

Oxygen Uptake to Work Rate Slope in Children with a Heart, Lung or Muscle Disease

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Key words

- exercise test
- child
- aerobic
- anaerobic
- oxygen transport

Abstract

The purposes of this study were all to determine if $\Delta\text{VO}_2/\Delta\text{WR}$ is dependent on age, body mass, height and fitness and if $\Delta\text{VO}_2/\Delta\text{WR}$ could discriminate between healthy children and children with a chronic disease that limits O_2 delivery or utilization. Four groups were included: muscle disease (Juvenile Dermatomyositis; JDM; $n=12$), lung disease (Cystic Fibrosis; CF; $n=13$), Congenital Heart Disease (CHD; $n=13$), and healthy children ($n=44$). All children performed a cardiopulmonary exercise test on a cycle ergometer with respiratory gas analysis. The $\Delta\text{VO}_2/\Delta\text{WR}$

was determined by linear regression using data from unloaded cycling to peak exercise. No associations were found between the $\Delta\text{VO}_2/\Delta\text{WR}$ and age, body mass and height in healthy children. $\Delta\text{VO}_2/\Delta\text{WR}$ was significantly correlated with $\text{VO}_{2\text{peak}}/\text{kg}$ ($r=0.44$; $p<0.01$). Children with JDM had lower $\Delta\text{VO}_2/\Delta\text{WR}$ values than healthy children ($p=0.02$), and $\Delta\text{VO}_2/\Delta\text{WR}$ tended to be lower in CHD and higher in CF ($p=0.09$ and $p=0.08$, respectively). $\Delta\text{VO}_2/\Delta\text{WR}$ may be more sensitive for conditions that are characterized by local hypo perfusion (as in JDM), than for conditions that are characterized by impaired oxygen delivery (i.e. CF or CHD).

Introduction

Cardiopulmonary exercise testing (CPET) is frequently performed in the diagnosis and follow-up of patients with heart, lung or muscle disease [21,25,31,36]. During CPET many different variables can be obtained from gas-exchange analysis during submaximal and maximal exercise [1,24,38]. One of these variables is the oxygen cost of work, calculated as the slope of the oxygen uptake (VO_2) as a response to work rate (WR) increment ($\Delta\text{VO}_2/\Delta\text{WR}$ slope) [2,8,16,41]. Normally, VO_2 increases approximately linearly as external WR increases linearly [9]. The slope of VO_2 versus external WR reflects the efficiency of the metabolic conversion of chemical potential energy to mechanical work and the mechanical efficiency of the musculoskeletal system [1]. The $\Delta\text{VO}_2/\Delta\text{WR}$ slope has remarkable linearity during graded exercise testing, and is explained by the rigid physiological coupling of these parameters, especially below the ventilatory threshold (VT). In healthy subjects the relationship remains either linear or shows a slight curvilinear trend above the VT [17]. In patients, however, the relationship might be shallower at

exercise intensities above the VT, due to reduced oxygen delivery or utilisation. The delta efficiency (energy equivalent of substrate utilisation divided by external work) is inversely related to $\Delta\text{VO}_2/\Delta\text{WR}$ [41], therefore a shallow slope is taken to indicate a better delta efficiency in healthy subjects [18], whereas in clinical conditions it is considered abnormal as it reflects a higher contribution from anaerobic energy sources [25].

In adults it is believed that the $\Delta\text{VO}_2/\Delta\text{WR}$ slope is independent of age, body mass and height [1], however it is unclear whether this is also the case in children. Few data are available for the healthy pediatric population. Values for $\Delta\text{VO}_2/\Delta\text{WR}$ slope between 10.1 and $13.2\text{ mL}\cdot\text{min}^{-1}\cdot\text{Watt}^{-1}$ have been previously reported [8,19,26]. Even less data are available for clinical pediatric populations. In addition, the discriminatory ability of the $\Delta\text{VO}_2/\Delta\text{WR}$ slope is yet unclear (e.g. does it differentiate between children with a muscle disease and healthy children).

Therefore, the first aim of this study was to determine whether the $\Delta\text{VO}_2/\Delta\text{WR}$ slope is affected by age, body mass, height and fitness level in children. The second aim was to study whether the

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$\Delta VO_2/\Delta WR$ slope discriminates between healthy children and children with a chronic disease that is associated with limited oxygen delivery or utilization. To answer these questions we performed graded exercise tests on a cycle ergometer in healthy children as well as three patient groups (Cystic Fibrosis; CF, Congenital Heart Disease; CHD and Juvenile Dermatomyositis; JDM).

