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Ventilatory efficiency slope correlates with functional capacity, outcomes, and disease severity in pediatric patients with pulmonary hypertension☆,☆☆,★

Christopher M. Rausch^{a,b,*}, Amy Lynne Taylor^b, Hayley Ross^a, Stefan Sillau^c, and D. Dunbar Ivy^{a,b}

^aUniversity of Colorado School of Medicine, Department of Pediatrics CO, USA

^bChildren's Hospital Colorado, Division of Pediatric Cardiology, CO, USA

^cColorado Biostatistics Consortium, Colorado School of Public Health, CO, USA

Abstract

Background—Cardiopulmonary exercise testing is widely used in a variety of cardiovascular conditions. Ventilatory efficiency slope can be derived from submaximal exercise testing. The present study sought to evaluate the relationship between ventilatory efficiency slope and functional capacity, outcomes, and disease severity in pediatric patients with pulmonary hypertension.

Methods—Seventy six children and young adults with a diagnosis of pulmonary hypertension (PH) performed 258 cardiopulmonary exercise tests from 2001 to 2011. Each individual PH test was matched to a control test. Ventilatory efficiency slope was compared to traditional measures of functional capacity and disease severity including WHO functional classification, peak oxygen consumption, and invasive measures of pulmonary arterial pressures and pulmonary vascular resistance.

Results—Ventilatory efficiency slope was significantly higher in patients with pulmonary arterial hypertension, with an estimated increase of 7.2 for each increase in WHO class ($p < 0.0001$), compared with normal control subjects (38.9 vs. 30.9, $p < 0.001$). Ventilatory efficiency slope correlated strongly with invasive measures of disease severity including pulmonary vascular resistance index ($r = 0.61$), pulmonary artery pressure ($r = 0.58$), mean pulmonary artery pressure/mean aortic pressure ratio ($r = 0.52$), and peak VO_2 ($r = -0.58$). Ventilatory efficiency slope in 12 patients with poor outcomes (9 death, 3 lung transplant), was significantly elevated compared to patients who did not (51.1 vs. 37.9, $p < 0.001$).

Conclusions—Ventilatory efficiency slope correlates well with invasive and noninvasive markers of disease severity including peak VO_2 , WHO functional class, and catheterization

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Corresponding author at: Children's Hospital Colorado, Division of Cardiology/B100, 13123 E 16th Avenue, Aurora, CO 80045, USA. Tel.: +1 720 777 6820; fax: +1 720 777 7290. christopher.rausch@childrenscolorado.org (C.M. Rausch).

variables in pediatric patients with PH. Ventilatory efficiency slope may be a useful noninvasive marker for disease severity.

Keywords

Ventilatory efficiency slope; VE/VCO₂ slope; Pulmonary hypertension; Cardiopulmonary exercise testing; Pediatric

1. Introduction

Cardiopulmonary exercise testing (CPET) allows for reproducible assessment of exercise capacity and provides valuable information on gas exchange, ventilation, and oxygen consumption. As a result, exercise testing has been widely used as a marker for functional capacity, disease severity, prognosis, and treatment response in a variety of cardiovascular conditions including pediatric pulmonary hypertension (PH) [1,2]. Peak oxygen consumption (peak VO₂) has historically been the most frequently analyzed cardiopulmonary exercise test parameter and correlates well with cardiopulmonary disease severity and survival [3]. Peak VO₂, however, can be particularly difficult to obtain in a pediatric population and may be underestimated because of a lack of patient motivation. Ventilatory efficiency slope (VE/VCO₂ slope), defined as the relationship between minute ventilation and carbon dioxide production obtained during exercise testing, has recently demonstrated prognostic value in adults with heart failure [4–6] and PH [3,7–9]. VE/VCO₂ slope can be derived from submaximal exercise testing and is therefore independent of patient motivation. There are no studies, however, that have described the relationship between VE/VCO₂ slope and disease severity in pediatric PH populations. The present study sought to evaluate the utility of VE/VCO₂ slope in relation to functional capacity, outcomes, and disease severity in pediatric patients with PH.

