

Expert Review of Respiratory Medicine

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierx20

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To cite this article: Tim Takken, Hazal Sonbahar Ulu & Erik H. J. Hulzebos (2020) Clinical recommendations for cardiopulmonary exercise testing in children with respiratory diseases, Expert Review of Respiratory Medicine, 14:7, 691-701, DOI: 10.1080/17476348.2020.1752195

To link to this article: https://doi.org/10.1080/17476348.2020.1752195

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Published online: 26 Apr 2020.

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EXPERT REVIEW OF RESPIRATORY MEDICINE
2020, VOL. 14, NO. 7, 691–701
https://doi.org/10.1080/17476348.2020.1752195

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REVIEW

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Clinical recommendations for cardiopulmonary exercise testing in children with respiratory diseases

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ABSTRACT

Introduction: Cardiopulmonary exercise testing (CPET) quantitates and qualitates the integrated physiological response of a person to incremental exercise and provides additional information compared to static lung function tests alone.

Areas covered: This review covers rationale for the use of CPET parameters beyond the usual parameters like peak oxygen uptake and peak minute ventilation in children with respiratory disease.

Expert opinion: CPET provides a wealth of data from rest, submaximal and maximal exercise and data during recovery from exercise. In this review, an interpretative approach is described for analyzing CPET data in children with respiratory disease.

ARTICLE HISTORY
Received 30 January 2020
Accepted 2 April 2020

KEYWORDS
Exercise; physiology; child

1. Introduction

Cardiopulmonary exercise testing (CPET) quantitates and qualitates the integrated physiological response of a person to incremental exercise. In this review, we discuss the physiologic responses to exercise in children with respiratory diseases.

CPET provides additional information compared to static lung function tests alone for children with respiratory (obstructive) diseases such as cystic fibrosis (CF) [1]. Static lung function tests are useful for diagnosis and management of children with respiratory diseases. However, these tests are not inclusive to measure respiratory abilities to perform exercise, which is considered as very important for the physical and psychosocial development of children.

Several studies have shown a very scattered relationship between static lung functions and exercise capacity in children with respiratory disease, indicating that static lung function indices are not able to predict exercise capacity of an individual patient [2,3].

2. Testing equipment and protocols

When testing children, one has to take the equipment into consideration. For small children, a small cycle ergometer is required or an exercise test can be performed on a treadmill. Treadmills do not have a height limit. Similarly, small facemasks/mouth pieces, electrocardiogram (ECG) electrodes, blood pressure cuffs, and oxygen saturation probes, as well as sensitive airflow meters, are required when testing children.

Pulse oximeters are useful in monitoring the efficacy of interventions, assessing the disease severity, and determining whether supplemental oxygen is needed during exercise in patients with respiratory diseases [4,5]. During exercise SpO_2 can change rapidly, for this reason continuous monitoring by pulse oximetry may be desirable and new oximeters have system of enhanced signal processing algorithms and ability to reduce sensitivity to motion and variations in perfusion. It is important to note that forehead sensors have a better precision compared to finger sensors [6]. Forehead sensors are less affected by motion and are less prone to measurement artifacts [6]. Therefore, the forehead is the preferred site for measurement during CPET. In addition, the testing environments and personnel should be child friendly, especially when testing young children.

Testing protocols should be adapted to the ability of the subject. If the goal of CPET is to obtain a reproducible $\dot{V}O_{2peak}$, the preferred duration for a CPET is between 6 and 10 min in children and between 8 and 12 min in adolescents [7,8]. When testing clinical populations with low $\dot{V}O_{2peak}$ values, an exercise protocol in which the work rate increases with small increments (so-called ramp protocol) is preferred. If the work rate increments are too big, the exercise test may be terminated prematurely, without actual maximally stressing the cardio-pulmonary and metabolic systems [9,10].

Patients with CF are able to perform a reliable CPET [11]. For instance, we and others found that the $\dot{V}O_{2peak}$ measured during CPET seems to reflect the 'true' $\dot{V}O_{2peak}$ in adolescents with CF as measured using a supramaximal verification test [11,12]. A supramaximal verification phase after the CPET is currently recommended not to perform in the recent European Respiratory Society statement [6].

As described in this article, much of the information on the respiratory response to exercise is obtained from submaximal exercise data, and not from $\dot{V}O_{2peak}$ alone.

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Article highlights

- Cardiopulmonary exercise testing (CPET) provides a wealth of information especially regarding the respiratory response and/or limitations to exercise;
- Growth and development have a significant impact on respiratory response to exercise;
- CPET can help to identify the pathophysiology of unexplained dyspnea or exercise intolerance in children with respiratory diseases;
- A systematic approach is advised for the analysis of CPET data.

It is our opinion that adding the supramaximal verification procedures to the already demanding CPET does not add significantly to the information obtained from the CPET in children with respiratory disease.

3. Respiratory response to exercise

During exercise, there are many physiologic changes in the human body to accommodate the increase oxygen demand and increased carbon dioxide (CO_2) production amongst others. When testing children with respiratory disorders, there are many respiratory variables that are important to consider in the analysis of a CPET.

First, there are several important 'general' CPET parameters to consider: (i) peak Heart Rate (HR_{peak}), this is the highest heart rate observed during an incremental exercise test (ii); Respiratory Exchange Ratio (RER), this is the ratio between $\dot{V}CO_2$ and $\dot{V}O_2$; (iii) Ventilatory Anaerobic Threshold (VAT), this is the point where anaerobic metabolism sets in during incremental exercise, (iv) Respiratory Compensation Point (RCP), this is the onset of hyperventilation (extra CO_2 production for the buffering of lactate $[H^+]$ with bicarbonate) during incremental exercise; (v) Oxygen pulse, this is the ratio between oxygen uptake and heart rate and is an index of stroke volume; (vi) Maximum/Peak Oxygen Uptake ($\dot{V}O_{2max}$/$\dot{V}O_{2peak}$), this is the highest oxygen uptake during incremental exercise. Usually, this is taken over a period of 30–60 sec.

