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Maximal versus sub-maximal effort during cardiopulmonary exercise testing in adults with congenital heart disease: outcome analysis of short-term cardiac-related events

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Abstract

Peak respiratory exchange ratio is an objective marker of patient effort during cardiopulmonary exercise testing. We evaluated exercise variables in 175 adult congenital heart disease patients and the impact of respiratory exchange ratio on the prognostic value of exercise variables for short-term cardiac-related events. Of 175 patients, 110 completed the exercise test with a peak respiratory exchange ratio of ≥1.10 and the remaining 65 had a peak respiratory exchange ratio of <1.10. Peak oxygen consumption, the percentage of oxygen consumption at the ventilatory threshold, peak heart rate, percentage predicted peak heart rate, double product, oxygen uptake efficiency slope, and the number of patients with exercise oscillatory ventilation were reduced significantly in patients with a respiratory exchange ratio of <1.10 compared to those with a respiratory exchange ratio of ≥1.10. After a median follow-up of 21 months, total cardiac-related events occurred in 37 (21%) patients. Multivariate Cox proportional hazard analysis showed that the percentage predicted peak oxygen consumption, and oxygen uptake efficiency slope were independent predictors of cardiac-related events only in patients with a peak respiratory exchange ratio of ≥1.10. Sub-maximal exercise performance can be preserved in adult congenital heart disease patients. The percentage predicted oxygen consumption and the oxygen uptake efficiency slope are two independent predictors for short-term cardiac-related events in adult congenital heart disease patients.

Cardiopulmonary 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 adult congenital heart disease (CHD) patients.[1–4] The measurement of functional capacity using peak oxygen consumption during the exercise test is a conventional indicator of cardiac-related events in adult CHD patients.[5,6] However, the peak oxygen consumption is highly influenced by age, sex, patient's effort and physical fitness, exercise test protocol, and underlying CHD.[7,8] Previous studies have shown that adult CHD patients sometimes terminate exercise tests before reaching their cardiovascular limit, which may be a serious shortcoming to the evaluation of the prognostic value of peak oxygen consumption.[1,9]

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.[10] Current exercise testing guidelines recommend to achieve a peak respiratory exchange ratio of ≥1.10 as a criterion for maximal effort.[11] The impact of respiratory exchange ratio on the prognostic role of exercise variables in adult CHD patients remains uncertain. Therefore, the objective of this study was to analyse the differences in exercise parameters in adult CHD patients who had maximal effort versus those who had sub-maximal effort during exercise tests and to evaluate whether attainment of a respiratory exchange ratio of ≥1.10 during the exercise test affects the prognostic value of exercise variables with their short-term cardiac-related events during follow-up.

Methods

The study protocol was approved by the ethics committee of the Memorial Healthcare System (MHS.2018.036). Given the anonymised nature of the data, the requirement for informed consent was waived. This was a retrospective, single-centre study cohort design evaluating adult CHD patients (≥18 years) who performed symptom-limited cardio-pulmonary exercise tests using a treadmill according to a modified Bruce-protocol between August, 2014 and April, 2018 at the adult CHD centre, Memorial Healthcare System, Hollywood, Florida. The indication for CPET was routine practice in all ACHD patients referred to our centre. All exercise tests were performed in accordance with the institutional protocol, and the guidelines from the American

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College of Cardiology/the American Heart Association,[12] using the Ultima2 CPX™ (MedGraphics, St Paul, MN, United States of America), Tango M2™ (German Healthcare Export Group, Germany) blood pressure cuff, and Mortara ECG™ (Spacelab Healthcare, United Kingdom). All three components interacted and input data into Breeze software™ (MedGraphics, St Paul, MN) for analysis. The exercise was terminated when the patient had subjective exhaustion (modified Borg score of 7 or more).