2. Methods

This study was reviewed and approved by the Colorado Multiple Institutional Review Board (protocol #12-1570) prior to initiation. At our institution, patients older than 7–8 years of age with PH routinely undergo cardiopulmonary exercise testing, typically on an annual basis. Younger children do not routinely undergo CPET due to an inability to reliably perform the testing or to tolerate metabolic data collection. We retrospectively reviewed all seventy six children and young adults with a diagnosis of PH that were followed on an outpatient basis and performed a total of 258 CPET studies from 2001 to 2011. The study sample was 52% male and ranged in age from 7 to 22 years. Each PH patient was assigned a World Health Organization Functional Class [10,11] at the time of CPET. Each individual PH test was age and gender matched to a control test (CON). Control tests were deemed to have no cardiac or pulmonary pathology on the basis of normal physical examination results, resting electrocardiograms, pulmonary function test results, and CPET results. In all subjects, exercise testing was performed with a Care Fusion (Yorba Linda, CA) metabolic cart using previously described methods [12,13]. Breath by breath data were collected and averaged over 20 s intervals. After a 1-min warm-up period of unloaded cycling, patients performed a symptom-limited test using a ramp protocol on a cycle ergometer. A respiratory quotient 1.1 at peak exercise was used to identify maximal effort [12]. Monitoring of oxygen saturation, electrocardiogram, and blood pressure was performed in addition to metabolic gas analysis. Any adverse events, including symptoms of chest pain, syncope, or dizziness, ST-segment depression ≥ 3 mm, arrhythmia, or desaturation ≥ 85% were noted. Peak oxygen consumption was measured in each test as the highest attained oxygen consumption that occurred beyond the anaerobic threshold. The VO₂ at the ventilatory anaerobic threshold was detected with the V-slope method supplemented by the

simultaneous observation of end-tidal gas concentrations [12]. Ventilatory efficiency was measured by plotting VE against VCO_2 [6]. The ventilatory efficiency during exercise is represented by the slope of all VE/VCO_2 values during incremental exercise excluding the nonlinear portion of this relationship after the ventilatory anaerobic threshold.

In a sub-analysis, 70 PH patients who underwent diagnostic cardiac catheterization within 30 days of their CPET were investigated for a relationship between both peak VO_2 and VE/VCO_2 and invasive measures of disease severity.

3. Statistical methods

Means tables were computed for each group of paired data and the differences between the group means were tested with paired T-tests. The effect of WHO functional class on VE/VCO_2 slope was investigated in PH patients, excluding patients with a WHO functional class of 4, due to the small number of patients in this group. A linear regression model treated WHO functional class as a continuous variable and determined the effect of an incremental increase in WHO functional class on expected VE/VCO_2 . An ANOVA model treated WHO functional class categorically and compared mean VE/VCO_2 between the WHO functional categories. Both approaches allowed error variance to differ by WHO functional category. Summary statistics and Pearson correlations were calculated and tested for each catheterization variable with peak VO_2 and VE/VCO_2 . The variables pulmonary vascular resistance/systemic vascular resistance and cardiac index each contained a severe outlier which was removed from the analysis for each variable. Mean differences for VE/VCO_2 between patients with a major clinical endpoint and controls were tested with a paired T-test.

4. Results

PH and CON subjects are described in Table 1. There were 258 maximal CPET performed by 76 patients with PH. Most patients had WHO group 1 PH, which was idiopathic in 24, familial in 4, associated with congenital heart disease in 32 (secondary to a septal defect in 13, Eisenmenger physiology in 4, pulmonary vein stenosis in 2, absent pulmonary artery in 3, coarctation in 4, patent ductus arteriosus in 2, d-transposition in 2, single ventricle physiology in 1 and heterotaxy with polysplenia in 1), and associated with a connective tissue disorder in 4. We also included patients from WHO group 3 (high altitude pulmonary edema in 5, pulmonary disease in 6) and WHO group 4 (thromboembolic disease in 1). There were 48 tests in 23 different PH patients in which desaturation to $\leq 85\%$ was recorded. There was ST segment depression ≥ 3 mm in 15 tests on 10 different PH patients. These tests were carried on to a symptom-limited maximum with no major adverse events observed. There was no desaturation or ST segment depression on any CON test. There was no syncope seen on any test in either group. Symptoms of chest pain and dizziness were reported in 12 PAH and 7 CON tests.

