

REVIEW PAPER

Cardiopulmonary exercise test as a diagnostic tool in chronic diseases in children and adolescents

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ABSTRACT

Exercise testing is a diagnostic tool, which is permanently used in the diagnostic process of children with cardiovascular diseases. The ergospirometric test, otherwise known as the cardiopulmonary exercise test, is a widely used, non-invasive method of assessing the cardiovascular and respiratory response to exercise, both in adults and in children. The usual exercise test broadened with the analysis of the concentration of oxygen and carbon dioxide in exhaled air allows a more precise diagnosis of exercise intolerance, provides a possibility of differentiating the aetiology of this condition, and allows the assessment of the applied treatment method. Paediatric standards for ergospirometry have not been determined yet. In Poland, the ergospirometric test is still an underestimated tool for assessing physical performance and the impact of various childhood diseases on the cardiovascular and respiratory systems.

KEY WORDS:

child, exercise test, oxygen consumption.

INTRODUCTION

Ergospirometry, also known as the cardiopulmonary exercise test (CPET), is a worldwide, commonly used, non-invasive method of assessing cardiovascular and respiratory response to physical exercise in both adults and children. The typical exercise test combined with analysis of the concentration of oxygen and carbon dioxide in exhaled air allows a more precise diagnosis of impaired exercise tolerance, creates the possibility of differentiating the aetiology of this condition, and allows the assessment of the effectiveness of the applied treatment. An abnormal result of the ergospirometric examination has been identified as a significant independent risk factor for morbidity and mortality in adults and in long-term follow-up of children with heart failure, pulmonary hypertension, Fontan circulation, after correction of the transposition of the great arteries, or correction of the tetralogy of Fallot.

Somatic development, pubescence, and physical fitness are factors affecting physiological response of an organism to a given physical load. For this reason, paediatric standards for ergospirometric testing have not yet been established. In Poland, the ergospirometric test is still an underestimated tool for assessing physical performance and the impact of various childhood diseases on the cardiovascular and respiratory systems. The purpose of this publication is to present ergospirometry as a valuable diagnostic tool also in the group of paediatric patients [1].

Exercise test is a diagnostic tool that has become a permanent part of the diagnostic process in children with cardiovascular diseases. In this population, impairment of physical exercise tolerance is often observed, which may be the result of a primary cardiac problem, applied treatment or reduced physical activity. The cardiopulmonary exercise test aims to provide objective information on exercise capacity, assess response to a given

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exercise load, and assess the efficacy of both pharmacological and surgical treatment in children with cardiovascular diseases, as well as evaluation of safety to engage in physical activities for cardiology patients by specifying individual physical performance standards, which results in better treatment outcomes in these patients [2].

CPET is increasingly used in the diagnosis of cardiovascular diseases. It provides new diagnostic data, facilitates the selection of optimal treatment and planning of rehabilitation, and provides important prognostic parameters. Ergospirometry is a non-invasive, reliable and safe diagnostic method that relies on the analysis of respiratory gases during increased physical exercise. During the test, respiratory minute ventilation and changes in exhaled gas concentrations ($p\text{CO}_2$, $p\text{O}_2$) are assessed, blood oxygen saturation and heart activity are monitored, and blood lactate concentration can be determined. The basic and most important parameter determined during CPET is the maximum oxygen consumption ($\text{VO}_2 \text{ max}$), or rather the peak oxygen consumption ($\text{VO}_2 \text{ peak}$), which is the volume of oxygen absorbed at the peak of exertion. Another important parameter derived from VO_2 is the so-called oxygen pulse (VO_2/HR), which is the ratio of the volume of oxygen consumed to the heart rate. This indicator is a measure of the metabolic efficiency of the myocardium because it indicates the volume of oxygen absorbed during one heart cycle [3].

