peak heart rate, bpm	0.64	0.35–0.93	0.336
OUES	0.51	0.23–0.80	0.923

Abbreviation: CI = confidence interval.

peak respiratory exchange ratio of < 1.10. It is worthy of note that an extremely low peak oxygen consumption in Fontan patients is still likely to be an important predictor, as the risk for the combined endpoint of death and hospitalisation is more than two times higher for patients with peak oxygen consumption of < 18.9 ml/kg/minute compared with patients with peak oxygen consumption of > 18.9 ml/kg/minute.[8]

Sub-maximal exercise variables useful to determine exercise capacity are the ratio of minute ventilation and carbon dioxide output slope, the oxygen consumption at the ventilatory threshold, and the oxygen uptake efficient slope.[23] In our study, an elevated ratio of minute ventilation and carbon dioxide output slope (>34) is not associated with an increased risk of cardiac-related events. Prior studies have shown that the ratio of minute ventilation and carbon dioxide output slope is not an adequate predictor of outcomes in Fontan patients.[8,9,22,24] This observation is most plausibly explained by the ratio of minute ventilation and carbon dioxide output slope elevation commonly encountered amongst Fontan patients that is mainly related to pulmonary blood distribution (and ventilation/perfusion mismatch) secondary to the absence of a sub-pulmonary ventricle and the consequent lack of normal pulmonary pulsatility.

The oxygen consumption at the ventilatory threshold is another useful sub-maximal exercise variable, but is only reported in a few studies as the ventilatory threshold is not always identifiable in all patients, and there is no clear evidence for its role as a potential predictor of cardiac-related events in Fontan patients.[25] In our study, oxygen consumption at the ventilatory threshold is slightly lower in the patients with a peak respiratory exchange ratio of < 1.10 compared to those with a peak respiratory exchange ratio of ≥ 1.10, but failed to demonstrate an important correlation with cardiac-related events. Similar to the oxygen consumption at the ventilatory threshold, the mean oxygen uptake efficiency slope value in Fontan patients with a peak respiratory exchange ratio of < 1.10 is slightly lower compared to those with a peak respiratory exchange ratio of ≥ 1.10, however, this trend has not reached statistical significance. There is only limited data available on the predictive value of the oxygen uptake efficient slope in Fontan patients. Giardini et al have reported that the oxygen uptake efficiency slope measured during the entire exercise was not linear in Fontan patients, as the oxygen uptake efficient slope measured during the first 50% of the exercise duration is usually lower compared to the second half of the exercise.[26]

Patients with a Fontan circulation have lower peak heart rate during exercise due to chronotropic incompetence and correlated with poor long-term outcomes.[9,10,21,27,28] Diller et al have reported that most cardiopulmonary exercise variables are related to increased risk of hospitalisation, only heart rate reserve was related to the risk of mortality during a short-term follow-up period in 321 Fontan patients.[21] In our study, patients with a peak respiratory exchange ratio of < 1.10 had a lower peak heart rate and percent-predicted peak heart rate compared to those with a peak respiratory exchange ratio of ≥ 1.10, although they do not reach statistical significance, perhaps due to small sample size. We have noted that a low peak heart rate is closely linked with the increased incidence of cardiac-related events only in patients with a peak respiratory exchange ratio of ≥ 1.10.

In adults with systolic heart failure, peak oxygen consumption, and the ratio of minute ventilation and carbon dioxide output slope provide a sensitive assessment of prognosis irrespective of the respiratory exchange ratio.[14] Mancini et al[29] observed a lower survival rate in patients with a low peak oxygen consumption who performed a "maximal" cardiopulmonary exercise test, but the peak respiratory exchange ratio was not reported. Mezzani et al,[12] who employed a peak oxygen consumption cut-off of 10 ml/kg/minute, demonstrated that patients with a peak oxygen consumption of <10 ml/kg/minute and a peak respiratory exchange ratio of > 1.15 had a significantly worse survival than did patients with peak oxygen consumption of < 10 ml/kg/minute and a peak respiratory exchange ratio of < 1.15. Furthermore, the latter group's survival rate was similar to that of patients with a peak oxygen consumption between 10 and 14 ml/kg/minute, which led to the conclusion that patients should be encouraged to exercise until the peak respiratory exchange ratio approaches 1.15.[12] Fontan patients unlike adults with two-ventricle physiology had other factors that could affect respiratory exchange ratio and a percent-predicted peak oxygen consumption of 70% is considered as normal exercise capacity.[18] Several factors may account for low peak respiratory exchange ratio in Fontan patients including age at Fontan operation, time since Fontan completion, deconditioning, absence of pulsatility in pulmonary circulation, progressively increased venous pressure, energy substrate in diet, chronic lung disease, chronic liver disease, depression, and anxiety. In Fontan patients, there is almost always associated with diastolic dysfunction and a state of chronic heart failure. These patients are near the plateau of the Frank–Starling curve, which leaves them unable to completely utilise the Frank–Starling mechanism and fully augment stroke volume during exercise, have limited stroke volume and which may contribute to increased dyspnoea beyond a patient's tolerance and lead to test termination before the exercising muscles are sufficiently stressed, thus producing a low peak respiratory exchange ratio.[30] The presence of depression is associated with lower functional capacity and increased dyspnoea with exertion in patients with chronic heart failure.[31] Though speculative, it is possible that Fontan patients with significant depressive symptoms may experience early dyspnoea, and higher subjective Borg score but limited respiratory exchange ratio.