At the time of CPET, 86 (33%) tests were performed by a PH patient in WHO Class I, 110 (43%) tests performed by patients in WHO Class II, 59 (23%) tests performed by patients in WHO Class 3, and 3 (1%) tests performed by patients in WHO Class IV [14]. It should be noted that a given patient's WHO class may have changed between CPET given the observational nature of this study.

VE/VCO_2 slope was significantly higher in PH than CON (38.9 vs. 30.9, $p < 0.001$). For a linear regression, expected VE/VCO_2 increased by an estimated 7.2 for each increase in WHO functional class ($p < 0.0001$). For an ANOVA type of analysis, with categorical WHO functional classes, both expected VE/VCO_2 and peak VO_2 significantly differ by WHO

functional class ($p < 0.0001$, F test). All pair-wise comparisons significantly differ ($p < 0.0001$, Tukey–Kramer adjustment).

In a sub-study analysis, 70 PH patients who underwent diagnostic cardiac catheterization within 30 days of their CPET were investigated for a relationship between both peak VO_2 and VE/VCO_2 and invasive measures of disease severity. Of these 70 instances, 17 (24%) were performed by WHO functional class I, 34 (49%) were performed by WHO functional class II, 18 (26%) were performed by WHO functional class III, and 1 (1%) was performed by WHO functional class IV. Table 3 presents the Pearson correlation between VE/VCO_2 slope and peak VO_2 and key invasive measurements of disease severity.

We tested for differences between the VE/VCO_2 slope in PH patients who had a poor outcome, as defined by death or listing for lung transplantation, and controls. The patient's last exercise test before reaching an endpoint was used. Twelve patients met a critical endpoint (9 deaths and 3 lung transplant listing) an average of 3 years after their last CPET (range 1–5 years). VE/VCO_2 slope was significantly elevated in these patients compared to PH patients who did not reach an endpoint (51.1 vs. 37.9, $p < 0.0001$).

5. Discussion

Pulmonary hypertension is an important cause of morbidity and mortality in children. For idiopathic PH and PH secondary to congenital heart disease, the point prevalence in a cohort in the Netherlands was 15.6 and 4.4 cases per million children [15]. Though somewhat dependent on the etiology, survival in pediatric patients with PH has improved significantly with the addition of medical therapy and overall survival in children at 1, 3, and 5 years is comparable to adults [16,17]. With these improvements in clinical outcomes and long term survival, the need for non-invasive monitoring of disease severity and response to treatment has become increasingly important. CPET has been widely employed as a non-invasive tool in patients with heart failure where measurements of peak VO_2 and VE/VCO_2 slope have been well correlated to prognosis and treatment response in adults with heart failure [4–6,18–23]. More recently the safety and utility of CPET for prognosis and monitoring have also been established in PH though the supporting literature is somewhat less robust, particularly in the pediatric population [1,2,24,25].

Alterations in measured VO_2 and VE/VCO_2 during CPET relates directly to disease physiology in PH. Decreased left ventricular filling secondary to abnormal pulmonary arteries and elevated pulmonary vascular resistances results in a decrease in cardiac output in patients with PH. Additionally, reduced red blood cell transit time in the pulmonary circulation leads to a decrease in oxygen diffusion and arterial oxygen saturation. These factors combine to reduce oxygen delivery to working muscles and thereby decrease oxygen consumption resulting in the reduction of peak VO_2 measured by CPET [26]. Reductions in peak VO_2 have been demonstrated to be a highly accurate predictor of survival in adults with PH [3]. The utility of the peak VO_2 measure, however, is effort dependent and therefore VO_2 can be falsely depressed in patients who stop exercise prior to their true symptom limited maximum. This can be particularly true in pediatric patients who may be unable or unwilling to perform maximal testing for a variety of reasons. As a result, measures that can be obtained from submaximal exercise are particularly useful in this population.