In the following paragraphs, we will address the ventilatory CPET parameters that can be of interest when evaluating a CPET performed in a child with respiratory disease.

3.1. Ventilation and ventilatory reserve

In healthy humans of all ages, the ventilatory response to exercise of up to some 10 to 20 fold greater than resting levels is achieved with remarkable precision and efficiency in terms of both CO_2, O_2 and pH regulation of arterial blood and economy of effort on the part of the respiratory muscles. The key primary drivers of this increased ventilation which are tightly and mysteriously linked to respiratory CO_2 exchange have been narrowed to a central command, feedforward stimulus with parallel recruitment of both locomotor and respiratory muscles and a feedback stimulus involving thiny myelinated afferents from contracting locomotor muscles [13].

From childhood to adolescence, specific developmental aspects occur regarding ventilation during exercise. With growth, an increase in minute ventilation ($\dot{V}E$) and efficiency of $\dot{V}E$ increases. This change in efficiency can be explained by an increasing in tidal volume (VT), coinciding with a decreasing in breathing frequency (BF) [5,11].

The performance of the respiratory system during standard pediatric CPET is generally assessed by the ventilatory response to the increasing metabolic demand along with assessment of the ventilatory reserve (VR) at peak exercise. Studies have shown that highly fit subjects achieved expiratory airflows that reached their volume-specific maximum during high-intensity exercise. It was observed that highly fit endurance athletes can reach a maximum exercise ventilation that is comparable to their maximum voluntary ventilation (MVV) [14]. During training, lung function does not improve in contrast to circulatory and muscular function. As a consequence, the higher fit a person becomes, increases the importance of an optimal pulmonary mechanics [15].

It is generally conceived that in the steady state both alveolar ventilation and $\dot{V}E$ increase as a linear function of $\dot{V}CO_2$ (rather than $\dot{V}O_2$) and, consequently, $PaCO_2$ is regulated at or very close to its resting value.

- $\dot{V}_E = 863 \times \dot{V}CO_2/PaCO_2 \times (1\text{-}VD/VT)$

where VD is the dead space ventilation and VD/VT is the physiological dead space fraction of a breath. Consequently, the ventilatory response to exercise is increased when $PaCO_2$ is low or VD is high or VT is low [15].

The calculation of the VR at peak exercise is used to evaluate whether ventilatory limitation affects exercise tolerance [10,16]. The VR at peak exercise compares the attained $\dot{V}E_{peak}$ during a CPET with the maximal capacity of the ventilatory system. The calculated MVV is a better surrogate of maximum ventilatory capacity in pediatrics than the measured MVV, as shown by significant correlation to other ventilatory parameters during CPET [17]. MVV which can be estimated by multiplying forced expiratory volume in 1 s (FEV_1) by a coefficient (values ranging from 30 to 40 have been proposed for children; we recommend 35 for children and 37.5 for CF) [18,19].

VR at peak exercise can then calculated via the following equation:

$$VR = 100 - ((\dot{V}E_{peak(measured)}/MVV_{(calculated)}) \times 100).$$

where 'VR' is the ventilatory reserve at peak exercise (%), $\dot{V}E_{peak}$ represents the minute ventilation at peak exercise ($L{\cdot}min^{-1}$), 'MVV' is the calculated maximal voluntary ventilation ($FEV_1 \times 40$ in $L{\cdot}min^{-1}$). In healthy adolescents, VR is seldom less than 30% when tested at sea level [20]. In healthy males, the VR varies and could be as low as 10–15% [10]. However, it has become clear the VR tells little about the specific reason(s) for ventilatory constraint during exercise [21].

In pediatric patients with respiratory disease, an association between pulmonary function (FEV_1) and VR is observed (see Figure 1). Patients with an FEV_1 below 70% seem to have a chance to have almost no or a negative ventilatory reserve. This is in agreement with data from young adult CF patient, where a cuff-off value of 68% of FEV_1 was suggested to have a ventilatory limitation for performing exercise [22].

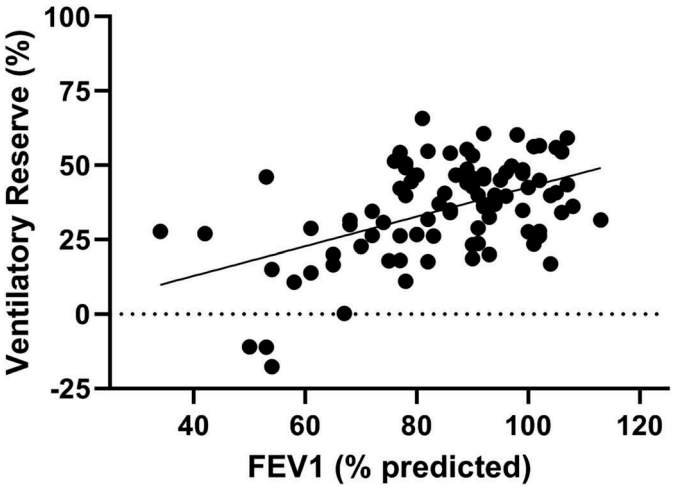


Figure 1. The relationship between FEV_1 and ventilatory reserve in pediatric CF patients. Unpublished data.

3.1.1. Tidal volume (VT)

During the initial stages of exercise, healthy subjects recruit inspiratory and expiratory reserve volumes to increase VT. Next, as exercise continues, they increase the BF. The augmented $\dot{V}E$ with increasing exercise intensity is caused by both an increased VT and BF. VT is increased by decreasing the inspiratory reserve volume and to a lesser extent by decreasing the expiratory reserve volume [16]. This can be accomplished by increasing the flow rate at a given inspiratory time or by lengthening inspiratory time at a given flow rate [17].

In children with cystic fibrosis, as the severity of diseases increases, rapid shallow of breathing is observed due to the increased work of breathing. According to the Campbell diagram, increased work of breathing leads to an increase in VT. Patients develop an adaptation to reduce the work of breathing and VT with increased minute ventilation [18,23]. Williams et al. also stated that there is an increase in breathing frequency to maintain gas exchange as a result of limiting the VT in pediatric CF patients [19] [24].

