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Cardiopulmonary Exercise Testing in Pediatrics

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Abstract

Aerobic fitness is an important determinant of overall health. Higher aerobic fitness has been associated with many health benefits. Because myocardial ischemia is rare in children, indications for exercise testing differ in children compared to adults. Pediatric exercise testing is imperative to unravel the physiological mechanisms of a reduced aerobic fitness and to evaluate intervention effects in children and adolescents with a chronic disease or disability. Cardiopulmonary exercise testing includes the measurement of respiratory gas exchange and is the gold standard for determining aerobic fitness, as well as for examining the integrated physiological responses to exercise in pediatric medicine. As the physiological responses to exercise change during growth and development, appropriate pediatric reference values are essential for an adequate interpretation of the cardiopulmonary exercise test.

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Remarkable physiological, anatomical, and psychological transformations due to growth, maturation, and development affecting physical fitness occur during childhood and adolescence. Physical fitness is a principal concept in (clinical) exercise physiology and can be considered as an integrated measure of most, if not all, body functions involved in the performance of daily physical activity and physical exercise[1]. These body functions include aerobic fitness, body composition, muscular strength, power, speed, balance, flexibility, and hand-eye coordination[2]. A high level of physical fitness in childhood and adolescence has been linked to reduced risk for obesity and cardiovascular diseases, and improved musculoskeletal health and mental health[1,3]. Pediatric exercise testing is a valuable, non-invasive procedure to evaluate physical fitness throughout childhood and adolescence.

Aerobic fitness is one of the most important components of physical fitness. A higher aerobic fitness has been related to a lower morbidity and mortality in healthy adults[4,5] and in adults with cardiovascular and pulmonary diseases[6]. In children and adolescents, aerobic fitness also has been reported to be an important marker of health. For example, aerobic fitness has been found to be inversely associated with total adiposity[7] and cardiovascular risk factors[8]. Moreover, in children and young adults with congenital heart or lung disease a low aerobic fitness predicts morbidity and mortality at later years[9-12].

The measurement of maximal oxygen uptake (VO_{2max}) or peak oxygen uptake (VO_{2peak}) during a progressive cardiopulmonary exercise test up to maximal exertion is widely considered the gold standard for assessing aerobic fitness[13,14]. The non-invasive and dynamic nature of the performed measurements during cardiopulmonary exercise testing provides important information that can be utilized for (differential) diagnostic, prognostic, and evaluative

purposes in medicine. As opposed to healthy children, children with a chronic condition are often restricted in their participation in physical activities and sport programs as a consequence of real or perceived limitations imposed by their condition. The chronic condition itself often causes hypoactivity, which leads to a deconditioning effect, a reduction in functional ability, and a downward spiral of further hypoactivity[15]. Hypoactive children are often at greater risk of preventable health problems such as obesity and cardiometabolic diseases. Many children with a chronic condition have reduced levels of aerobic fitness, as can be seen in Figure 1. This figure depicts VO_{2peak} z-scores in different chronic conditions collected in studies performed by our research group. The reduced levels of aerobic fitness are generally caused by a combination of disease-related pathophysiology, treatment (e.g., medication), hypoactivity, and deconditioning.

Next to adjusting and optimizing treatment and disease management, results from pediatric exercise testing are increasingly utilized to compose individually tailored exercise training programs. A physical exercise training program might be indicated when aerobic fitness is significantly reduced compared to sex- and age-matched normative values (i.e. lower than -2 standard deviations). Through individualized physical exercise training, the capacity of the pulmonary, cardiovascular, hematopoietic, neuromuscular, musculoskeletal, and metabolic systems, and thereby aerobic fitness, increases considerably.

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Pediatric Exercise Physiology

During physical exercise, adequate interactions are required between different physiological systems, in order to transport an adequate amount of oxygen and nutrients to the exercising muscles, and to remove metabolically produced products like carbon dioxide from the exercising muscles. These responses of the individual physiological systems are linked to cell respiration with the aim to maintain homeostasis, with adequate responses to exercise-induced allostatic load (allostasis). The cardiopulmonary system is continuously stressed during progressive physical exercise to facilitate an increase in oxygen transport. Oxygen transport enlarges due to increases in cardiac output (heart rate × left ventricular stroke volume), minute ventilation (breathing frequency × tidal volume), and the arteriovenous oxygen difference, when the exercising muscles require more oxygen to sustain muscular contractions.