Since the $\Delta VO_2/\Delta WR$ slope might be an index of oxygen delivery and utilization during exercise in active muscle tissue, we hypothesized that the $\Delta VO_2/\Delta WR$ slope will be lower in these conditions compared to healthy children.

Methods



Subjects

Four groups of subjects were included in this study: muscle disease (Juvenile Dermatomyositis; JDM; $n=12$), lung disease (Cystic Fibrosis; CF; $n=13$), congenital heart disease (CHD; $n=13$), and healthy children ($n=44$). The healthy children were tested using the same equipment and protocols as the three patient groups. These healthy subjects were free from chronic disease at the time of testing and were recruited from family members of the hospital staff.

The patients with CF consisted of 13 subjects with mild to moderate respiratory dysfunction (Forced Expiratory Volume in 1 s [FEV₁]; 70.2 ± 18.4 percent of predicted). The patients with CHD comprised of 13 children with either a Fontan type circulation ($n=4$) or a repair of the tetralogy of Fallot ($n=9$). The group of patients with JDM consisted of 12 subjects and were diagnosed according to the Bohan and Peter criteria [4] by a pediatric rheumatologist. All children had an active myositis. Patient data was obtained from the database of the Child Development & Exercise Center. Descriptive characteristics of the subject groups are presented in **Table 1**.

The study procedures were approved by the Medical Ethics Committee of the University Medical Center Utrecht. All healthy children and/or their parents gave their written informed consent to participate in the study. The study has been performed in accordance with the ethical standards of the journal [12].

Cardiopulmonary exercise test

Subjects performed a cardiopulmonary exercise test (CPET) using an electronically braked cycle ergometer (Ergoline 9000, Germany). The patients started with 1 min of unloaded cycling. The work rate (WR) was increased 10, 15, or 20 watt per minute according to the Godfrey protocol [10]. This protocol was continued until the patient stopped because of volitional exhaustion, despite strong verbal encouragement of the investigators. The height of the seat was adjusted to the length of the legs. In addition, subjects were instructed to keep the cadence at 70 (range 60 to 80) revolutions per minute. During the maximal exercise

test, subjects breathed through a face mask (Hans Rudolph Inc, Kansas City, MO) connected to a calibrated expired gas analysis system (Oxycon Pro, Cardinal Health, Houten, the Netherlands). Expired gas was passed through a flow meter, an oxygen analyzer, and a carbon dioxide analyzer. The flow meter and gas analyzers were connected to a computer, which calculated breath-by-breath minute ventilation, oxygen uptake, carbon dioxide production, and respiratory exchange ratio (RER) from conventional equations. Heart rate (HR) was measured continuously during the maximal exercise test by a bipolar electrocardiogram. Transcutaneous oxygen saturation (SpO₂%) was measured using pulse oximetry (Nellcor 200E, Breda, The Netherlands) at the index finger.

Raw breath by breath data was averaged by the Oxycon Pro software into 10s intervals. Peak oxygen uptake (VO_{2peak}) was defined by the mean value of the last 30s during the maximal exercise test. Relative VO_{2peak} (VO_{2peak}/kg) was calculated as absolute VO_{2peak} divided by body mass. Predicted VO_{2peak} values were obtained from established values from age- and sex-matched Dutch controls [3, 33].

Ventilatory threshold

The VT was determined by a trained clinical pediatric exercise physiologist using the criteria of an increase in both the ventilatory equivalent of oxygen (VE/VO₂) and end-tidal pressure of oxygen (PETO₂) with no increase in the ventilatory equivalent of carbon dioxide (VE/VCO₂) [5,40]. PETO₂ and PETCO₂ pressures were taken into account to differentiate lactate buffering from hyperventilation. This method has been validated in pediatric patients [23]. VT was expressed as a percentage of predicted-VO_{2peak} [36].

$\Delta VO_2/\Delta WR$ -relationship

$\Delta VO_2/\Delta WR$ was determined by linear regression using the least squares method. The mean values for VO₂ in the last 30s of each incremental step were used. $\Delta VO_2/\Delta WR$ was calculated by linear regression using MS Excel for Windows (Microsoft Office 2003). This method is very similar to those reported previously [8, 16].