The maximal VT during exercise is usually between 50% and 60% of the resting vital capacity of a participant [25]. The VT/VC ratio indicated the depth of breathing is the same or lower at submaximal exercise and lower at maximal exercise in children as compared to adults [26]. VT at peak exercise depends on growth (size dependent and proportional to increase in body mass and height) with higher values seen in older children [26]. During exercise, VT can increases two to five times from rest to peak exercise in children and adolescents, respectively [26].

3.1.2. Breathing frequency (BF)

The increase in BF seen in exercise is achieved through a decrease in both inspiratory time and expiratory time [27]. At exercise intensities beyond 70% to 80% of peak exercise, increases in BF are mainly accountable for further increases in $\dot{V}E$ [20]. In pre-pubertal children, the BF at peak exercise was two to four times the resting BF and similar in boys and girls. The attained BF at peak exercise decreases with age, associated with an increase in both inspiratory time and expiratory

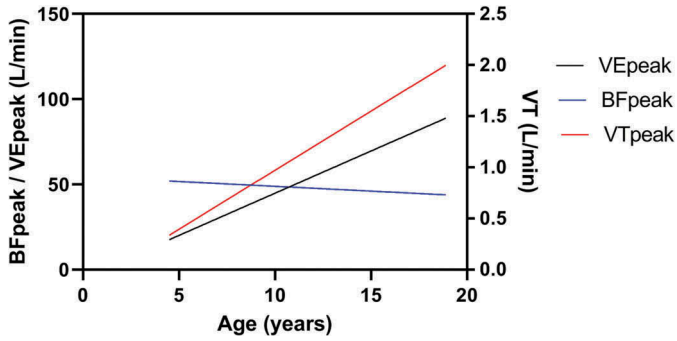


Figure 2. The $\dot{V}E$, VT, and BF at peak exercise in relation to age in pediatric CF patients. Unpublished data.

time [20]. The age-related decline in breathing frequency is compensated by an even greater increase in VT so that absolute $\dot{V}E$ at peak exercise increases significantly with growth [23,24,27,28]. Also in patients with CF, the age-related decline in breathing frequency and the increase in VT is observed as depicted in Figure 2.

Regardless of the exercise test protocol, the inflection (or plateau) in the VT response and increased BF marked the point where dyspnea intensity rises abruptly and is a transition in the dominant qualitative descriptor choice from 'work and effort' to 'unsatisfied inspiration.' Intensity and quality of dyspnea evolve separately and are strongly influenced by mechanical constraints on the increase in VT during exercise in COPD [29].

3.2. Exercise flow-volume loops

Measuring the tidal exercise flow-volume loops during a CPET and plotting them within the maximal flow-volume envelope, gives more specific information on the sources (and degree) of ventilatory constraint. This includes the extent of expiratory flow limitation, inspiratory flow reserve, alterations in the regulation of end expiratory lung volume (dynamic hyperinflation), end-inspiratory lung volume relative to total lung capacity (or tidal volume/inspiratory capacity). Children have smaller lungs than adults. Due to structural properties of children's lungs, flow-volume loops may reveal ventilatory limits during peak exercise in children. Breathing at higher lung volume eliminates expiratory flow limitation but greater work to overcome greater elastic force is needed. It can lead to ventilatory constraint and dynamic hyperinflation [30,31]. By assessing these types of changes, the degree of ventilatory constraint can be quantified and a more thorough interpretation of the CPET response is possible [30]. One should realize, however, that in the youngest age groups measurement of FEV_1 is often challenging, because most young children are unable to perform the required full forced expiration during a total second; consequently, plotting exercise-flow-volume loops is often quite challenging as well [26,32]. VT at peak exercise depends on growth (size dependent and proportional to increase in body mass) with higher values observed in older children [27,28].

Patients with chest hyperinflation (such as the children with CF) are unable to recruit significant inspiratory and expiratory reserve volumes, and therefore, maintain a relatively high respiratory rate

during exercise. When these patients have to increase ventilation, they can neither increase their expiratory flow nor decrease their end expiratory lung volume. In general, patients with CF and a normal spirometry results do not exhibit expiratory flow limitation during exercise and are able to decrease end expiratory lung volume in a manner similar to healthy subjects [33]. Not only does this decrease in end expiratory lung volume optimize diaphragm length but, in addition, the abdominal wall recoil following expiration aids inspiration. In contrast, patients with CF with severe lung disease exhibit expiratory flow limitation both at rest and during exercise, despite the progressive increase in end expiratory lung volume (dynamic hyperinflation) [34]. An important mechanical consequence of dynamic hyperinflation is the severe restriction of VT expansion during exercise: to increase VE, the patient must rely on increasing their BF. However, as a result, this tachypnea causes further dynamic hyperinflation in a vicious cycle.

3.3. The ventilatory equivalent for oxygen uptake and carbon dioxide exhalation

The ventilatory equivalent for oxygen ($\dot{V}E/\dot{V}O_2$) represents the ventilatory response to the aerobic metabolic requirements of exercise. Usually, the lowest point or the point at the VAT is taken. More specifically, it represents the average number of liters of air that a child has to ventilate in order to take up, transport, and utilize 1 l of oxygen. A higher $\dot{V}E/\dot{V}O_2$ is an indication of a less efficient ventilation and can be caused by non-physiological hyperventilation, increased VD/VT, or irregular breathing [35]. It has been found that ventilatory efficiency improves with age during childhood [36,37]. Hence, children attain higher values for the $\dot{V}E/\dot{V}O_2$ than adolescents and adults.

Other ways to express this relationship is to calculate the Oxygen Uptake Efficiency Slope (OUES) using the relation between $\dot{V}O_2$ and the common logarithm of the $\dot{V}E$ [38]. However, it was previously shown that the OUES is not a valid CPET parameter in children with CF [39].