CPET is an important diagnostic test that can help clinicians diagnose exercise intolerance and dyspnoea on exertion. $\text{VO}_2 \text{ max}$ is the gold standard for measuring aerobic capacity and is dependent, according to the Fick rule, on the cardiac output and the systemic arteriovenous difference in oxygen concentration in blood ($\text{VO}_2 = \text{SV} \times \text{HR} \times \text{AVd}$). In healthy people, the efficiency of the cardiovascular system is the factor that is most responsible for limitation of physical exercise tolerance, because ventilation and gas exchange are sufficient to maintain arterial O_2 content up to the peak of exercise. Although cardiac and pulmonary aetiologies are the most common causes of dyspnoea and intolerance of exercise, neurological, metabolic, haematological, endocrine, and psychiatric disorders may contribute to these symptoms. Data collected from an ergospirometric study can provide valuable information to distinguish these causes because it provides the most comprehensive and objective assessment of functional impairment and provides information on metabolic, cardiovascular, and respiratory responses to a given exertion. In addition to its role in the diagnostic process of dyspnoea and exercise intolerance, ergospirometric testing may be used for other purposes, such as determining the severity of the disease, recommending rehabilitation exercises, or assessing the effectiveness of the treatment [4].

Because the peak absorption of oxygen is influenced by age and gender, chronic diseases, pharmacological treatment and physical condition, an accurate interpre-

tation of the data obtained through this test requires appropriate reference values for each patient. The opinion of the American College of Chest Physicians/American Thoracic Society (CHEST/ATS) regarding cardiopulmonary exercise test defines $\text{VO}_2 \text{ max}$ as $< 84\%$ of the predicted value as abnormal. However, $\text{VO}_2 \text{ max}$ below the predicted value for age, but still within the limits of typical values (75–100% of the predicted value), is associated with increased mortality and therefore has clinical significance [4].

Aerobic capacity is one of the most important elements of physical fitness assessment. Better aerobic capacity is associated with lower morbidity and mortality in healthy adults as well as in adults with cardiovascular diseases and lung diseases. In children and adolescents, aerobic fitness is also taken into account as an important determinant of health. In studies conducted on this group of patients, it has been found that aerobic capacity is inversely correlated with obesity and cardiovascular risk factors. In addition, in children and young adults with congenital heart or lung defect, low aerobic capacity is a predictor of early mortality in later years [5].

The gold standard for physical fitness assessment is aerobic capacity, commonly referred to as maximum or peak oxygen uptake during an exercise test with maximum load. $\text{VO}_2 \text{ peak}$ is expressed as an absolute value in litres of oxygen per minute (l/min) or as a relative value in millilitres of oxygen per kilogram of body mass per minute (ml/kg/min). A relative value is often used to compare performance levels of patients with chronic diseases, in relation to age, weight, and severity of disease [4].

PHYSIOLOGY OF EXERCISE IN CHILDREN AND ADOLESCENTS

During the initial phase of physical exertion, the increased cardiac output is regulated mainly by the increased left ventricular ejection volume in response to the increase in cardiac blood volume (end-diastolic volume) when all other factors remain constant (Frank-Starling mechanism). It is assumed that when the intensity of the exercise increases (from about 50% of $\text{VO}_2 \text{ max}$) cardiac output is increased mainly by accelerated heart rate. Maximum heart rate is predetermined genetically, and in children and adolescents it does not depend on age. While in adults the maximum heart rate decreases with age, in children and adolescents it remains relatively stable from around 195 beats per minute (on cycloergometer) to 200 beats per minute (on treadmill). In addition, the maximum ejection volume of the left ventricle during increasing physical activity varies greatly between children and adults. Compared to adults, children have lower left ventricular ejection fraction during exercise, which is compensated by a higher heart rate. Lower left ventricular ejection fraction in children and adolescents is an important factor limiting oxygen transport during exercise [5].

In addition to the well-known value of ergospirometry in the field of cardiology, pulmonology, and sports medicine, many other medical specialties (e.g. metabolic disorders, oncology) find parameters and interpretation of data that can be obtained during cardiopulmonary exercise tests interesting and useful [5].

For the population of paediatric patients, reaching a heart rate of at least 95% of 195 beats per minute while achieving maximum rate of oxygen consumption is recommended, and the respiratory exchange ratio (RER, carbon dioxide production divided by oxygen uptake) at peak exertion should reach at least 1.00, as complementary criteria determining the maximum effort during exercise testing. In addition, the subjective criteria of maximum effort (e.g. sweating, facial flushing, unstable cycling, and a clear reluctance to continue exercising despite strong encouragement) are also taken into account as indicators of achieving maximum effort in a given patient [5].