During CPET, measurement of the relationship between minute ventilation and carbon dioxide production can be plotted throughout submaximal exercise. Worsening pulmonary vascular disease and the resultant increase in pulmonary vascular resistance, as seen in PH, leads to an increase in physiologic dead space secondary to ventilation-perfusion mismatch.

Falling arterial oxygen saturations lead to earlier development of lactic acidosis which, combined with decreased mixed venous oxygen content and other neural signals, triggers an exaggerated ventilatory response resulting in an elevation of the VE/VCO₂ ratio and slope during progressive exercise [9,27,28]. VE/VCO₂ slope therefore allows for a noninvasive measure of disease severity that is effort independent.

As has been shown previously in PH, we found a reduction in peak VO₂ of pediatric PH patients when compared with controls [1,3,26] and demonstrate that this reduction is progressive with worsening functional class (Table 2). We also found that peak VO₂ correlates negatively with several invasive measures of disease severity (Table 3). Similarly we found that VE/VCO₂ slope is increased in pediatric PH as has been seen in adults [3,8,9] and that, likewise, this is progressive with worsening functional class with a predicted increase in VE/VCO₂ slope of 7.2 for each increase in functional class. We have also demonstrated for the first time that the progressive increase in VE/VCO₂ slope correlates significantly with invasive measures of PH severity including pulmonary vascular resistance (both raw and indexed), mean pulmonary arterial pressure, and mean pulmonary artery pressure/mean aortic pressure (Table 3). We found moderate, yet still significant, correlation between VE/VCO₂ and pulmonary vascular resistance/systemic vascular resistance and mean right atrial pressure. Only a weak correlation was seen between VE/VCO₂ and cardiac index measured at the time of catheterization. Finally, in the small subset of patients with PH who went on to meet a clinical endpoint (death or listing for lung transplantation) we found a significant elevation in the VE/VCO₂ slope with a mean of 51.1.

Our study was limited by its retrospective design. Some patients underwent multiple CPET and therefore any confounding variables related to those patients may have been over-represented. Additionally, nearly all PH patients underwent CPET after the PH diagnosis had been made and therefore medical treatment was initiated prior to CPET. The number of patients tested before and after initiation of medical therapy was insufficient to provide meaningful analysis of treatment effect.

The search for an acceptable endpoint in clinical trial design in children with pulmonary hypertension remains elusive. In the STARTS-1 trial of sildenafil in children with PH, peak VO₂ was used as a primary endpoint. Although the study did not meet the predefined statistical value, 115 children were able to perform cardiopulmonary exercise testing. Due to the difficulty of enrolling 115 children capable of performing maximal CPET, the study took nearly 5 years to enroll. It is possible that a submaximal test using VE/VCO₂ may have allowed for more rapid enrollment [29].

6. Conclusions

The present study demonstrates for the first time that VE/VCO₂ slope correlates well with invasive and noninvasive markers of disease severity including peak VO₂, WHO functional class, pulmonary vascular resistance, and pulmonary artery pressures in pediatric patients with PH. Given that CPET is noninvasive and reproducible, combined with the ability to measure VE/VCO₂ slope from submaximal exercise, VE/VCO₂ slope may prove useful as a clinical measure of disease severity and marker for treatment response in pediatric pulmonary arterial hypertension.

Abbreviations

CPET	cardiopulmonary exercise test
PH	pulmonary hypertension

VE/VCO₂ slope ventilatory efficiency slope

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Biographies

Christopher M. Rausch, MD: has made substantial contributions to conception and design, acquisition, and interpretation of data; has drafted the submitted article; and has provided final approval of the version to be published. Dr. Rausch had full access to all the data in the study and takes responsibility for all aspects of the reliability and freedom from bias of the data presented and the discussed interpretation.