The fact that children ventilate more for a certain aerobic metabolic demand compared to adolescents and adults might be the result of a higher dead space ventilation and a lower $PaCO_2$ set point, which can be estimated by the $PETCO_2$ in children and adolescents. Higher $PETCO_2$ values as well as higher $\dot{V}E/\dot{V}CO_2$-slopes were found during exercise in children compared to adolescents [36,40]. The less efficient ventilation in children results in a greater oxygen cost of ventilation, which might partly explain the relatively high metabolic demands during sub-maximal exercise in children compared to adults [41].

The ventilatory equivalent for carbon dioxide exhalation ($\dot{V}E/\dot{V}CO_2$) represents the ventilatory response to the production of carbon dioxide during exercise. Usually, this is expressed as the slope of the relation between the $\dot{V}E$ and $\dot{V}CO_2$ ($\dot{V}E/\dot{V}CO_2$-slope) or as the lowest $\dot{V}E/\dot{V}CO_2$ value during a CPET.

$\dot{V}E$ increases linearly with $\dot{V}CO_2$ during CPET, even throughout the period of isocapnic buffering which is preceded by the VAT. At exercise intensities above the RCP, $\dot{V}E$ increases excessively due to the metabolic acidosis, resulting in the loss of linearity in the relation between $\dot{V}E$ and $\dot{V}CO_2$ [42]. The RCP is usually between 60% and 90% of an individual's $\dot{V}O_{2max}$. In a group of healthy children, Vandekerckhove et al. found that the RCP appeared at 89.3 ± 4.6 of their $\dot{V}O_{2max}$ [43]. In children who show an RCP during CPET, a significant lung disease is unlikely.

In children with CF, an increased ventilatory response during exercise is often observed (Figure 3). This is merely observed in an increased $\dot{V}E/\dot{V}O_2$ during submaximal exercise with a normal $\dot{V}E/\dot{V}CO_2$ ratio during exercise [44]. This pattern can be explained by an increased muscular CO_2 production [44]. An increased RER during (sub-)maximal exercise is frequently reported in patients with CF [45,46]. The higher RER in patients with CF is suggested to reflect a higher reliance on glucose oxidation and/or anaerobic glycolysis to meet energy demands during exercise [29,30]. The higher CO_2 production might explain the ventilatory inefficiency (higher $\dot{V}E/\dot{V}O_2$) in pediatric CF, with a normal ventilatory response to CO_2 production ($\dot{V}E/\dot{V}CO_2$).

3.4. Rapid shallow breathing index (RSBI)

RSBI is a parameter that is infrequently reported in CPET, but maybe of interest when testing patients with respiratory disease (hyperinflation). RSBI is calculated by dividing breathing frequency (BF) by tidal volume (VT) [47]. Patients that are hyperventilating in rest and during exercise tend to breathe rapidly (high frequency) and shallowly (low tidal volume), and have therefore a high RSBI. Rapid shallow breathing has a lower energetic cost than deep breathing but is less efficient in terms of alveolar ventilation due to the relative increase in dead space ventilation [48].

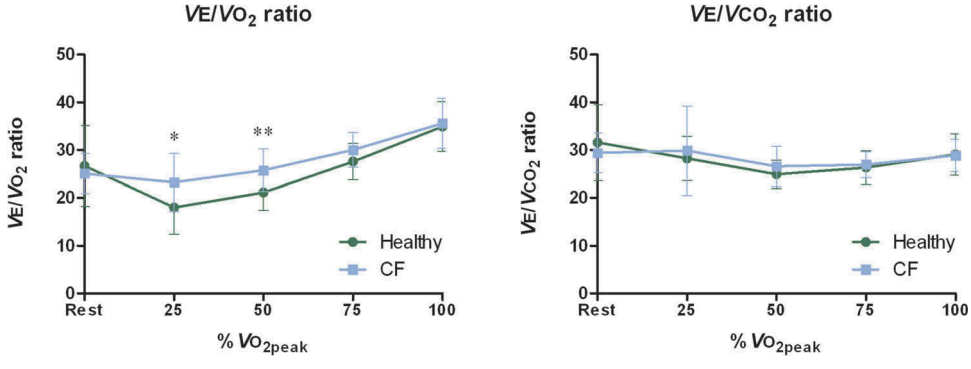


Figure 3. The $\dot{V}E/\dot{V}CO_2$ ratio in adolescents with CF and healthy subjects. Figure drawn after data from [44].

The age-related decline in BF at peak exercise, accompanied by the age-related increase in VT at peak exercise results in an age-related decline of the RSBI at peak exercise.

A reduction in RSBI at peak exercise is also observed in pediatric patients with CF (See Figure 4). The result of a decrease in BF and a concomitant increase in VT.

Expiratory flow limitation is the pathophysiologic hallmark of obstructive pulmonary disease, but dyspnea (breathlessness) is its most prominent and distressing symptom [27,49]. Dynamic lung hyperinflation is a mechanistic consequence of expiratory flow limitation and has serious mechanical and sensory consequences of the respiratory system. It is associated with excessive loading of inspiratory muscles, and with restriction of normal VT expansion during exercise. There is a strong correlation between the intensity of dyspnea, at a standardized point during exercise, the end-expiratory lung volume, and the increased ratio of inspiratory effort to volume displacement (VT as a % of predicted VC) [49].

3.5. Exercise-induced bronchoconstriction (EIB)

EIB is defined as a transient narrowing of the airways that follows vigorous physical activity or exercise [50–52]. EIB occurs in 70% to 90% of patients with asthma and it is present in 10% to 15% of healthy children [51,53–58].

EIB is classified by a fall in post-exercise FEV_1 of ≥10% to 15% from baseline, in very young children however, an exercise-induced decrease in $FEV_{0.5}$ of 13% or greater from baseline is being used to classify EIB [52]. FEV_1 in young children is likely to be less reliable than $FEV_{0.5}$ because most young children are unable to perform the required full forced expiration during a total second. EIB starts typically 2 to 4 min after exercise, peaking at 5 to 10-min post-exercise and disappearing spontaneously within 20 to 40 min. In some cases, it may be sustained for more than 1 h [59,60].