Aerobic fitness, aerobic capacity, aerobic power, maximal aerobic power, aerobic work capacity, cardiopulmonary fitness, cardiorespiratory fitness, cardiovascular fitness, and VO_{2max} all refer to the same concept and can be defined as the maximal capacity of the pulmonary and cardiovascular system to take up and transport oxygen to the exercising muscles, and of the exercising muscles to extract and utilize oxygen from the blood for aerobic energy production during progressive exercise with large muscle groups up to maximal exertion. According to the Fick equation[24], VO_{2max} is the product of the maximal cardiac output and the maximal arteriovenous oxygen difference. Each of the systems involved in the pathway for oxygen from the atmosphere to the mitochondria might be a physiological limiting factor for VO_{2max}. A 'true' VO_{2max} requires a clear plateau (asymptote) in oxygen uptake despite an increasing work rate

(exercise intensity). Since this plateau is infrequently observed in adults[25], as well as in children and adolescents[26,27], the highest measured oxygen uptake (VO_{2peak}) is often used interchangeably with VO_{2max} to define aerobic fitness.

During the initial phase of progressive physical exercise, increased cardiac output is primarily regulated by an increased left ventricular stroke volume, in response to an increase in the volume of blood filling the heart (the end diastolic volume), when all other factors remain constant (Frank-Starling mechanism). It is assumed that when exercise intensity increases (as of about 50% of VO_{2max}), cardiac output will increase mainly by further increases in heart rate. It is of great importance to realize that maximal heart rate is genetically predetermined, as well as that the maximal heart rate achieved by children and adolescents is independent of age[28]. While maximal heart rate decreases with age in adults[29], the maximal heart rate remains relatively stable around 195 (bicycle) to 200 beats per min (treadmill) in children and adolescents[30]. Furthermore, the maximal left ventricular stroke volume during progressive physical exercise differs significantly between children and adults. Compared to adults, children obtain a smaller left ventricular stroke volume during exercise, which they compensate for by a higher heart rate during exercise. The smaller left ventricular stroke volume in children and adolescents is an important limiting factor of their oxygen transport system.

The increased minute ventilation during the early stages of progressive physical exercise can be almost completely explained by increases in tidal volume. When the tidal volume equals approximately 50% of the vital capacity of the lungs, minute ventilation increases merely exclusively by increases in breathing frequency. There are specific developmental aspects noticeable during childhood and adolescence, such as an increase in minute ventilation and the

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efficiency of ventilation with age[30]. The latter can be explained by a decreasing breathing frequency, coinciding with an increasing tidal volume and depth of breathing[30].

During progressive physical exercise up to maximal exertion, ventilation is seldom an exercise-limiting factor. Children with significant lung disease can develop a pulmonary limitation to exercise which can contribute to exercise intolerance and dyspnea. In these children, ventilation may be insufficient for the metabolic demand, as demonstrated by an inadequate breathing reserve (BR): BR = [(maximal voluntary ventilation (MVV) – minute ventilation at peak exercise (VE_{peak}))/(MVV × 100)]. BR is normally higher than 15% at peak exercise; a BR below 15% might be indicative of expiratory flow limitation, dynamic hyperinflation, and or the retention of arterial carbon dioxide. In children, MVV can be estimated by multiplying FEV_1 by 35[31]. It is possible that a ventilatory limitation restricting maximal exercise capacity only exists in children and adolescents with a moderately-to-severely reduced lung function (predicted forced expiratory volume in one second, FEV_1, below 65%)[15]. These children might also develop gas exchange impairments with exercise, as demonstrated by decreased peripherally measured oxygen saturation (SpO_2) and or an increased partial end-tidal carbon dioxide tension ($P_{ET}CO_2$).

The arteriovenous oxygen difference and the oxygen transport capacity of the blood are also of importance during physical exercise. The arteriovenous oxygen difference refers to the difference in oxygen concentration between the arterial blood and the venous blood. This represents the amount of oxygen that is extracted from the blood and utilized by the exercising muscles and organ systems. During maximal exercise, there is no difference in arteriovenous oxygen difference between prepubertal boys and girls[32,33]. However, postpubertal boys have

higher arteriovenous oxygen difference than that of postpubertal girls. Adult men and women have a considerably greater maximal arteriovenous oxygen difference compared to boys and girls[34]. In adults, men demonstrate higher arteriovenous oxygen difference than women. During submaximal exercise, the arteriovenous oxygen difference is somewhat higher in children compared to adults[15,34]. This phenomenon can be explained by the fact that children compensate for their lower cardiac output by extracting relatively more oxygen from the blood. The oxygen transport capacity of the blood increases slowly during childhood, resulting in significant sex-differences in adulthood. On average, adult men have a higher hemoglobin concentration in their blood compared to adult women[35]. The most commonly observed cardiovascular, pulmonary, and metabolic adult-child differences are depicted in Table 1.