The focus of single-ventricle palliation has moved from preventing mortality to improving quality of life. An increased risk of complications including death, transplantation, and functional deterioration occurs over time in patients with single-ventricle physiology who have undergone a Fontan procedure. Symptom-limited incremental exercise testing is a frequently used measure of cardiovascular health, as it allows insight into cardiac and pulmonary responses to exercise and is a robust tool for predicting worse cardiovascular outcomes in heart failure, including patients with Fontan circulation. However, it is important to pay attention to the protocol for exercise testing and how the test is terminated. Every effort should be made to achieve a maximal respiratory exchange ratio rather than relying on subjective parameters like the Borg score. We suggest considering using a Raise, Mobilise, Potentiate (RAMP) protocol rather than Bruce protocol, which could be a less stressor for Fontan patients during exercise testing and may achieve a higher respiratory exchange ratio as patients may tolerate the gradual increase in stress better before termination of exercise. However, we do not suggest exercise should be terminated based on the respiratory exchange ratio. The risk of over-exercise would pose serious risks to Fontan patients.

Limitations

Despite the importance of the findings presented here, there are a few limitations to our study. First, this is a single-centre retrospective observational study with the inherent limitations of a study of this design. The exercise testing was performed with a Bruce protocol with incremental exercise and the test was terminated based on symptoms perceived by patients with a Borg score of ≥ 7 on a modified Borg 10-point scale. Second, a small number of cases may have led to the insignificant differences in areas under the receiver-operating curve of the percent-predicted peak oxygen consumption, peak heart rate, and oxygen uptake efficient slope. It is, therefore, not ideal to draw any definitive conclusions on the power of the percent-predicted peak oxygen consumption, peak heart rate, and oxygen uptake efficient slope in predicting the outcome in patients with Fontan circulation. Additionally, several factors may affect the exercise performance, which includes autonomic dysregulation, presence of pacemakers, use of medication, comorbidities (such as obesity, anaemia, and diabetes mellitus), Fontan-associated liver disease, vascular dysfunction, muscle abnormalities, and most importantly, psychological well-being of the patient and motivation to exhibit maximum effort during cardiopulmonary exercise testing.

Conclusions

Fontan patients can be heterogeneous with many confounding factors for exercise intolerance. The cardiopulmonary exercise testing is most commonly performed as a symptom-limited test and is terminated based on the rating of perceived exertion such as the Borg score, but patients may not have achieved a maximal effort as evidenced by the respiratory exchange ratio of ≥ 1.1. The value of peak cardiopulmonary exercise variables become limited for the determination of prognosis and assessment of interventions in Fontan patients with sub-maximal effort. Our study underscores the importance to pay attention to the exercise protocol used and how the exercise test is terminated while interpreting data.

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Conflicts of interest. None.

Ethical standards. The study protocol was approved by the Memorial Healthcare System's Institutional Review Board (MHS.2018.036).

References

1. Burstein DS, Menachem JN, Opotowsky AR. Exercise testing for assessment of heart failure in adults with congenital heart disease. Heart Fail Rev 2019. doi: 10.1007/s10741-019-09867-1
2. Wensel R, Opitz CF, Anker, SD, et al. Assessment of survival in patients with primary pulmonary hypertension: importance of cardiopulmonary exercise testing. Circulation 2000; 106: 319–324.
3. Ogawa T, Spina RJ, Martin WH, et al. Effects of aging, sex, and physical training on cardiovascular responses to exercise. Circulation 1992; 86: 494–503.
4. Woo JS, Derleth C, Stratton, JR, Levy WC. The influence of age, gender, and training on exercise efficiency. J Am Coll Cardiol 2006; 47: 1049–1057.
5. Inuzuka R, Diller GP, Borgia F, et al. Comprehensive use of cardiopulmonary exercise testing identifies adults with congenital heart disease at increased mortality risk in the medium term. Circulation 2012; 125: 250–259.
6. Ramos-Barbon D, Fitchett D, Gibbons WJ, Latter DA, Levy RD. Maximal exercise testing for the selection of heart transplantation candidates: limitation of peak oxygen consumption. Chest 1999; 115: 410–417.
7. Driscoll DJ. Cardiorespiratory responses to exercise after the Fontan operation. Circulation 1990; 81: 2016–2017.
8. Fernandes SM, Alexander ME, Graham DA, et al. Exercise testing identifies patients at increased risk for morbidity and mortality following Fontan surgery. Congenit Heart Dis 2011; 6: 294–303.
9. Ohuchi H, Negishi J, Noritake K, et al. Prognostic value of exercise variables in 335 patients after the Fontan operation: a 23-year single-center experience of cardiopulmonary exercise testing. Congenit Heart Dis 2015; 10: 105–116.
10. Udholm S, Aldweib N, Hjortdal VE, et al. Prognostic power of cardiopulmonary exercise testing in Fontan patients: a systemic review. Open Heart 2018; 5: e000812.
11. Baba R, Nagashima M, Goto M, et al. Oxygen uptake efficiency slope: a new index of cardiorespiratory functional reserve derived from the relation between oxygen uptake and minute ventilation during incremental exercise. J Am Coll Cardiol 1996; 28: 1567–1572.