Constant intensity exercise at an intensity of 70% to 85% of $\dot{V}O_{2peak}$ triggers bronchoconstriction the most. The duration of exercise is of influence in the emergence of EIB. The optimal exercise duration seems to be of 6 to 8 min to induce bronchoconstriction [5].

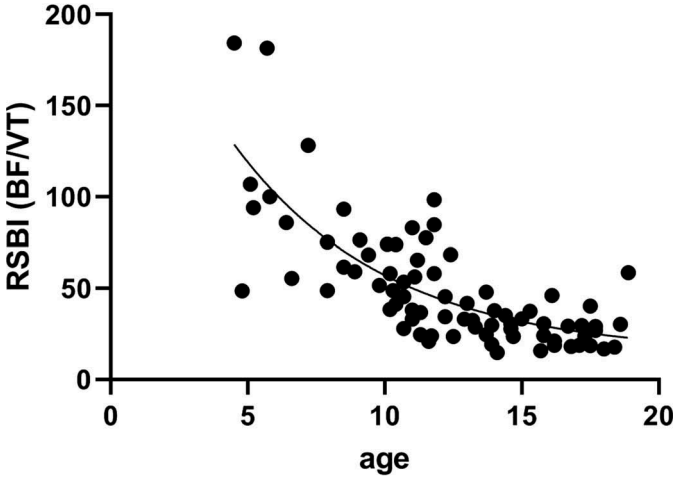


Figure 4. The age-related decline in RSBI at peak exercise in adolescents with CF. Unpublished data.

EIB is often observed in children with respiratory diseases. It is known that bronchoconstriction is one of the features of asthma [61]. Studies indicated that 40–60% of asthmatic children had EIB [62,63]. Park et al. also showed that asthmatic children with EIB had decreased pulmonary function after exercise [64]. Joshi et al. observed that EIB was common in school-aged children who have had chronic lung disease in infancy [65].

3.6. Minute ventilation to work rate ratio

The minute ventilation to work rate ratio ($\dot{V}E/WR$) corresponds to the ventilatory response in relation to the WR:

$$\dot{V}E/WR = (\dot{V}E \times 1{,}000)/WR$$

where '$\dot{V}E/WR$' represents the absolute minute ventilation to work rate ratio ($mL \cdot min^{-1} \cdot W^{-1}$), '$\dot{V}E$' stands for the minute ventilation ($L \cdot min^{-1}$), '1,000' represents the multiplying factor to convert $L \cdot min^{-1}$ to $mL \cdot min^{-1}$, and 'WR' is the work rate (Watt). It represents the ventilatory demand for the generated muscle power output (work rate, exercise intensity). Godfrey et al. found a resting $\dot{V}E$ of roughly 10 $L \cdot min^{-1}$ and an increase in $\dot{V}E$ of 9.4 $L \cdot min^{-1}$ for each increase in work rate of 25 W in children [66]. The authors underlined that children ventilated more at any work rate than adolescents; however, they reported no large differences. In healthy children, $\dot{V}E$ increases by 0.36 $L \cdot min^{-1}$ for each W (Watt) increase in work rate. This results in the following equation:

$$\dot{V}E/WR\%pred. = (\dot{V}E\times)/(9 + (0.36 \times WR))$$

where '$\dot{V}E/WR\%pred.$' stands for the ventilatory response in relation to the applied work rate (% of predicted, based on the 'rule of nine' by Rühle), '$\dot{V}E$' represents the measured minute ventilation ($L \cdot min^{-1}$), '100' is the multiplying factor to convert the ventilatory response in relation to the applied work rate to a percentage of predicted, '9' represents the minute ventilation at rest, '0.36' represents the increase in minute ventilation for each W (Watt) increase in WR ($L \cdot min^{-1}$), and 'WR' represents the measured work rate (W).

In adolescents with mild-to-moderate CF, it was found that $\dot{V}E/WR$ ratio values were significantly higher in CF during the entire range of the CPET compared to healthy peers (see Figure 5) [44]. However, this was without any apparent signs of pulmonary insufficiency [44].

3.7. Saturation

Metabolic requirements increase with the intensity of work and muscles need oxygen during the increase of these requirements. If oxygen is not adequate, production of lactate increases and tissues release lactate into the plasma [67]. The products of metabolism remove through circulation and oxygen transports from lung to the tissues and carried by the hemoglobin. The arterial oxygen saturation (SaO_2) presents the percentage of the binding sides on hemoglobin [68,69]. Pulse oximetry is often used in clinical settings to provide an estimate of SaO_2; the peripheral oxygen saturation (SpO_2).

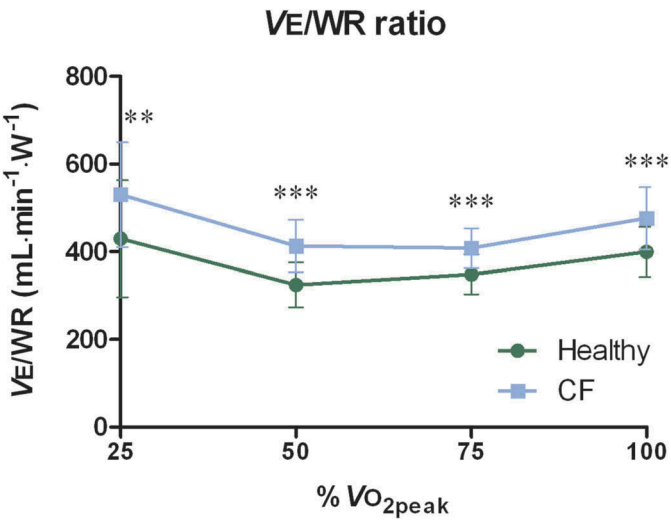


Figure 5. V̇E/WR relationship during exercise in pediatric CF patients compared to healthy peers. Redrawn after Bongers et al. [44].