Statistics

Goodness of fit of the $\Delta VO_2/\Delta WR$ relationship was investigated using coefficient of determination (R^2) between VO₂ and WR for individual CPET data. Associations with $\Delta VO_2/\Delta WR$ were calculated using Pearson correlation coefficients. Data of the four groups were compared by analysis of variance (ANOVA, SPSS version 15, SPSS Inc, Chicago Ill, USA). When an effect was found, LSD post hoc testing was performed to identify differing groups. Chi squared was used to test for differences in the proportion of children with JDM, CF and CHD that had a slope either below the 5th or above the 95th percentile of the values in healthy children. Differences between groups were expressed as effect sizes, and calculated as difference in mean between the two groups divided

	Healthy	JDM	CF	CHD
sex (male/female)	26/18	7/5	8/5	7/6
age (years)	12.3 ± 2.3 ^{c,d}	10.8 ± 2.1 ^{c,d}	15.8 ± 1.8 ^{a,b}	14.0 ± 2.8 ^{a,b}
height (m)	1.56 ± 0.14 ^{b,c}	1.43 ± 0.13 ^{a,c,d}	1.65 ± 0.09 ^{a,b}	1.56 ± 0.12 ^b
weight (kg)	44.1 ± 12.2	40.9 ± 13.6 ^c	50.8 ± 8.4 ^b	43.3 ± 8.1
BMI (kg · m ⁻²)	17.7 ± 2.3	19.7 ± 4.2	18.5 ± 1.7	17.7 ± 1.3

Table 1 Patient characteristics.

Legend: All values are mean ± SD; ^a significantly different from healthy ($p < 0.05$); ^b significantly different from JDM ($p < 0.05$);

^c significantly different from CF ($p < 0.05$); ^d significantly different from CHD ($p < 0.05$)

Table 2 Physiological outcome of the CPET in the four groups.

	Healthy	JDM	CF	CHD
HR _{peak} (beats · min ⁻¹)	193 ± 7 ^{b,d}	176 ± 20 ^{a,d}	188 ± 10 ^d	164 ± 28 ^{a,b,c}
RER _{peak}	1.16 ± 0.07	1.18 ± 0.14	1.19 ± 0.06	1.19 ± 0.15
WR _{peak} (Watt)	176 ± 57 ^{b,d}	72 ± 29 ^{a,c,d}	176 ± 43 ^{b,d}	129 ± 55 ^{a,b,c}
VO _{2peak} (mL · min ⁻¹)	2163 ± 657 ^{b,d}	1021 ± 212 ^{a,c}	2167 ± 534 ^{b,d}	1473 ± 502 ^{a,d}
VO _{2peak} % of predicted (%)	106.8 ± 22.1 ^{b,c,d}	58.9 ± 13.6 ^{a,c}	82.1 ± 15.1 ^{a,b}	68.4 ± 21.4 ^a
VO _{2peak} /kg (mL · kg ⁻¹ · min ⁻¹)	49.3 ± 7.9 ^{b,c,d}	27.1 ± 10.0 ^{a,c}	42.5 ± 6.8 ^{a,b,d}	33.7 ± 8.9 ^{a,c}
SpO ₂ % at VO _{2peak} (%)	97.1 ± 2.2 ^{c,d}	98.0 ± 1.1 ^{c,d}	90.4 ± 3.0 ^{a,b,d}	93.4 ± 6.1 ^{a,b,c}
VT as % VO _{2peak} (%)	64.2 ± 8.9 ^d	68.4 ± 13.5 ^{c,d}	59.7 ± 14.2 ^{b,d}	81.7 ± 13.8 ^{a,b,c}
VT as % of predicted VO _{2peak} (%)	67.8 ± 14.2 ^{b,c,d}	38.3 ± 11.9 ^{a,d}	48.1 ± 11.4 ^a	54.9 ± 16.9 ^{ab}
ΔVO ₂ /ΔWR (mL · min ⁻¹ · Watt ⁻¹)	9.2 ± 1.0 ^b	8.0 ± 2.8 ^{a,c}	10.1 ± 1.3 ^{b,d}	8.4 ± 1.9 ^c
effect size ΔVO ₂ /ΔWR	NA	0.85	1.19	0.66

Legend: All values are mean ± SD; ^asignificantly different from healthy (p < 0.05); ^bsignificantly different from JDM (p < 0.05); ^csignificantly different from CF (p < 0.05); ^dsignificantly different from CHD (p < 0.05); NA: not applicable

	No. (%) of patients above normal ^a	χ ²	p	No. (%) of patients below normal ^b	χ ²	p
healthy	3/44 (6.8)	–	–	2/44 (4.5)	–	–
JDM	1/12 (8.3)	0.043	0.84	7/12 (58.3)*	80.0	<0.01
CF	4/13 (30.8) *	11.7	<0.01	1/13 (7.7)	0.297	0.59
CHD	1/13 (7.7)	0.016	0.90	3/13 (23.1)*	10.3	<0.01

Legend: ^anormal value was set at the 95th percentile of the values for healthy children (10.80 for ΔVO₂/ΔWR); ^bnormal value was set at the 5th percentile of the values for healthy children (7.45 for ΔVO₂/ΔWR); * significantly different from healthy children

Table 3 Discriminatory ability of ΔVO₂/ΔWR.

by the weighted mean standard deviation [6]. A p-value less than 0.05 was considered to be statistically significant.