Pediatric Exercise Testing in Clinical Practice

The determination of oxygen and carbon dioxide concentrations in expired air at regular intervals throughout a cardiopulmonary exercise test up to maximal exertion is the gold standard for the determination of VO_{2max} or VO_{2peak}. In addition, the integrated response of different physiological systems (the cardiovascular, pulmonary, hematopoietic, neuromuscular, musculoskeletal, and metabolic systems) can be objectively evaluated at rest, during progressive exercise up to maximal exertion, and during recovery. This integrative approach and analysis of the different physiological systems are of additional value compared to the evaluation of each physiological system separately at rest. The non-invasive and dynamic nature of the performed measurements provides the clinician important information that can

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be used for diagnostic, prognostic, and evaluative purposes[30]. Exercise testing can be used to identify physiological causes for exercise-related complaints and symptoms, as well as to assess (functional) exercise capacity and exercise limiting factors, including pathophysiological changes. Therefore, cardiopulmonary exercise testing can support physiological reasoning and clinical decision-making. Next to its well-recognized value in cardiology, pulmonology, and in sports medicine, many other medical specialties (e.g., metabolic disorders, oncology) are currently showing their interest in the data and interpretation of cardiopulmonary exercise testing, often omitting more comprehensive assessments.

VO_{2max} or VO_{2peak} is one of the best known and most frequently determined cardiopulmonary exercise test parameter. For clinicians and researchers, normative values for VO_{2peak} facilitate adequate interpretation of aerobic fitness. Pediatric normative values for VO_{2peak} normalized for body mass are depicted in Figure 2. However, in addition to VO_{2peak}, several other parameters should be determined to help an adequate and complete interpretation of the cardiopulmonary exercise test. These parameters, their derivatives, and perceptual responses of the child are a direct or indirect reflection of the previously mentioned integrated physiological interactions during physical exercise. A selection of relevant exercise parameters is summarized in Table 2.

There are different methodologies to perform a cardiopulmonary exercise test, and many exercise laboratories use their own standardized protocols. When a child's performance is compared to reference values, it is necessary to standardize the cardiopulmonary exercise test according to the testing procedures and methodology that were used to establish the reference values[30]. In addition, the choice for an appropriate exercise protocol is dependent on

the complaints and symptoms, as well as on the physical fitness level of the child. The Bruce protocol is the most frequently used treadmill protocol for cardiopulmonary exercise testing in children and adolescents[37]. However, important physiological measurements during exercise, including the electrocardiogram and blood pressure, are easier to assess and of better quality using a cycle ergometer. Moreover, maximal work rate can be assessed accurately using a cycle ergometer, which is not feasible when using a treadmill. In young children, the speed of the treadmill protocol is often a restrictive factor. When performing a cardiopulmonary exercise test using a cycle ergometer, the Godfrey protocol[38] is very frequently used in children and adolescents. A strong advantage of cycle ergometry is the fact that the test will not be easily constrained by mechanical limitations of a patient (e.g., deviant walking patterns, soreness in ankle and knee joints) and a lower chance of movement artefacts in the electrocardiogram and blood pressure measurements.

For an adequate and complete interpretation of the acquired cardiopulmonary exercise test data, it is essential that the participant delivers a maximal effort. Although the integrated physiological response to exercise is measured objectively during cardiopulmonary exercise testing, performance during exercise testing strongly depends on the motivation of the participant. Consequently, motivating and encouraging the participant prior to and during the cardiopulmonary exercise test is very important, especially in children. As already mentioned, the leveling-off of oxygen uptake despite continuing exercise and increasing work rate is considered the best evidence of a maximal effort. The absence of a clear plateau in oxygen uptake at the end of an exercise test results in a dilemma. Has the participant performed an effort at, or near, the maximal level, despite the lack of a plateau in oxygen uptake? There are

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other objective physiological criteria available for this decision. For pediatric populations, it is recommended to use heart rate at VO_{2peak} of at least 95% of 195 beats per min and the respiratory exchange ratio (RER, carbon dioxide production divided by oxygen uptake) at VO_{2peak} of at least 1.00 as supplementary criteria of a maximal effort during cardiopulmonary exercise testing on a cycle ergometer[39]. In addition, subjective criteria of a maximal effort (e.g., sweating, facial flushing, unsteady biking, and clear unwillingness to continue exercising despite strong encouragement) are valuable factors in drawing this conclusion.