A ≥ 5% fall in SpO_2 during CPET is defined as an exercise-induced hypoxemia [6]. A fall below 85% or 80% is considered as an indication to stop an exercise test [6]. Desaturation is observed in children with serious lung diseases. It is known that oxygen desaturation is seen in children with CF had decreased pulmonary function as FEV_1 < 50% and DLCO<60% [67]. Bader et al. also stated that decreased arterial oxygen desaturation and increased transcutaneous CO_2 tension were observed in children with bronchopulmonary dysplasia (BPD) due to the pulmonary limitation to exercise, even if the $\dot{V}O_{2peak}$ was the same in children with BPD as compared to healthy children [67]. Santuz et al. showed that although oxygen saturation was 98% or more in BPD patients at rest, 4% or more decline occurred in oxygen saturation at peak exercise [67].

3.8. Symptom perception

The modified Borg scale is the most used method in assessing a person's rating of perceived exertion. It is a vertical scale that evaluates dyspnea and fatigue perception between 0 (nothing at all) – 10 points (very very strong). The verbal descriptions can help to choose a number describing how the body feels during exercise [70]. Higher scores indicate that dyspnea and fatigue are more severe [70]. This scale must be perceived by the individuals and responses to the scale change in different ages. The Borg scale can be used in children older than 9 years old because of the cognitive capacity for perceiving the exertion. It may be difficult to respond to the scales such as Borg scale in children and adolescents because Borg developed the original scale for adults [70]. There are some scales specifically developed for use in children and adolescents, the OMNI scale is one of the most used scales in children [71]. OMNI includes verbal and visual descriptors. It evaluates the perceived exertion between 0 (not tired at all) and 10 points (very, very tired) [71].

Children with respiratory diseases such as CF have increased ventilatory demand, physical and airflow limitation, and peripheral muscle abnormalities amongst others. Due to these causes, symptoms such as dyspnea and increased fatigue perception are seen during and after exercise [72]. Arikan et al. [73] compared the symptom perception before and after functional capacity test between children with CF and healthy children. It was observed that children with CF had a higher dyspnea perception compared to healthy children [71,73]. Simsek et al. showed that perceived dyspnea and fatigue after exercise capacity test were higher in children with primary ciliary dyskinesia (PCD) than healthy peers [71,74]. Basso et al. [75] assessed dyspnea and leg fatigue perception before and after exercise capacity testing in asthmatic children, and found that leg fatigue was higher in asthmatic children as compared to healthy children. Malo et al. also indicated that breathlessness was associated with severity of disease [76].

4. Interpretation/analysis CPET

It is advised that after performing the CPET, the CPET results are written down in a clear report. Because of the wealth of CPET data, and the various reference values of each parameter, this is not always very easy to do [77]. Therefore, a systematic approach is very helpful for the interpretation of CPET data. Further, the interpretation is facilitated when the person who writes the report also assisted in performing the actual CPET. He can have a clue how the subject performed and behaved during the test. A proper execution of the CPET helps in the interpretation of the CPET data.

A correct interpretation of the CPET parameters requires knowledge about the normal response to exercise of these parameters. The 9-panel plot of Wasserman can help with the visual inspection of the normalcy of the exercise response [78]. An example with typical responses is shown in Figure 6. Normal responses of trajectories during exercise are important in this regard, because they provide the frame of reference for a normal response to exercise [77]. Recently we have reviewed the most recently published CPET parameters for both children and adults [79]. One should use appropriate pediatric reference values for proper interpretation of the CPET data [79]. This is important since we have outlined above that children's physiological response to exercise differs from that of adults. Growth, gender, and geographical region are important Each exercise laboratory must select an appropriate set of reference values that best reflect the characteristics of the (patient) population tested, and equipment and methodology utilized [79].

In addition, we have developed a systematic approach for the analysis of pediatric CPET data (see Figure 7) [80]. First, when a patient is referred for a CPET there should be a clear rationale for doing the test. Secondly, a check on technical and systematic errors should be done and potential errors should be reported (e.g. malfunctioning saturation probe, talking during the test, a non-steady cadence during cycling, etc.).

Thirdly, one should check whether the patient performed a maximal effort. In children with respiratory disease, the peak heart rate is often below 195 bpm because of the ventilatory limitation. RER_{peak} is an important parameter to check, it should be at least 1.0 at peak exercise in children.

Fourthly, the determination of the aerobic fitness is the next step. The $\dot{V}O_{2peak}$ is of great clinical relevance as it uncovers the (patho)physiological mechanisms impairing this parameter. Both