The Ultima2 CPX™ provides a conventional Wasserman 9 plot graphs and data were analysed for peak oxygen consumption, carbon dioxide production, minute ventilation, ventilatory anaerobic threshold, and oxygen consumption at the anaerobic threshold as a percentage of total oxygen consumption. Peak respiratory exchange ratio, peak heart rate and blood pressure were taken at maximum exercise. The anaerobic threshold was measured using the V-slope method.[12] A peak respiratory exchange ratio was measured at peak exercise, and value ≥1.10 was considered as maximum exercise effort.[11] Other variables included in the analysis were the oxygen uptake efficiency slope, double product, and exercise oscillatory ventilation during exercise tests. The oxygen uptake efficiency slope was calculated by plotting logarithmically transformed minute ventilation over the entire exercise duration against the oxygen consumption.[13,14] The myocardial oxygen uptake, defined as the amount of oxygen consumed by the myocardium during exercise, was estimated by the product of peak heart rate and systolic blood pressure (double product).[15,16] The exercise oscillatory ventilation was defined as regular oscillations with amplitude >15% of average minute ventilation during the exercise test, which were present for >60% of total exercise duration.[17] Patients were excluded if they had incomplete exercise test data.

Demographic and clinical characteristics were obtained via medical record extraction, and consisted of age, gender, body mass index, and New York Heart Association (NYHA) functional class. Patients were followed up for a median of 21 months from the day of exercise test for the incidence of cardiac-related events, including death, heart transplantation, hospitalisation for heart failure, cardiac device implantation (pacemaker or ICD), and corrective cardiac surgery for an underlying cardiac condition. A principal diagnosis was determined for every patient and classified according to the 32nd Bethesda conference.[18] The NYHA class was determined for each patient by physician assessment of patients' self-reported symptoms before the exercise test or estimated from the patient narrative from the medical record.

Statistical analysis

Results are expressed as mean ± SD for continuous variables and as a number or percentage for categorical variables. Comparisons between subgroups were performed using unpaired t-test or the Chi-square test, as appropriate. Exercise variables were first assessed using univariable Cox hazard analysis, and subsequent multi-variable Cox analyses were performed to detect independent predictors associated with cardiac-related events. For all analyses, a two-sided p value of <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 (Graph Pad Software Inc., La Jolla, CA, United States of America).

Results

A total of 175 adult CHD patients were included in the study (mean age = 29 ± 11 years, male (55%), had cardiopulmonary exercise tests and follow-up data. Of the 175 patients, 110 (63%) reached a respiratory exchange ratio of ≥1.10, whereas 65 (37%) patients had a ratio of <1.10. There was no significant difference in duration of exercise and reason for termination of exercise between two groups. The mean Borg score was 7 ± 2 in both respiratory exchange ratio <1.1 and ≥1.10 groups. The patient's demographic and clinical characteristics based on the respiratory exchange ratios are summarised in Table 1. The median peak oxygen consumption for the entire patient cohort was 24.4 ± 6.6 ml/kg/minute, percentage predicted oxygen consumption was 64.2 ± 15, the median percentage oxygen consumption at the anaerobic threshold was 46.8 ± 10.8 (expressed as a percentage of peak oxygen consumption), peak heart rate was 159 ± 11 bpm, and percentage predicted peak heart rate in percentage was 81 ± 11. Upon comparison between maximal effort versus sub-maximal effort, age and gender distributions were comparable between the two groups. Patients with high body mass index and body weight were noted more frequently among those in a respiratory exchange ratio of ≥1.1 sub-group compared to a respiratory exchange ratio of <1.1, with p values of 0.018 and 0.047, respectively. There were more patients with NYHA functional class III in a respiratory exchange ratio of <1.1 sub-group (p = 0.028). Tetralogy of Fallot was the most common diagnosis (26.3%), followed by complex CHD (25.7%). Complex CHD consisted of single-ventricle physiology and all patients were palliated with Fontan surgery. All other diagnoses including tetralogy of Fallot, transposition of great arteries, congenitally corrected transposition, aortic stenosis, and coarctation of aorta were completely repaired. The common exercise variables were compared between the two groups and are presented in Table 2. Of the variables, peak oxygen consumption, oxygen consumption at the anaerobic threshold, peak heart rate, percentage predicted peak heart rate, double product, and oxygen uptake efficiency slope were significantly decreased in patients with a respiratory exchange ratio of <1.10 compared to those with a respiratory exchange ratio of ≥1.10. However, there was no significant difference in percentage predicted peak oxygen consumption between both groups. Furthermore, oxygen consumption at the anaerobic threshold in both groups was >40%, suggesting normal sub-maximal exercise capacity. Interestingly, the number of patients with exercise oscillatory ventilation is higher in respiratory exchange ratio <1.1 versus respiratory exchange ratio ≥1.1 group despite the higher number of patients with NYHA class III in the latter group.

