Cardiopulmonary exercise testing in adult cardiology: expert opinion of the Working Group of Cardiac Rehabilitation and Exercise Physiology of the Polish Cardiac Society

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ABSTRACT
Cardiopulmonary exercise testing (CPET) is an important diagnostic tool in contemporary clinical practice. This document presents an expert opinion from the Working Group on Cardiac Rehabilitation and Exercise Physiology of the Polish Cardiac Society concerning the indications, performance technique, and interpretation of results for CPET in adult cardiology. CPET is an electrocardiographic exercise test expanded with exercise evaluation of ventilatory and gas exchange parameters. It allows for a global assessment of the exercise performance including the pulmonary, cardiovascular, hematopoietic, neuropsychological, and musculoskeletal systems. It provides a noninvasive dynamic evaluation during exercise and is a reference modality for exercise capacity assessment. Moreover, it allows the measurement of numerous prognostic parameters. It is useful in cardiology, pulmonology, oncology, perioperative assessment, rehabilitation as well as in sports medicine and in the evaluation of healthy people. This test not only helps to diagnose the causes of exercise intolerance but also supports the evaluation of the treatment. New opportunities are offered by combining CPET with imaging such as exercise stress echocardiography. These tests are complementary and synergistic in their diagnostic and prognostic strength.

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Introduction Cardiopulmonary exercise testing (CPET) is an important diagnostic tool that is increasingly used in cardiology. It allows to comprehensively evaluate and differentiate the causes of the limited exercise tolerance. Although this method is becoming increasingly popular, to this date, an unambiguous position of the Polish Cardiac Society (PCS) was not available. This document presents an opinion of experts from the Working Group on Cardiac Rehabilitation and Exercise Physiology of the Polish Cardiac Society concerning the indications, performance technique, and interpretation of results for CPET in adult cardiology.

Cardiopulmonary exercise testing CPET is an electrocardiographic exercise test expanded with exercise evaluation of ventilation and

gas exchange parameters. We chose the name CPET as the most consistent with international nomenclature, although other terms can be found in the literature, that is, ergospirometry and spiroergometry. In CPET, by measuring direct oxygen uptake (VO_2), physical capacity can be determined more precisely than during the electrocardiographic exercise test, while all the parameters evaluated in the electrocardiographic exercise test can also be measured in CPET.[1-4] CPET is increasingly used not only in scientific research but also in daily clinical practice. It is useful in many clinical settings in cardiology, pulmonology, and rehabilitation, as well as in sports medicine and in evaluation of healthy people.[5] In CPET, the physical capacity is reflected as maximum VO_2 ("maximal aerobic capacity"). It represents the volume of oxygen that a person can take up from inhaled air within a minute during physical exercise involving a large part of their muscle mass.

Historical background The concept of exercise VO_2 dates back to the end of the 18th century. Antoine Lavoisier performed the first measurements of aerobic metabolism during controlled physical exercise in 1790. The first spirometer combined with an ergometer was constructed by Hugo W. Knipping and L. Brauer in 1929. In 1925, Archibald V. Hill was the first to describe maximum oxygen uptake (VO_{2max}) as the main parameter of cardiopulmonary capacity. CPET was included in the clinical practice in the 1950s.[6] In the 1980s and 1990s, the widespread CPET use in cardiology followed publications of Weber et al[7] and Mancini et al,[8] who demonstrated a relationship between the disease prognosis and oxygen uptake at peak exercise (VO_{2peak}).

Physiology of exercise Physical exercise means any movement of the body effected by skeletal muscles and related to energy expenditure.[9] It requires the coordinated functioning of many systems: cardiovascular, respiratory, musculoskeletal, endocrine, and the nervous system. Based on the nature of muscle contraction, we can distinguish dynamic exercise, in which the length of muscles changes during the contraction and work is performed, and static exercise, in which the muscle tension increases, but the length remains unchanged.[10] In natural conditions, the exercise is usually of a mixed character.