The ideal duration of the maximum exercise test is from 6 to 10 minutes for children and from 8 to 12 minutes for adolescents and adults, and it depends on the person's fitness. Experience has shown that children from the age of six years old can perform an exercise test in a cardiac stress testing lab. Because of the individual differences in each child, the debate on the minimum age at which children should be able to perform an exercise test is still ongoing. The main assumption is that the child must be able to understand instructions and perform the test according to these instructions [5].

INDICATIONS FOR ERGOSPIROMETRIC TESTING

Ergospirometric tests have been used in clinical practice since the 1980s. They are mainly used to assess patients with chronic heart failure, especially their exercise tolerance, to determine prognosis, and to assess the impact of treatment. The most important parameter of this test is peak VO_2 [6].

The American Heart Association (AHA), American College of Cardiology (ACC), and the American Thoracic Society/American College of Chest Physicians (ATS/CHEST) recommend ergospirometry as the primary diagnostic tool for the differential diagnosis of exercise dyspnoea (class I – strong recommendation). Ergospirometry, as a test considering both cardiological and pulmonological assessment, allows simultaneous non-invasive evaluation of the haemodynamic efficiency of the heart and respiratory system response to physical exercise. It seems to be an indispensable test, especially in patients with high levels of natriuretic peptides (BNP/NT-proBNP). Only ergospirometry enables an objective diagnosis of the cause of dyspnoea upon exertion in patients with high concentrations of natriuretic peptides. It allows us to conclude whether, in a given clinical situation, we

deal with the primary dysfunction of the left ventricular muscle or the failure of the right ventricle in the course of lung or pulmonary vessels diseases. In such cases, echocardiographic diagnosis is often not accurate enough, and the result of oxygen absorption or ventilation equivalent alone will not correlate with resting morphological parameters of echocardiography [6].

The main indications for cardiopulmonary exercise testing in children with cardiac problems are the assessment of exercise capacity and the identification of exercise-induced arrhythmias, for example in preexcitation syndromes. The mechanism of dyspnoea caused by the presence of accessory pathway during sinus rhythm seems to be related to the asynchrony of ventricular contraction or a reflex response to stimulation of the heart or lung mechanoreceptors. This phenomenon occurs in patients with typical heart palpitations (Wolff-Parkinson-White syndrome), as well as in patients with no history of arrhythmia (previously recognised as patients with asymptomatic preexcitation) [7].

Children with congenital or acquired heart diseases often have impaired exercise capacity. This happens in both the preoperative and postoperative period and can be the result of the primary cardiological problem, its treatment, or reduced activity leading to physical deterioration. Lunt *et al.* stated that teenagers with congenital heart disease are less likely to achieve even minimal requirements during exercise tests. Ventricular dysfunction, residual leaks, and valvular dysfunctions may also interfere with the cardiopulmonary response to a given physical load [8].

Measurement of exercise capacity and other physiological responses provides objective information on the functional state of the heart, lungs, and peripheral muscles. This information can be crucial in the process of making clinical decisions, which result in improvement of physical performance and quality of life [8].

It is known that physical activity is also indicated in children with congenital heart defects, at every stage of treatment, also after correction of the defect. Ergospirometry is helpful in the assessment of heart function and indications for treatment, and it helps to choose the method of treatment and to assess its effectiveness. Univentricular heart, ventricular dysfunction, valvular disease, shunts, obstructions, abnormal pulmonary vasculature, and associated pulmonary and musculoskeletal disorders may impair the cardiopulmonary response to exercise. Patients with serious heart disease are advised to avoid high-intensity competitive sports, but they benefit from participation in less competitive, recreational activities. In such an approach, cardiopulmonary exercise testing can provide an individualised recommendation after interpretation of peak VO_2 [2].

As more and more children and adolescents decide to attend sports regularly, dyspnoea associated with exercise is an increasingly frequent reason for visiting a paedia-

trician. In healthy children, exercise-induced dyspnoea is often attributed to exercise-induced bronchoconstriction. In fact, exercise-induced bronchoconstriction occurs only in 8%-23% of healthy children who complain of dyspnoea during exercise. In otherwise healthy people, lung or heart disease is rarely the cause of exercise dyspnoea; however, it is necessary to exclude such a cause of dyspnoea, because it can be life-threatening. Hypertrophic cardiomyopathy (HCM) is the leading cause of sudden cardiac death in young athletes. People most at risk of sudden death are people with a history of cardiac arrest (i.e. ventricular fibrillation), ventricular tachycardia, fainting, left ventricular hypertrophy, or sudden cardiac death in the family, associated with the occurrence of HCM. The ergospirometric examination allows the differentiation of shortness of breath caused by bronchial constriction from other more serious causes of these ailments. Patients with dyspnoea during physical exercise, especially those who do not react to bronchodilators, are candidates for CPET. This test helps in the diagnostic process of the above-mentioned causes of dyspnoea induced by exercise along with bronchoconstriction also induced by exercise [9].