During a median follow-up period of 21 months (mean 18 ± 8 months with IQR, 13–28 months), the cardiac-related event rate was 21% (37/175). The univariate analysis of exercise variables that can be associated with cardiac-related events in the group with respiratory exchange ratio ≥1.1 and respiratory exchange ratio <1.1 are shown in Tables 3 and 4. Older age, female sex, obesity, higher ventilatory equivalent for carbon dioxide value, percentage predicted heart rate and the oxygen uptake efficiency slope were found to be associated with cardiac-related events (hazard ratio >1). The multivariate Cox proportional hazard analysis showed that lower percentage predicted peak oxygen consumption and oxygen uptake efficiency slope corresponded with a higher risk of cardiac-related events only in patients who had a respiratory exchange ratio of ≥1.1 during exercise testing (Table 3), but not with a respiratory exchange ratio of <1.1 (Table 4).

Discussion

A number of studies have found that the peak oxygen consumption is one of the best predictors of morbidity or mortality in a variety of

Table 1. Demographic and clinical characteristics by peak RER status

Variables	Total (n = 175)	Peak RER <1.1 (n = 65)	Peak RER ≥1.1 (n = 110)	p values
Age, years	29 ± 11	31 ± 14	29 ± 10	0.315
Male gender, n (%)	97 (55)	29 (45)	68 (62)	0.071
Weight, kg	76 ± 22	71 ± 21	79 ± 22	0.018
BMI, kg/m^2	27 ± 7	26 ± 6	28 ± 7	0.047
NYHA class, n (%)				
I	118 (67)	41 (63)	77 (70)	0.282
II	45 (26)	16 (25)	29 (26)	0.946
III	12 (7)	8 (12)	4 (4)	0.028
Cardiac diagnosis				
TOF	46	19	27	0.496
Complex defects	45	19	26	0.413
AS/AR/COA	29	8	21	0.244
TGA	27	11	16	0.674
PS/PR	11	2	9	0.241
Shunt lesions	11	4	7	0.244
Congenitally corrected TGA	6	2	4	0.844
Follow-up, days	643.7 ± 241.6	671.7 ± 242.7	627.1 ± 240.6	0.241
Cardiac events	37	13	24	0.776

AS = aortic stenosis; AR = aortic regurgitation; COA = coarctation of aorta; BMI = body mass index; PS = pulmonary stenosis; PR = pulmonary regurgitation; RER = respiratory exchange ratio; TGA = transposition of great arteries; TOF = tetralogy of Fallot