A direct measure of exercise intensity is the amount of oxygen consumed by working muscles. Based on volumes of VO_2 and carbon dioxide output (VCO_2) per time unit, biochemical processes occurring at the tissue level can be evaluated. Oxidation of organic substances in the body provides roughly the same amount of energy as their combustion outside the body; it also requires the same amount of oxygen. Consumption of 1 l of oxygen provides 19.6 kJ when fats are oxidized, and 21.1 kJ when carbohydrates are oxidized (a difference of 10%).[10] Below the anaerobic threshold (AT), oxygen and carbon dioxide volumes measured at the mouth level correspond to volumes of these gases at the tissue level. The respiratory exchange ratio (RER) is measured by VCO_2/VO_2 at the mouth level and reflects a carbon dioxide production and oxygen consumption quotient at the tissue level called the metabolic respiratory quotient (RQ). In the steady state, when there is no hyperventilation or uncompensated metabolic acidosis, RER equals RQ. Glucose is oxidized at RQ of 1.0 (eg, 6 molecules of carbon dioxide are produced, and 6 molecules of oxigen are consumed). When 1 glucose molecule is oxidized in the oxidative phosphorylation process, 36 molecules of adenosine triphosphate (ATP) are regenerated from adenosine diphosphate (ADP) in the presence of phosphocreatine, and the ratio of ATP molecules to oxygen molecules is 6.0 (36 ATP/6 O_2). Fats (eg, palmitate) are oxidized at RQ of 0.71 (eg, 16 molecules of carbon dioxide are produced, and 6 molecules of oxygen are consumed). When 1 molecule of palmitic acid is oxidized, 130 molecules of ADP are rephosphorylated to ATP, and the ratio of ATP molecules to oxygen molecules is 5.65 (130 ATP/23 O_2).[11] RQ values are in a steady state, reflecting the corresponding rates of carbohydrates and fats used in metabolic processes. The use of individual substrates during physical exercise depends on its intensity and duration. During light exercise (30%–40% VO_{2max}), the primary source of energy is glucose from hepatic glycogen and free fatty acids. During moderate exercise (50%–70% VO_{2max}), muscle glycogen and free fatty acids are consumed. During high-intensity exercise (>70% VO_{2max}), muscle glycogen resources are used mainly in the mechanism of anaerobic glycolysis, and this leads to an increased level of lactates. RQ at rest is approximately 0.8, and during moderate exercise, it increases up to 0.95 (at this RQ value, approximately 84% of energy comes from carbohydrates).[11] Bergström et al[12] demonstrated a positive relationship between intense exercise duration and the glycogen content in muscles before the exercise. More physically fit people use fats at a higher rate during exercise, thus delaying the depletion of glycogen resources and fatigue. Because fat stores are larger, they are a better energy substrate, while carbohydrates are more efficient. Sources of glucose include glycogen stored in muscles and plasma glucose from glycogen degradation in the liver, and sources of free fatty acids are triglycerides stored in muscles and adipose tissue. Proteins are used solely during starvation and prolonged physical exercises when glycogen is exhausted.

In humans, the skeletal mass represents ca. 38% of total body weight, so in a person with a body weight of 70 kg this equals approximately

27 kg.[13] Skeletal muscles contain 3 types of muscle fibers: I, IIa, and IIx. This classification is based on their biochemical properties and contractility. Type I is called slow oxidative fibers, and are characterized by the red color of fibers and slowly increasing tone (ca. 80 ms). Type IIa fibers are fast oxidative-glycolytic fibers, and type IIx are fast glycolytic fibers. Type IIa and IIx fibers are called fast-twitch fibers, with their tone increasing very fast (about 30 ms). Type I fibers are characterized by a higher content of mitochondria and a higher level of myoglobin containing iron (hence their red color). They also contain more oxygen-processing enzymes and enzymes associated with the oxidation of fatty acids. Type II fibers, on the other hand, are white due to their lower content of hemoglobin, contain fewer mitochondria and higher levels of anaerobic-processing enzymes. Type I fibers contract slower but are more resistant to fatigue, and type II fibers contract faster, but their resistance to fatigue is lower. The distribution of different types of fibers in human skeletal muscles is different in different muscle groups. Proportions of fiber types in muscles vary, depending on physical activity. In long-term immobilization or reduction in physical activity due to chronic disease, a shift towards type II fibers occurs. Low intensity exercise involves recruitment of mainly type I fibers, and type II fibers are recruited during heavy loads, especially those exceeding 70% to 80% of oxygen capacity.[11]