Performance at a cardiopulmonary exercise test on a cycle ergometer is primarily measured by the attained VO_{2peak} and the achieved peak work rate. When it is expected that a pediatric patient has a significantly reduced aerobic fitness, an exercise protocol in which the work rate increases more slowly is preferred. If the work rate increases too fast, the maximal cardiopulmonary exercise test will be terminated prematurely, without maximally stressing the pulmonary, cardiovascular, and metabolic systems. The latter indicates that the child performed a submaximal effort, which severely restricts the interpretation of the cardiopulmonary exercise test. The ideal duration for a maximal cardiopulmonary exercise test is between 6 and 10 minutes for children[40], and between 8 and 12 minutes for adolescents and adults[41], and depends on the child's fitness. Experience has shown that children from six years of age can validly perform a cardiopulmonary exercise test in an exercise laboratory[42]. There is still debate concerning the minimal age for performing a cardiopulmonary exercise test, since there are large inter-individual differences. The main premise is that the child is able to understand instructions, as well as to cooperate according to these instructions. A necessity for measuring younger children is the availability of special equipment such as a pediatric treadmill

or cycle ergometer, especially for children below 125 cm in stature. In the Wilhelmina Children's Hospital of the University Medical Center Utrecht, children as young as 4 to 5 years of age have been tested successfully.

Conclusion

The cardiopulmonary exercise test is an important physiological investigation that can aid clinicians in their evaluation of exercise intolerance and dyspnea, as well as in their physiological reasoning and clinical decision-making. VO_{2max} is the gold-standard measure of aerobic fitness and is determined by the variables that define oxygen delivery in the Fick equation (VO_2 = cardiac output × arteriovenous oxygen difference). Of the variables involved in oxygen delivery and utilization, the limitations of the cardiovascular system are the major factors responsible for limiting exercise in healthy children, as ventilation and gas exchange are sufficient to maintain arterial oxygen content up to peak exercise.

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Figure Legends:

Figure 1. Aerobic fitness (VO_{2peak}) of children with a chronic condition. Abbreviations: ALL=acute lymphoblastic leukemia; AP=achondroplasia; CF=cystic fibrosis, CP=cerebral palsy; ESRD=end-stage renal disease; JIA=juvenile idiopathic arthritis; OI=osteogenesis imperfecta; SB=spina bifida; VO_{2peak}=highest measured oxygen uptake. Note: data is extracted from studies of our research group[16-23].

Figure 2. Age-related centile charts for aerobic fitness (VO_{2peak}/kg) for boys (left graph) and girls (right graph). Abbreviations: VO_{2peak}=highest measured oxygen uptake per kilogram body mass**.** Note: adapted from Bongers et al.[30]

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Table 1: Commonly observed differences in exercise physiological parameters between adults and children.

Variable	Difference with Adults
Cardiovascular	
VO_{2peak} ($L \cdot min^{-1}$)	Lower
VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$)	Higher
Submaximal HR ($beats \cdot min^{-1}$)	Higher
HR_{peak} ($beats \cdot min^{-1}$)	Higher
Stroke volume (sub)max ($mL \cdot beat^{-1}$)	Lower
Cardiac output (at $\%VO_{2peak}$)	Lower
Arteriovenous oxygen difference (at $\%VO_{2peak}$)	Higher
Blood flow to muscle	Higher
Systolic and diastolic blood pressure (mm Hg)	Lower
Myocardial ischemia	Rare
Pulmonary	
Tidal volume (L)	Lower
Breathing frequency ($breaths \cdot min^{-1}$)	Higher
VE_{peak} ($L \cdot min^{-1}$)	Lower
Ventilatory drive (VE/VCO_2-slope)	Higher
Ventilatory efficiency (VE/VO_2)	Lower
Metabolic	
Fat oxidation	Higher
Carbohydrate oxidation	Lower
Peak blood lactate	Lower
Glycolytic capacity	Lower
A-lactic capacity	Lower
Lactate clearance	Same
Recovery after high-intensity exercise	Faster

Abbreviations: HR=heart rate; HR_{peak}=peak heart rate; VE_{peak}=peak minute ventilation; VCO_2=carbon dioxide exhalation; VO_{2peak}=peak oxygen uptake.

Table 2: Selection of important parameters measured during cardiopulmonary exercise testing in pediatric populations.