Amy L. Taylor, PhD: has made substantial contributions to conception and design and interpretation of data; has revised the submitted article critically for important intellectual content; and has provided final approval of the version to be published.

Hayley Ross, MD: has made substantial contributions to acquisition and interpretation of data; has revised the submitted article critically for important intellectual content; and has provided final approval of the version to be published.

Stefan H. Sillau, MS: has made substantial contributions to the analysis and interpretation of data; has revised the submitted article critically for important intellectual content; and has provided final approval of the version to be published.

D. Dunbar Ivy, MD: has made substantial contributions to conception and design and interpretation of data; has revised the submitted article critically for important intellectual

content; and has provided final approval of the version to be published. Dr. Ivy assumes full responsibility for the integrity of the submission as a whole, from inception to published article.

Table 1

Description of subjects.

Variable (mean $\pm$ SD)	PH	CON
Age (years)	14.3 $\pm$ 3.7	13.8 $\pm$ 3.2
Height (cm)	155.6 $\pm$ 14.5	157.8 $\pm$ 15.3
Weight (kg)	51.5 $\pm$ 16.9	50.6 $\pm$ 15.4
Body surface area (m ²)	1.5 $\pm$ 0.3	1.5 $\pm$ 0.3
Body mass index (kg/m ²)	20.7 $\pm$ 4.4	19.8 $\pm$ 3.5

PH=pulmonary hypertension subjects; CON=age and gender matched control subjects.

Table 2

Exercise results in CON and PAH by WHO class (mean $\pm$ SD).

	CON	WHO I	WHO II	WHO III	WHO IV
Peak watts	149.9 $\pm$ 62.4	144.9 $\pm$ 55.5	101.4 $\pm$ 48.9	79.3 $\pm$ 38.7	73.3 $\pm$ 33.3
Peak V _{O2} (ml/kg/min)	35.9 $\pm$ 9.3	31.6 $\pm$ 8.9	25.1 $\pm$ 8.2	19.7 $\pm$ 7.9	14.2 $\pm$ 1.71
Peak HR (bpm)	186.1 $\pm$ 11.7	177.9 $\pm$ 15.4	170.0 $\pm$ 17.5	163.5 $\pm$ 18.2	152.7 $\pm$ 10.3
Peak oxygen saturation (%)	95.5 $\pm$ 2.3	92.5 $\pm$ 4.4	89.2 $\pm$ 11.2	83.9 $\pm$ 15.4	86.7 $\pm$ 17.1
VE/VCO ₂ slope	30.9 $\pm$ 4.6	32.6 $\pm$ 5.0	38.3 $\pm$ 9.1	48.7 $\pm$ 12.2	51.1 $\pm$ 15.5

CON=age and gender matched controls; WHO I, II, III, IV=subjects according to World Health Organization functional classification.

Table 3Pearson correlation between VE/VCO₂ slope or peak VO₂ and invasive measurements.

Variable	VE/VCO ₂ slope (<i>p</i> value)	Peak VO ₂ (<i>p</i> value)
Pulmonary vascular resistance, indexed	0.63 (<0.0001)	−0.51 (<0.0001)
Pulmonary vascular resistance	0.61 (<0.0001)	−0.45 (<0.0001)
Mean pulmonary artery pressure	0.58 (<0.0001)	−0.50 (<0.0001)
Pulmonary vascular resistance/systemic vascular resistance	0.56 (0.0003)	−0.46 (<0.0001)
Mean pulmonary artery pressure/mean aortic pressure	0.52 (<0.0001)	−0.43 (<0.0002)
Mean right atrial pressure	0.36 (0.0025)	−0.19 (0.1224)
Cardiac index	−0.03 (0.7940)	0.16 (0.2859)