Dyspnoea is a common symptom induced by exercise, which is often treated improperly because the pathophysiology causing intolerance of exercise is not well understood. The problem may occur in the lungs, heart, peripheral or pulmonary circulation, concerning the content and quality of haemoglobin, metabolic disorders, psychogenic disorders, the muscles themselves, or there may be a combination of these defects. CPET allows simultaneous examination of cardiovascular and ventilatory response by measuring and interpreting numerous parameters [10].

In the diagnostic process of the problem of dyspnoea, which is commonly encountered in clinical practice, resting tests, such as lung function tests and echocardiograms, are usually conducted; however, sometimes they may be non-diagnostic. Cardiopulmonary exercise test measures physiological parameters during exercise, which can enable accurate identification of the cause of dyspnoea. Although this test has been available for decades and provides valuable and relevant physiological information about the integrated cardiopulmonary response to exercise, it remains underused [10].

In some cases, exercise-induced dyspnoea may be associated with obesity and physical deterioration, which

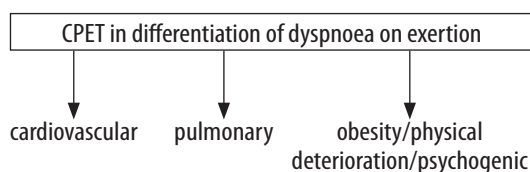


FIGURE 1. Cardiopulmonary exercise test (CPET) as a main diagnostic tool in the evaluation of unexplained dyspnoea [11]

can also be confirmed by ergospirometry and prevent further unnecessary diagnostic testing of exercise intolerance (Fig. 1) [10].

In contrast to healthy children, those with chronic diseases often have limited physical capacity and abilities as a consequence of the risks or limitations presented by the disease. Decreased exercise will worsen efficiency and reduce physical fitness. Children who are not physically active have an increased risk of acquired cardiovascular diseases and obesity. Some diseases that have been found to reduce exercise capacity in paediatric patients include: acute lymphoblastic leukaemia, kidney diseases, cystic fibrosis, juvenile idiopathic arthritis, or achondroplasia. Impaired exercise tolerance and reduced aerobic capacity may result from the combination of changes associated with the pathophysiology of the disease, the applied treatment, reduced activity, and worse physical condition. The results of paediatric cardiopulmonary exercise tests are used to optimise treatment and create individual exercise programs for patients to improve aerobic fitness by acting on the respiratory, circulatory, haematopoietic, nervous, and musculoskeletal systems [5].

One of the most common diseases of childhood age, in which oxygen impairment is observed, is juvenile idiopathic arthritis (JIA). It has been shown that aerobic capacity is impaired in children as well as in young adults with JIA. These impairments may be related to the pathophysiology of this disease, resulting from its treatment, limited physical activity, or progressive disability of the osteoarticular system. Other potential factors contributing to the reduction of aerobic capacity in JIA may include anaemia, decreased cardiac output, and muscle dysfunction [12].

It is believed that children with JIA have lower cardiopulmonary capacity and worse exercise tolerance. This means that they have more problems with performing daily activities compared to healthy children. Anaerobic capacity is important because most everyday activities performed by children are anaerobic. In the most recent study from 2016 Acer *et al.* examined whether children with JIA have lower cardiac output compared to healthy children and identified clinical features that may be associated with low aerobic capacity in children with JIA. The following were taken into consideration: age, gender, height, weight, body mass index, duration of the disease, subtype of the disease, and treatment applied in the study group. An ergometric exertion test was performed by all participants to determine cardiac output. Participants started the test with a load equal to half of their body weight and driving at 100 rpm and continued with the load, which increased by one watt for every three minutes. The peak oxygen uptake values (maximum oxygen volume consumed per minute) were recorded to assess aerobic performance. The time elapsed after exceeding the thresholds (anaerobic performance) and total test time were also recorded to measure the entire (aerobic