Set-up for CPET	Apparatus	Primary outcome	Derivative
	Pulse oximeter	SpO_2	
	Spirometry	FEV_1	Ventilatory reserve
	Volume measurements	V_E, TV, BF	EqO_2, $EqCO_2$ V_E/VO_2, V_E/VCO_2 OUE, OUEP, OUES
	Respiratory gas analysis	$P_{ET}O_2$, $P_{ET}CO_2$, VO_2, VCO_2	
	ECG	Heart rhythm, HR	RER Ventilatory threshold
	Cuff with a detector for Korotkoff sounds	Blood pressure	O_2-pulse
	Ergometer	WR	$\Delta VO_2/\Delta WR$
	Borg-scale or VAS	Dyspnea, leg fatigue	

Abbreviations: BF=breathing frequency (breaths·min^{-1}); CPET=cardiopulmonary exercise testing; ECG=electrocardiogram; EqO_2=ventilatory equivalent for oxygen; $EqCO_2$=ventilatory equivalent for carbon dioxide; FEV_1=forced expiratory volume in one second (L); HR=heart rate (beats·min^{-1}); OUE=oxygen uptake efficiency; OUEP=oxygen uptake efficiency plateau; OUES=oxygen uptake efficiency slope; $P_{ET}CO_2$=partial end-tidal carbon dioxide tension (mmHg); $P_{ET}O_2$=partial end-tidal oxygen tension (mmHg); RER=respiratory exchange ratio; SpO_2=peripheral oxygen saturation (%); TV=tidal volume (L); VAS=visual analog scale; VCO_2=carbon dioxide production (L·min^{-1}); V_E=minute ventilation (L·min^{-1}); V_E/VCO_2=slope of the relationship between the minute ventilation and carbon dioxide production; V_E/VO_2=slope of the relationship between the minute ventilation and oxygen uptake; VO_2=oxygen uptake (L·min^{-1}); $\Delta VO_2/\Delta WR$=oxygen cost of work (mL·min^{-1}·W^{-1}); WR=work rate (W).

Note: adapted and modified from Bongers[36].

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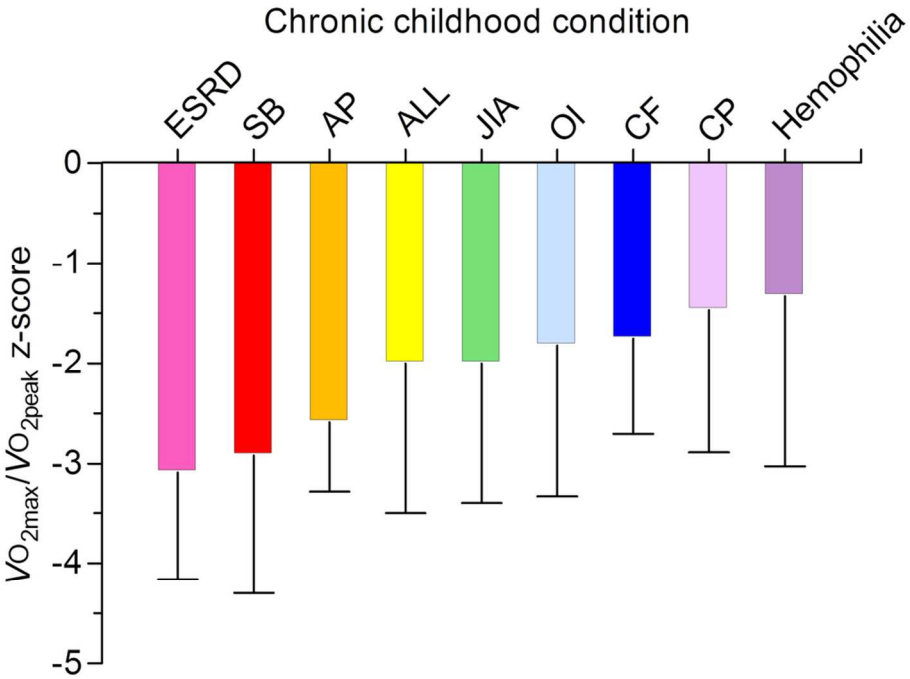

Figure 1

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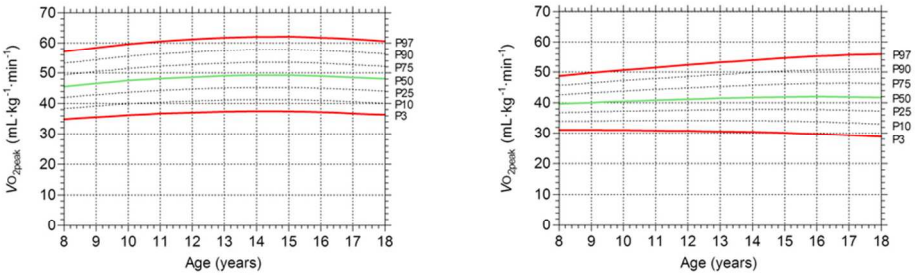

Figure 2

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