12. Mezzani A, Corra U, Bosimini E, et al. Contribution of peak respiratory exchange ratio to peak VO2 prognostic reliability in patients with chronic heart failure and severely reduced exercise capacity. Am Heart J 2003; 145:1102–1107.
13. Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). J Am Coll Cardiol 2002; 40: 1531–1540.
14. Chase PJ, Kenjale A, Cahalin LP, et al. Effects of respiratory exchange ratio on the prognostic value of peak oxygen consumption and ventilator efficiency in patients with systolic heart failure. JACC Heart Failure 2013; 1: 427–432.
15. Kakutani N, Fukushima A, Yokota T, et al. Impact of high respiratory exchange ratio during submaximal exercise on adverse clinical outcome in heart failure. Circ J 2018; 82: 2753–2760.
16. Fletcher GF, Balady GJ, Amsterdam EA, et al. Exercise standards for testing and training: a statement for healthcare professionals from American Heart Association. Circulation 2001; 104: 1694–1740.
17. Hollenberg M, Tager IB. Oxygen uptake efficiency slope: an index of exercise performance and cardiopulmonary reserve requiring only submaximal exercise. J Am Coll Cardiol 2000; 36: 194–201.
18. Kempny A, Dimopoulos K, Eebing A, et al. Reference values for exercise limitations among adults with congenital heart disease: relation to activities of daily life-single center experience and review of published data. Eur Heart J 2012; 33: 1386–1396.
19. Rostagno C, Olivo G, Comeglio M, et al. Prognostic value of 6-minute walk corridor test in patients with mild to moderate heart failure: comparison with other methods of functional evaluation. Eur J Heart Fail 2003; 5: 247–52.
20. Bongers BC, Hulzebos EH, Helbing WA, et al. Response profiles of oxygen uptake efficiency during exercise in healthy children. Eur J Prev Cardiol 2016 23: 865–873.
21. Diller GP, Giardini A, Dimopoulos K, et al. Predictors of morbidity and mortality in contemporary Fontan patients: results from a multicenter study including cardiopulmonary exercise testing in 321 patients. Eur Heart J 2010; 31: 3073–3083.
22. Ackermann M, van Brussel M, Hulzebos E, et al. The oxygen uptake efficiency slope; what do we know? J Cardiopulm Rehab Prev 2010; 30:357–373.
23. Malhotra R, Bakken K, D'Elia E, Lewis GD. Cardiopulmonary exercise testing in heart failure. JACC Heart Failure 2016; 4:607–16.
24. Dimopoulos K, Okonko DO, Diller GP, et al. Abnormal ventilator response to exercise in adults with congenital heart disease relates to cyanosis and predicts survival. Circulation 2006; 113: 2796–2802
25. Atz AM, Zak V, Mahony L, et al. Longitudinal outcomes of patients with single ventricle after the Fontan procedure. J Am Coll Cardiol 2017; 69:2735–2744.
26. Giardini A, Specchia S, Gargiulo G, et al. Accuracy of oxygen uptake efficiency slope in adults with congenital heart disease. Int J Cardiol 2009; 133:74–79
27. Classen G, La Gerche A, Van De Bruaene A, et al. Heart rate reserve in Fontan patients: chronotropic incompetence or hemodynamic limitation? J Am Heart Assoc 2019; 8:e012008
28. Egbe AC, Driscoll DJ, Khan AR et al. Cardiopulmonary exercise test in adults with prior Fontan operation: the prognostic value of serial testing. Int J Cardiol 2017; 235: 6–10.
29. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH Jr., Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation 1991; 83: 778–786.
30. Clark AL, Poole-Wilson PA, Coats AJ. Exercise limitation in chronic heart failure: central role of the periphery. J Am Coll Cardiol 1996; 28: 1092–1102.
31. Blumenthal JA, Babyak MA, O'Connor C, et al. Effects of exercise training on depressive symptoms in patients with chronic heart failure: the HF-ACTION randomized trial. JAMA 2012; 308: 465–474.