Table 2. Cardiopulmonary exercise testing data by RER status

CPET parameters	Total (n = 175)	RER <1.1 (n = 65)	RER ≥1.1 (n = 110)	p values
Exercise duration (min)	7.42 ± 2.8	6.4 ± 2.2	8.5 ± 3.2	0.152
Peak VO_2, ml/kg/min	24.4 ± 6.6	22.8 ± 5.5	25.4 ± 7.0	0.007
% predicted peak VO_2	64.2 ± 15.0	62.3 ± 14.3	65.2 ± 15.4	0.209
VO_2 at VAT	46.8 ± 10.8	42.9 ± 9.6	49.1 ± 10.8	0.0001
VE/VO_2 slope	31.7 ± 5.4	32.2 ± 6.1	31.4 ± 4.9	0.370
Peak HR, bpm	159.2 ± 22.0	152.7 ± 19.9	163.1 ± 22.4	0.002
% predicted peak HR	81.2 ± 11.3	77.9 ± 9.5	83.1 ± 11.8	0.002
Double product	26602.2 ± 6126.8	25137.4 ± 4570.1	27467.7 ± 6754.6	0.007
OUES	2564.7 ± 824.9	2350.6 ± 694.5	2691.2 ± 871.6	0.005
Oscillatory ventilation, n (%)	37 (21)	23 (35)	14 (13)	0.0004

HR = heart rate, OUES = oxygen uptake efficiency slope; VAT = ventilator anaerobic threshold

cardiovascular conditions including congestive heart failure,[19,20] pulmonary hypertension,[21] tetralogy of Fallot,[22] transposition of the great arteries,[23] and Fontan circulations.[3] The study by Inuzuka et al[1] found that peak oxygen consumption and heart rate reserve data can be used to generate estimates for 5-year survival in many adults with CHD. However, in their study a majority of patients had low peak respiratory exchange ratio values <1.1, suggesting that a large fraction of the patients did not expend adequate effort and terminated exercise before reaching their cardiovascular limit. This may constitute a serious shortcoming for a study that seeks to evaluate the prognostic value of peak exercise data, for it permits factors unrelated to a subject's cardiovascular health (e.g. the patient's level of motivation on the day of the exercise test) to contaminate the data and analyses.

Previous studies have shown that one-third of patients with heart failure were unable to reach the maximal effort

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Table 3. Risk factors of the cardiac events in patients with RER ≥ 1.1

Variables	Hazard ratio	95% CI	p values
Univariable			
Demographics			
Age (years)	1.06	1.02–1.10	0.004
Female	1.12	0.46–2.71	0.810
BMI, kg/m^2	1.02	0.96–1.08	0.507
CPET parameters			
Peak VO_2, ml/kg/min	0.94	0.88–1.00	0.056
% predicted peak VO_2	0.97	0.94–0.99	0.041
VO_2 at VAT	0.98	0.94–1.02	0.245
VE/VO_2 slope	1.01	0.93–1.09	0.811
Peak HR, bpm	0.99	0.98–1.01	0.509
% predicted peak HR	1.01	0.97–1.04	0.896
Double product	1.00	1.00–1.00	0.288
OUES	1.00	1.00–1.01	0.546
Exercise oscillatory ventilation	0.45	0.23–2.00	0.482
Multi-variable			
% predicted peak VO_2	0.94	0.91–0.98	0.004
OUES	1.00	1.00–1.02	0.021

HR = heart rate; OUES = oxygen uptake efficiency slope; VAT = ventilator anaerobic threshold

Table 4. Risk factors of the cardiac events in patients with RER < 1.1

Variables	Hazard ratio	95% CI	p values
Univariable			
Demographics			
Age (years)	1.04	1.00–1.08	0.035
Female	1.99	0.65–6.17	0.231
BMI, kg/m^2	1.14	1.00–1.28	0.048
CPET parameters			
Peak VO_2, ml/kg/min	0.97	0.86–1.08	0.540
% predicted peak VO_2	0.97	0.92–1.01	0.135
VO_2 at VAT	1.00	0.95–1.06	0.964
VE/VO_2 slope	1.00	0.91–1.10	0.987
Peak HR, bpm	1.01	0.98–1.04	0.382
% predicted peak HR	1.02	0.97–1.08	0.426
Double product	1.00	1.00–1.00	0.571
OUES	1.00	0.99–1.00	0.599
Exercise oscillatory ventilation	0.49	0.16–1.47	0.204
Multi-variable			
None			