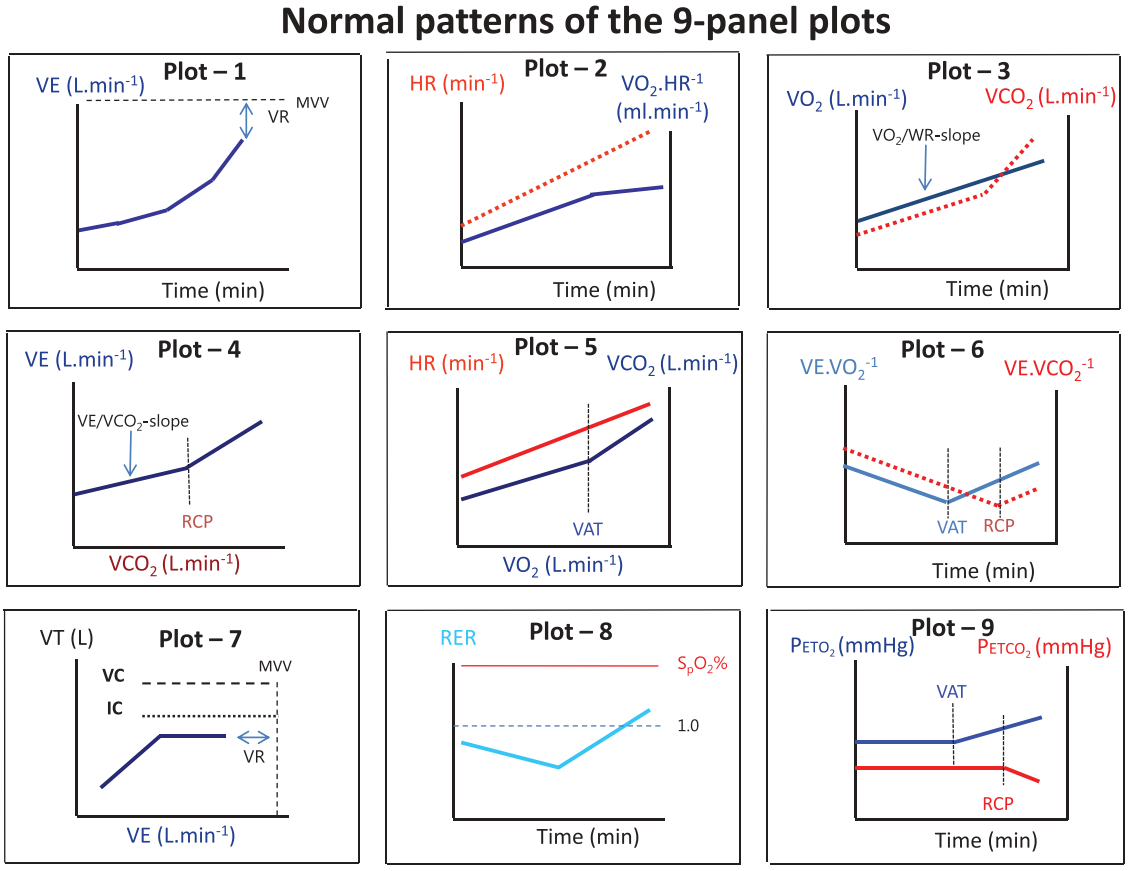


Figure 6. Typical responses of CPET data.

$\dot{V}O_{2peak}$ and $\dot{V}O_{2peak/kg}$ should be considered. Patients with overweight/obesity will have a relatively better $\dot{V}O_{2peak}$ and a lower $\dot{V}O_{2peak}$. Patients with a low body mass have a better $\dot{V}O_{2peak/kg}$ relative to $\dot{V}O_{2peak}$. In case of a submaximal effort, conclusions concerning aerobic fitness based on $\dot{V}O_{2peak}$ cannot be drawn and these CPET data should be interpreted with caution.

The fifth step is the determination of physiological limitations. The analysis of the data includes the question of which physiological limitation contributes most dominantly to exercise capacity. The potential limitations can be subdivided into respiratory responses, gas-exchange, cardiovascular responses, and muscle metabolism responses. Additionally, deconditioning should also be included as a possible exercise-limiting factor as this is often inherent to a chronic medical condition.

The sixth step is symptom perception of a child during exercise. Symptom perception is an important element that should be done when performing a CPET (See paragraph 3.8).

Seventhly, a complete and clear report including 9-panel plots (see below) is necessary to provide specific feedback and information on the conclusions and physiological findings of the test. The format of the report follows the above described steps.

Normal responses during exercise are often displayed using a graphical approach, the so-called 9-panel plots [78]. In plot 1: ventilation versus time is displayed. Also from this graph, the VR can be seen since this is the difference between the $\dot{V}E_{peak}$ and MVV. In plot 2, the heart rate and oxygen pulse (= $\dot{V}O_2$/HR) against time are displayed. Heart rate should increase toward the predicted value (± 195 bpm in healthy children). The peak heart rate might be somewhat lower in children with a ventilatory limitation. VR might be reached before the cardiac function reaches its maximum. The oxygen pulse should increase with exercise and might plateau during sub-maximal exercise intensity. In plot 3: $\dot{V}O_2$ en $\dot{V}CO_2$ vs time are shown. $\dot{V}O_2$ should increase linearly with exercise intensity, while the $\dot{V}CO_2$ should display a breakpoint.

Near maximal exercise $\dot{V}CO_2$ should become higher than $\dot{V}O_2$. From this graph, the $\dot{V}O_2$/WR-slope can be calculated as well. In plot 4 ventilation vs $\dot{V}CO_2$ is depicted. From this graph, the $\dot{V}E/\dot{V}CO_2$-slope can be calculated. An increased $\dot{V}E/\dot{V}CO_2$-slope is indicative of hyperventilation and/or a ventilation perfusion mismatch. In plot 5 heart rate vs $\dot{V}O_2$ and $\dot{V}CO_2$ vs $\dot{V}O_2$ are depicted. Using the V-slope method, the VAT can be determined in this graph [81]. Also the normalcy of the heart rate increase for exercise intensity (VO_2) can be observed. In plot 6, the $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ are depicted over time. Ventilatory efficiency as well as the VAT and RCP can be appreciated form this graph. In plot 7, the VT is displayed against ventilation. Exercise-induced bronchoconstriction can be seen in this graph as a sudden decrease in VT during exercise. Also VR can be appreciated from this graph. In plot 8 the RER and saturation are displayed over time. When exercise start, RER decreases somewhat from resting value. Usually resting RER is between 0.7 and 0.9. With increasing exercise intensity, RER is also increasing. In children, a minimal RER of 1.0 should be reached if the child does not have a ventilatory