Results

All subjects completed the CPET without any complications or adverse effects. Descriptive statistics of the exercise tests are presented in **Table 2**. The children with CF, CHD, and JDM, showed significantly reduced VO_{2peak} values as percentage of predicted for age and sex compared to healthy children. VT as percentage of predicted VO_{2peak} for age and sex was also significantly lower in children with CF, CHD and JDM compared to healthy children.

VO₂ and WR were tightly coupled, coefficients of determination (R²) between the two variables was 0.98 ± 0.03. ΔVO₂/ΔWR was moderately correlated to VO_{2peak}/kg (r = 0.44; p < 0.01), however, no correlations were observed with age, body mass or height in healthy children.

ΔVO₂/ΔWR values for the four groups are presented in **Table 2**. ΔVO₂/ΔWR was lower in children with JDM (p = 0.02), and tended to be lower in children with CHD (p = 0.09) compared to healthy children (**Table 2**). Children with CF tended to have higher values for ΔVO₂/ΔWR than healthy children (p = 0.08). Expressed as effect sizes, the differences between the patient groups and healthy children were moderate (CHD), to large (CF and JDM).

Data on the discriminatory ability of ΔVO₂/ΔWR is provided in **Table 3**. Based on individual data, ΔVO₂/ΔWR yielded a higher proportion of patients with JDM and CHD with reduced values compared to healthy children. A significantly higher proportion of CF patients had increased ΔVO₂/ΔWR values compared to healthy children.

Discussion

Relationship between ΔVO₂/ΔWR and age, height and body mass in healthy children

We confirmed that the ΔVO₂/ΔWR is independent of age, height or body mass in healthy children. Moreover, ΔVO₂/ΔWR was significantly correlated with VO_{2peak}/kg. These findings substantiate the observations in healthy adults [11, 18] and children [8].

ΔVO₂/ΔWR in CF

In contrast to a previous often cited study [19], children with CF did not show a decreased ΔVO₂/ΔWR and even tended to be higher (p = 0.08). This was surprising because Moser et al. [19] reported significantly reduced values in CF patients. They found a ΔVO₂/ΔWR of 8.7 ± 0.26 mL · min⁻¹ · Watt⁻¹ in a group of twenty-two 6.5 to 17.7 year old mild to moderate CF patients. Based on their findings, Moser et al. [19] suggested a muscle-related abnormality in oxygen metabolism in patients with CF. The high ΔVO₂/ΔWR values in CF, found in the present study, might be the result of a higher work of breathing in patients with a pulmonary disease like CF [28]. These high ΔVO₂/ΔWR values are in line with several other studies in children and adolescents with CF [7, 14, 29]. However, high ΔVO₂/ΔWR values do not rule out any metabolic abnormality in the muscles of these children. For example, increased values of ΔVO₂/ΔWR have been reported in patients with Glycogen Storage Disease 5 (McArdle's Disease) [22].

ΔVO₂/ΔWR in CHD

ΔVO₂/ΔWR in children with CHD tended to be lower than healthy children (p = 0.09). Low values for the ΔVO₂/ΔWR slope were previously reported in children with a repaired coarctation of the aorta as well [26]. Increasing demands in muscular as well as

in cardiac oxygen utilization will lead to an increasing cardiac work rate. Because of the combination of right-to-left shunting in the heart, failure to increase the cardiac output (stroke volume and/or heart rate), impaired pulmonary gas exchange, and reduction in arterial oxygen saturation, oxygen transport from lung to muscle is impaired [27,35,39]. These alterations result in a reduced $\Delta\text{VO}_2/\Delta\text{WR}$ slope [37]. Based on the Fick principle, when cardiac output is limited during exercise, the increased O_2 demand in children with CHD can be augmented by an increase in artero-venous oxygen extraction [30]. The trend for lower $\Delta\text{VO}_2/\Delta\text{WR}$ values indicates that O_2 delivery might be limited in this patient group.