HR = heart rate; OUES= oxygen uptake efficiency slope; VAT = ventilator anaerobic threshold

(peak respiratory exchange ratio ≥1.10) and that the test results are deemed insufficient for estimating prognosis.[24,25] The main difference between our study and prior studies published[1,3,19–23] is that we emphasised the peak respiratory exchange ratio to determine maximal or sub-maximal effort during CPET rather than subjective Borg score. In our study, adult CHD patients (63%) had attained a respiratory exchange ratio of ≥1.1, and is the highest percentage compared to most prior studies published. We analysed the commonly used exercise variables to evaluate whether attainment of the peak respiratory exchange ratio of ≥1.1 during exercise test affects the prognostic power of exercise variables among adult CHD patients all of whom have achieved a Borg score of ≥7. This is the novel finding in our study.

The peak respiratory exchange ratio is a useful variable, both as a marker of effort and as an indicator of the contribution of anaerobic metabolism.[10,26] The respiratory exchange ratio is the ratio of CO_2 exhaled to the O_2 uptake per unit time[10] and reflects tissue level exchange of gasses (measured by the respiratory quotient). For normal adults, respiratory exchange ratio values at peak oxygen consumption during treadmill exercise are 1.10.[10] As expected, exercise variables such as peak oxygen uptake, oxygen uptake at ventilatory anaerobic threshold, peak heart rate, percentage predicted heart rate, double product, OUES are all decreased substantially with sub-maximal efforts in adult CHD patients. But, there was no difference in the median percentage predicted oxygen consumption between the two groups. Furthermore, the median oxygen consumption at the anaerobic threshold in both groups were above the lowest cut-off of normal value (<40% has been suggested as a threshold to determine the functional capacity).[12] Previously suggested, children with CHD can have normal sub-maximal exercise performance.[27] Perhaps, a selected cohort of ACHD patients, as seen in our study, may have normal sub-maximal exercise performance.

In our study, the exercise test was performed as a part of the routine evaluation of adult CHD patients. When we analysed the exercise variables obtained whether these variables can predict cardiac-related events in short-term follow-up, percentage predicted peak oxygen consumption and the oxygen uptake efficiency slope were independently associated with the risk of cardiac-related events only in patients who had the peak respiratory exchange ratio of ≥1.1. None of the CPET parameters were found to be predictive of cardiac-related events in ACHD patients who had peak respiratory exchange ratio was <1.1 during the exercise test despite both groups reached a Borg score of 7 or more subjectively. There was no significant difference in how exercise is terminated and exercise duration between those with peak respiratory exchange ratio ≥ 1.1 and peak respiratory exchange ratio < 1.1. Our findings suggest that if patients did not achieve adequate peak respiratory exchange ratio during the exercise stress test, the exercise variables obtained are not be predictive of cardiac-related events in adult CHD patients.

Exercise variables that are reported to be useful as prognostic markers during sub-maximal exercise tests include the ventilator equivalent for carbon dioxide, the oxygen consumption at the anaerobic threshold as a percentage of peak oxygen consumption, and the oxygen uptake efficiency slope.[28] In our study, an elevated ventilator equivalent for carbon dioxide (>34)[5] was not associated with an increased risk of cardiac-related events. Prior studies have shown that ventilator equivalent for carbon dioxide is not an adequate predictor of outcomes in Fontan patients[29,30] and has weak prognostic value in ACHD patients.[1,31]

In our study, the oxygen consumption at the anaerobic threshold was found normal (>40%) in adult CHD patients with both respiratory exchange ratio groups. In daily life, peak oxygen consumption does not reflect the amount of oxygen needed to cope with daily activities of normal life. This suggests that adult CHD patients reach normal sub-maximal results and these explain why they are asymptomatic with their normal activities but have markedly decreased exercise capacity. The oxygen consumption at the anaerobic threshold is only reported in a few studies as the anaerobic threshold is not always identifiable in all patients.[32] In our study, there is no clear evidence for its role as a potential predictor for cardiac-related events.