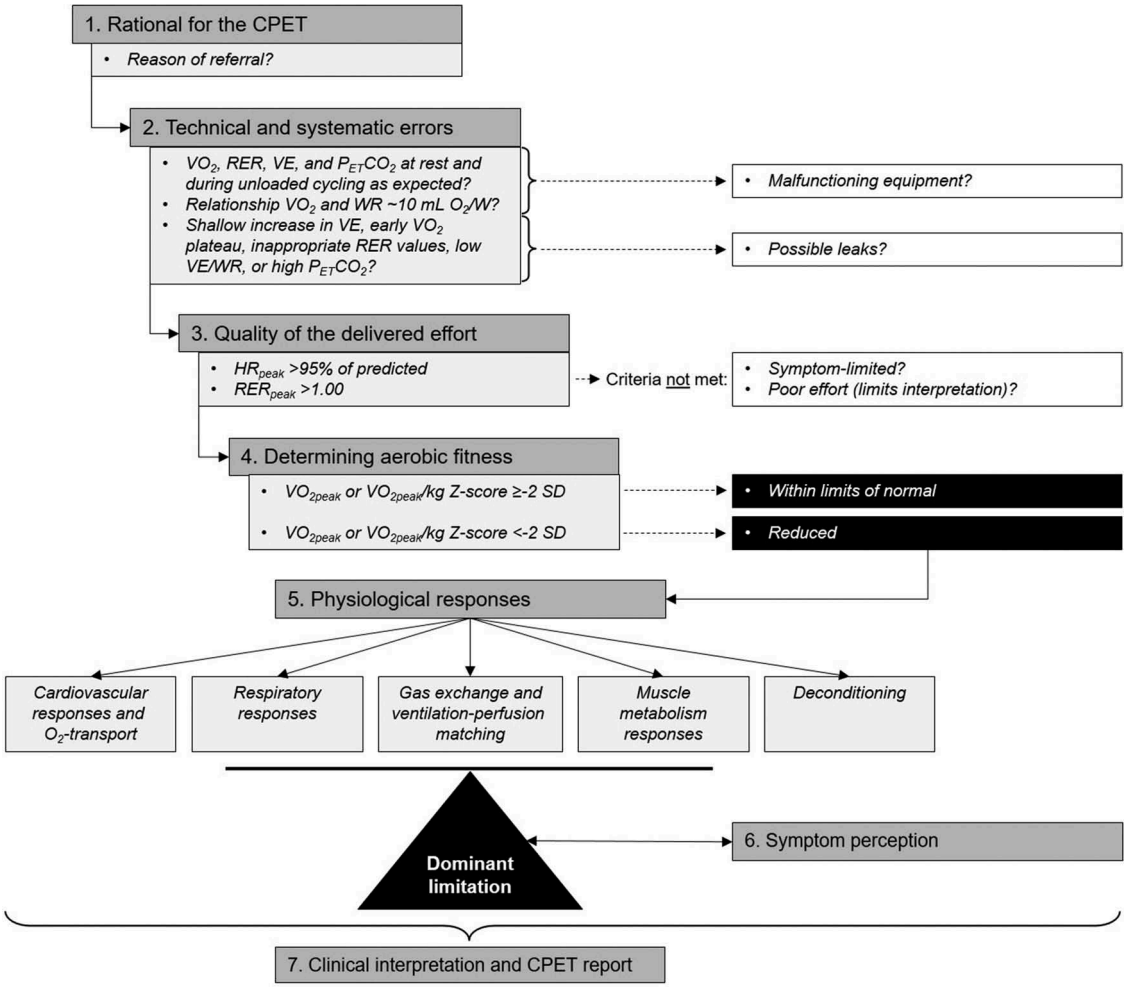


Figure 7. The seven-step interpretative strategy for a pediatric CPET.

Abbreviations: BR = breathing reserve; CPET = cardiopulmonary exercise test; HR_{peak} = heart rate at peak exercise; HRR = heart rate reserve; $PETO_2$ = partial end-tidal oxygen tension; RER = respiratory exchange ratio; RER_{peak} = respiratory exchange ratio at peak exercise; SD = standard deviation; VE = minute ventilation; VE/WR = ratio between the minute ventilation and work rate; VO_2 = oxygen uptake; WR = work rate. From [80] with permission.

limitation. Saturation should be stable between 96% and 100% during exercise. In plot 9, the $PETCO_2$ en $PETO_2$ versus time is displayed. From this graph, the VAT (point where $PETO_2$ is increasing) and RCP (point where $PETCO_2$ is decreasing) can be appreciated. In the case of hyperventilation, $PETO_2$ values are high, with low $PETCO_2$ values.

Efforts to standardize CPET reports have previously been made [27]. In our experience with physicians referring children for a CPET, the most important information they would like to receive is regarding the normalcy of exercise responses, whether dominant limiting physiological systems or even pathophysiological patterns can be observed, and whether their clinical question(s) can be answered. Although not all CPET parameters make sense to physicians, a comprehensive and standardized pediatric CPET report including a clear interpretation of the exercise data is indispensable to provide specific feedback about the CPET results [27].

5. Conclusions and future directions

The respiratory response to exercise is very informative to study during growth and development. Many patients who are referred for exercise-induced respiratory complaints, only experience these complaints during exercise when the respiratory system is challenged. Studying the exercise response using a CPET can help to identify and quantify the limitations during exercise and evaluate/treat to minimize these limitations.

However, many of the ventilatory CPET parameters are not commonly reported in scientific publications. Moreover, parameters are calculated and reported using different methods. This impedes the comparison between studies and the establishment of a database with reference values. There is a strong call for pediatric CPET data harmonization [82].

6. Expert opinion

CPET is still an underused testing modality. Many clinicians are not yet familiar with the diagnostic and prognostic possibilities of cardiopulmonary exercise testing. However, CPET is increasingly being recognized as a supplementary diagnostic and evaluative tool in the clinic. Cardiorespiratory fitness has been recognized by the American Heart Association as a vital sign [83].

CPET is an important instrument to identify the causes of unexplained dyspnea on exertion or exercise intolerance in

children with respiratory diseases. Many different parameters can be obtained during a CPET. More information beyond the $\dot{V}O_{2max}$ and the $\dot{V}E_{max}$ can be obtained from the test. Ventilatory reserve is one of them. It is an important parameter to assess the ventilatory demands and ventilatory capacity. Children have smaller lungs compared to adults. When they breathe at higher lung volume, it requires a greater work to overcome the increased elastic force. The length–tension relationship can be impaired in children with respiratory diseases because of the dynamic hyperinflation in rest and during exercise. Correct interpretation of ventilatory responses during exercise can help to guide a respiratory and/or physical therapy treatment program.

In this review, we have described the response of many ventilatory parameters and its change during growth and development. In addition, we have provided an approach for the systematic interpretation of CPET data. However, as CPET results are influenced by age, gender, body composition, and physical activity level, ethnicity/nationality, etc., we need to address these factors in our reference values [79]. We therefore need to have more and better reference values to assess the normalcy of CPET results. A lot of work is still required for this. In addition, many reference values are lacking for young children between 4 and 8 years of age. In this age group, there are many children with respiratory complaints and reference values for respiratory parameters are very welcome.

Funding

This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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