$\Delta\text{VO}_2/\Delta\text{WR}$ in JDM

$\Delta\text{VO}_2/\Delta\text{WR}$ was significantly reduced in children with JDM, who have a limitation in muscular oxygen utilization [13] and no defect in oxygen delivery (no reduction in $\text{SpO}_2\%$). Our data confirm the results of Drinkard et al., [8] who found a reduced $\Delta\text{VO}_2/\Delta\text{WR}$ in JDM patients compared to healthy controls. They found a $\Delta\text{VO}_2/\Delta\text{WR}$ of $7.4 \pm 1.4 \text{ mL} \cdot \text{min}^{-1} \cdot \text{Watt}^{-1}$ in twelve JDM patients versus $10.8 \pm 1.2 \text{ mL} \cdot \text{min}^{-1} \cdot \text{Watt}^{-1}$ in twenty healthy controls. Pathological changes associated with JDM may influence peripheral muscle oxygen delivery and/or oxidative capacity and hence lead to a reduced oxygen utilization [34]. In JDM capillary destruction could possibly lead to disturbed perfusion of the muscle tissue and thereby causing hypoxia or impaired delivery of energy substrates [15,20,32]. The impaired muscle oxygenation in patients with JDM becomes problematic when oxygen demand is increased as during exercise [32]. As a consequence, the energy requirements must therefore be fulfilled via anaerobic pathways. This impaired muscle oxygenation is reflected by the very low VT and the reduced $\Delta\text{VO}_2/\Delta\text{WR}$ values in patients with JDM [22].

Discriminatory ability of $\Delta\text{VO}_2/\Delta\text{WR}$

On the individual level, roughly half of the JDM patients showed reduced values for $\Delta\text{VO}_2/\Delta\text{WR}$, whereas in the CHD and CF group, this was considerably less. This may suggest that $\Delta\text{VO}_2/\Delta\text{WR}$ is a better indicator of impaired oxygen utilization than impaired oxygen delivery pediatric patients.

Limitations

One limitation is that the patient groups were relatively small in size, however, the difference between the three clinical groups and the healthy children, calculated as effect size, were quite large (see Table 2). Because the difference in $\Delta\text{VO}_2/\Delta\text{WR}$ did not reach significance in CHD, additional studies in this patient group are warranted. One other limitation concerns the method of calculating $\Delta\text{VO}_2/\Delta\text{WR}$ relationship. In most studies the $\Delta\text{VO}_2/\Delta\text{WR}$ relationship is calculated by ramped protocols and is consequently corrected for a transit delay of the intervening venous blood volume arriving at the pulmonary capillaries. The protocol in our exercise lab (the "Godfrey-protocol") consisted of discrete incremental steps per minute. We therefore implicitly corrected for a transit delay (if any) by only considering the last 30 s of each incremental step for the linear regression analysis.

Clinical implications and future directions

It is suggested that $\Delta\text{VO}_2/\Delta\text{WR}$ is relatively non-specific in establishing an aetiology [1]. We found reduced values in children with JDM (O_2 utilization dysfunction) and a trend for lower values in children with CHD (O_2 delivery dysfunction) as well.

Interestingly, the children with CF did not show a reduced $\Delta\text{VO}_2/\Delta\text{WR}$, although they showed a significant reduction in $\text{SpO}_2\%$ (reduced O_2 delivery). In addition, nearly 60% of patients with JDM had reduced $\Delta\text{VO}_2/\Delta\text{WR}$ values, whereas in the CHD group only 23% had reduced values (see Table 3). Together these findings indicate that $\Delta\text{VO}_2/\Delta\text{WR}$ might be more sensitive for conditions that are characterized by local hypoperfusion, than conditions that are characterized by impaired oxygen delivery. We acknowledge that the ability of $\Delta\text{VO}_2/\Delta\text{WR}$ to discriminate between healthy children and patients seems somewhat limited compared to other exercise parameters such as $\text{VO}_{2\text{peak}}/\text{kg}$. Future studies should address the sensitivity to change of $\Delta\text{VO}_2/\Delta\text{WR}$, e.g. after exercise training, or medical interventions in pediatric populations. In addition it would be of interest to determine the $\Delta\text{VO}_2/\Delta\text{WR}$ in patients with a reduction in muscular oxygen extraction which is not attributable to local hypoperfusion (e.g. mitochondrial myopathies).

Conclusion

To summarize, we found that $\Delta\text{VO}_2/\Delta\text{WR}$ was independent of age, height and body mass in healthy children. $\Delta\text{VO}_2/\Delta\text{WR}$ was reduced in children with Juvenile Dermatomyositis and tended to be reduced in children with Congenital Heart Disease. There was a trend for increased $\Delta\text{VO}_2/\Delta\text{WR}$ values in children with Cystic Fibrosis. This study shows that $\Delta\text{VO}_2/\Delta\text{WR}$ may be more sensitive for conditions that are characterized by local hypoperfusion (as in JDM), than for conditions that are characterized by impaired oxygen delivery (i.e. CF or CHD).

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