There are limited publications investigating the predictive value of the oxygen uptake efficiency slope in adult CHD patients.[31,33] The oxygen uptake efficiency slope represents the rate of increase of oxygen uptake in response to a given ventilator equivalent during incremental exercise, indicating how effectively oxygen is extracted and taken into the body.[13,14] The oxygen uptake efficiency slope is influenced by both the metabolic acidosis and the physiological pulmonary dead space. The oxygen uptake efficiency slope is a variable that indicates the status of both systemic and pulmonary perfusion, and which explains the high correlation with percentage predicted oxygen consumption. The advantage of the oxygen uptake efficiency slope is that it can be calculated from sub-maximal exercise test data and is therefore effort-independent.[13] The oxygen uptake efficiency slope seems to have an additive value to the percentage predicted oxygen consumption in adult CHD patients. However, possible use of oxygen uptake efficiency slope in cyanotic patients is debatable, as it is s not linear during the exercise tests in Fontan patients.[23]

Previously, in adults with heart failure, Stelken et al[34] found that 50% of predicted peak oxygen consumption was the most significant predictor of cardiac death and that the area under the curve for percent of predicted peak oxygen consumption was superior to peak oxygen consumption. Other studies, did not find any difference in prognostic values between these two parameters.[35] Unlike, adults with normal heart, in the CHD population, predicted peak oxygen consumption is different for different underlying cardiac diagnoses, e.g. in single-ventricle physiology 60% predicted is normal. Those patients, who are unable to perform the maximal exercise, sub-maximal exercise data should be useful. But in adults with CHD, although sub-maximal exercise capacity is preserved the exercise parameters found to be not useful for prognostication for cardiac-related events. The peak oxygen consumption is somewhat dependent on patient motivation as well as investigator analysis, but this is less true if the patient reaches a respiratory quotient $\geq$1.1. In conclusion, the percentage predicted oxygen consumption is more useful for risk stratification than peak oxygen consumption for adult CHD patients and oxygen uptake efficiency slope data has additional value for the risk prediction.

Exercise oscillatory ventilation refers to regular oscillations in minute ventilation during exercise.[17] Its presence correlates with heart failure severity and worse prognosis in adults with acquired heart failure and Fontan physiology.[36,37] However, wide-scale data in adult CHD cohorts are not available to compare with our study.

Limitations

Despite the importance of the findings presented here, there are a few limitations to our study. Firstly, this was a single-centre retrospective observational study with the inherent limitations associated with a study of this design. The exercise stress tests are done in most patients presenting to adult CHD clinics for routine evaluation and most patients are stable haemodynamically at the time of testing. Some patients underwent exercise stress tests as part of an anticipatory surgical procedure for residual lesions or newly developed cardiac valve disease, therefore selection bias cannot be excluded. Secondly, the influence of medications and other comorbidities may be interesting and worthwhile, but not included in the analysis. Due to overall small data, there are possibilities of Type I errors in the correlation analysis of the power of the percentage predicted peak oxygen consumption, peak heart rate, and oxygen uptake efficiency predicting cardiac-related events in adult CHD patients. Also, several factors may affect the exercise performance, including autonomic dysregulation, comorbidities (such as obesity, anaemia, and diabetes mellitus), Fontan-associated liver disease, vascular dysfunction, muscle abnormalities, and most importantly, patient psychological wellbeing and motivation to exhibit maximum effort during the exercise stress test.

Conclusions

Sub-maximal exercise performance can be preserved in stable adult CHD patients. The percentage predicted oxygen consumption rather than peak oxygen consumption and the oxygen uptake efficiency slope are two independent predictors for short-term cardiac-related events in ACHD patients only with the respiratory exchange ratio of $\geq$1.1 during the cardiopulmonary exercise test.

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Conflicts of Interest. None.

Ethical Standards. The study protocol was approved by IRB (MHS-2018-036).

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