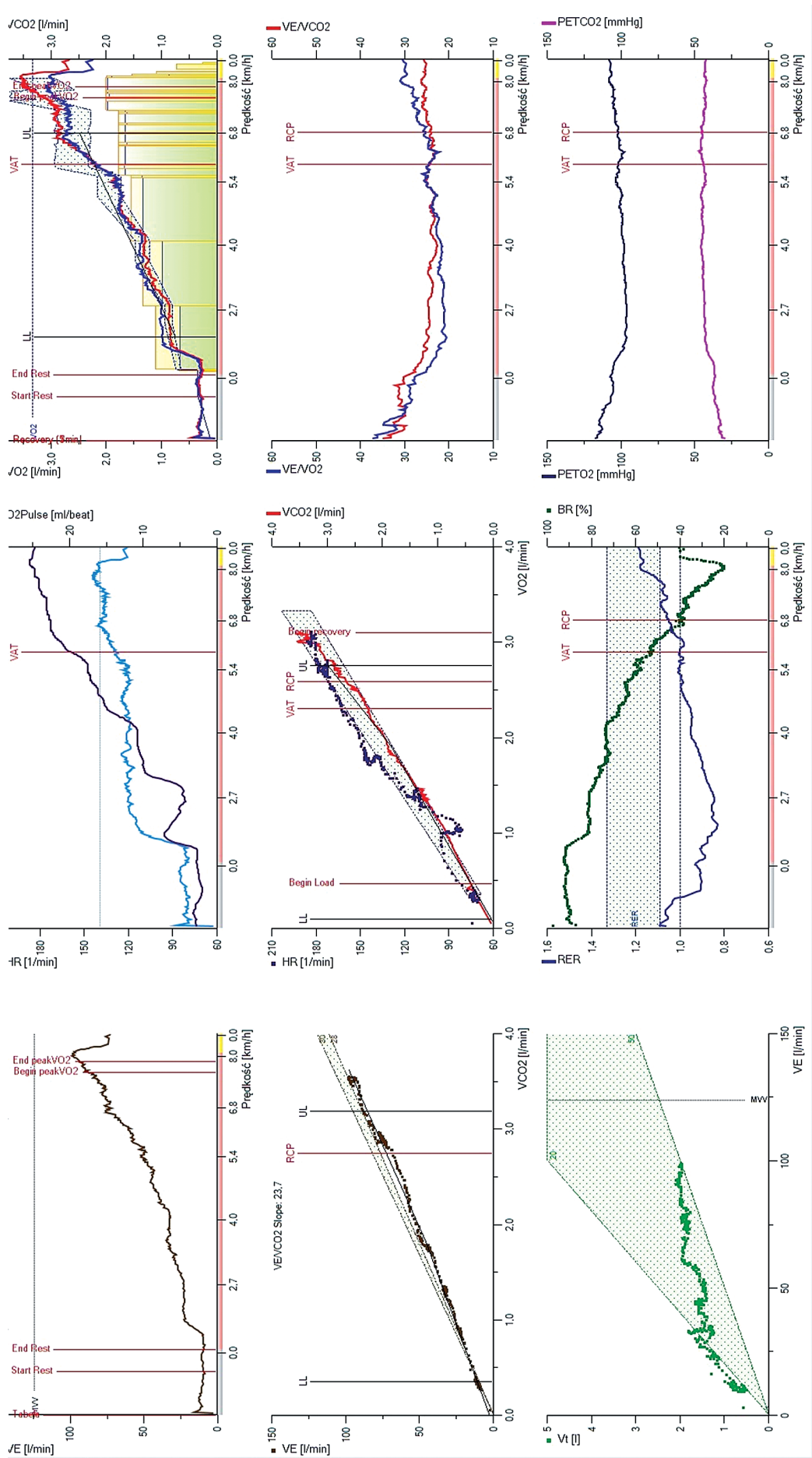


FIGURE 2. Results of cardiopulmonary exercise test presented in the form of nine graphs according to the Wasserman algorithm

TABLE 1. Mean values of cardiopulmonary exercise test results from a study conducted on paediatric patients in Holland. A study conducted by Bongers *et al.* [17]

Mean values	Boys	Girls
Age (years)	11.8 ± 2.2	12.9 ± 2.6
BMI (kg/m ²)	17 ± 2	19 ± 3
Max HR (beats/min)	193 ± 8	194 ± 8
Max RER	1.15 ± 0.06	1.16 ± 0.08
Peak VO ₂ /kg (ml/kg/min)	52.9 ± 6.7	43.6 ± 5.5

Values are presented as means with standard deviations (SD), BMI – body mass index, HR – heart rate, RER – respiratory exchange ratio

and anaerobic) cardiac output capacity. Mean cardiac volume parameters (VO₂ level for aerobic capacity and total test time for cardiac endurance) in the JIA children group were significantly lower than in the control group. Study of parameters affecting the peak oxygen uptake showed that girls had a lower peak oxygen uptake compared to boys and children with knee or hip involvement had a lower level of VO₂ peak in comparison to children without seizure of these joints. Gender and results of the disease activity questionnaire were identified as the most influential on deterioration of results in this group of patients [13].

The ergospirometric test also found application in paediatric oncology, especially in patients who survived acute lymphoblastic leukaemia (ALL) and received anthracycline treatment. Many studies have confirmed a negative effect of anthracyclines on the diastolic function of the left ventricle and exercise capacity. In a systematic review from 2005 on the subject of decreased physical fitness in survivors of childhood leukaemia VO₂ peak and physical fitness tended to be reduced in survivors of childhood ALL compared to healthy control subjects. Adequate physical activity is recommended in cancer survivors because it significantly influences the function of the left ventricle and overall body fitness [14].

The literature also contains reports on the usefulness of the ergospirometric test in the assessment of the clinical status of patients with metabolic and neuromuscular disorders. CPET may be helpful in diagnosing the disease as well as prescription of appropriate physical activity [15].

CONDUCTING THE EXAMINATION AND INTERPRETATION OF RESULTS

The ergospirometric test is an exercise test combined with the analysis of exhaled gases (oxygen and carbon dioxide). ECG electrodes are placed on the examined child, and the heart's electrical activity is visible throughout the entire examination. A special silicone mask with a mouthpiece through which patient breathes is placed over the child's mouth and nose, and the device to which it is connected analyses the composition of respiratory gases during the exercise test. CPET can be performed

on a bicycle or treadmill using appropriate protocol. An exercise test in this age group is usually performed on a treadmill using the Bruce protocol. In the Bruce protocol, participants start to exercise on a treadmill at a speed of 2.7 km/h with an incline of 10% for every three minutes. The exercise test is divided into stages, during which, after every three minutes, the effort load is increased by faster movement and increased angle of the treadmill, until reaching maximum effort or exhaustion of the patient [16]. The test is interrupted after the child reaches the appropriate parameters or after occurrence of alarming symptoms (i.e. pain, shortness of breath, dizziness). Afterwards the patient is monitored for six minutes in a state of rest and is then detached from the device. Before starting the test, the patient and doctor set signals according to which, if the patient feels tiredness or disturbing symptoms, the test is immediately interrupted. The whole test takes about 30-40 minutes and is supervised by a trained doctor at each stage.

After obtaining the basic parameters of respiratory exchange such as oxygen absorption and exhalation of carbon dioxide, so-called secondary parameters, which include: peak oxygen absorption (VO₂ max, peak VO₂), respiratory exchange ratio (RER), or anaerobic threshold (AT), are determined. The results are presented in the form of nine graphs according to the Wasserman algorithm (Fig. 2).

Interpretation of the results obtained during ergospirometric testing in children should be referred to the values due to gender, age, and body size. Despite several attempts to create standards for paediatric patients, there are very few studies in this subject conducted only for a given population (i.e. norms for Dutch children) (Table 1). It is important to conduct new studies for patients in this age group in order to create universal standards for cardiopulmonary exercise tests in children. A control exercise test carried out in a given patient may constitute a point of reference for the following CPET results, as well as helping to monitor the patient's performance over time [18].

In summary, cardiopulmonary exercise testing is still an underrated but very useful tool in the diagnostic process of many childhood diseases that cause changes in the cardiovascular or respiratory system. Due to the lack of standards for paediatric populations, especially in Poland, it is important to conduct further research in this area.

DISCLOSURE

The authors declare no conflict of interest.

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