ATP generated during the oxidation of energy compounds is used for changes in the internal configuration of actin and myosin, reflected as muscle shortening or increased tension. The effectiveness of muscle cells depends on ATP supply and possibilities for its regeneration. The amount of ATP stored in the rested muscle is sufficient for only 1 to 2 seconds, so it has to be constantly renewed during exercise. Biochemical processes used to replenish stores of cellular ATP include glycolysis with generation of pyruvate or (in anaerobic conditions) lactate, oxidative phosphorylation in the respiratory chain, in which pyruvate, free fatty acids, and ketone bodies are used as substrates, phosphocreatine transformation into creatinine, and ATP synthesis from 2 ADP molecules.[14]

Even before the dynamic exercise begins, the cardiac output is increased due to a reduction in vagal tone, which is a way of preparing the body for physical activity. VO_2 by the cardiac muscle depends on the wall tension, contractility, heart rate (HR), and, to a lesser extent, on external work, energy required for activation, and basic cardiac metabolism. In physiological conditions, cardiac metabolism is solely aerobic. Energy substrates for the cardiac muscle include glucose, free fatty acids, lactic acid and ketone bodes. An increase in the venous blood flow to the heart causes the following changes in hemodynamic parameters: an increase in the end-diastolic volume of atria and ventricles, an increase in ventricular diastolic pressure due to greater filling of the ventricles, an increase inatrial diastolic pressure due to the increased inflow and higher ventricular diastolic pressure; an increase in atrial and ventricular contractile strength leading to an increase in the stroke volume (SV), and thus, in the cardiac output.

The greatest oxygen consumption (80%) by the cardiac muscle occurs during isovolumetric contraction. During that event, the cardiac energy expenditure depends on the afterload, end-diastolic pressure, and the rate of the wall tension increase. The VO_2 by the cardiac muscle is increased by the stimulation of the sympathetic system and reduced by the activity of the parasympathetic system. During exercise, HR accelerates first due to the inhibition of the parasympathetic system, and then by the stimulation of the sympathetic system. Additionally, the increase of sympathetic tone causes contraction of veins and arteries in most organs, excluding working muscles, the central nervous system, and the coronary circulation. These reactions increase ventricular filling volume and accelerate HR. During exercise, the systolic blood pressure (SBP) increases, and the diastolic blood pressure remains the same or is slightly reduced. The cardiac index changes within a range from 3.5 l/m^2/min at rest to 22 l/m^2/min during exercise. Its increase is caused by a mechanism dependent on cardiac stretch (according to the Frank–Starling law) and a mechanism dependent on the nervous regulation of its rate and contractility.[15]

During exercise, the respiratory system's task is to supply a sufficient amount of oxygen to cover the increased metabolic demand and to remove the generated carbon dioxide on an ongoing basis. It also affects acid-base homoeostasis through the elimination of carbon dioxide. During exercise, the minute ventilation (VE) of the lungs increases. Initially, it is due to the increased tidal volume (VT), and then (>60%–70% of the maximum load) due to the increased breathing frequency (BF). Physiologically, VE does not reach the maximum voluntary ventilation (MVV), and if there is no respiratory disease, its function does not limit the exercise capacity.

Fatigue during exercise, apart from a subjective perception, is reflected in a reduced rate and strength of muscle contractions. It can be caused by myocyte acidification (accumulation of hydrogen ions) leading to a reduced calcium release and subsequent reduced binding of calcium to myocyte contractile components, or by a drop in ATP levels in situations when more ATP is consumed than produced.[16]

Physical capacity Physical capacity (exercise capacity, exercise tolerance) is understood as maximum fatigue caused by physical exercise that is tolerated by the patient.[17] It is the capability to perform aerobic exercise determined by VO_{2max}. In practice, it means the ability to undertake daily activities based on aerobic metabolism.[18] Physical capacity also includes the ability to tolerate fatigue-related metabolic changes and the ability to quickly eliminate them when the work is completed.[19]

Physical capacity evaluated in CPET is the cardiopulmonary (aerobic) capacity, which is a component of a widely understood physical fitness. Physical fitness includes fitness dependent on the health status (cardiopulmonary capacity, muscular endurance, muscular strength, body composition, and flexibility) and fitness dependent on skills (agility, balance, motor coordination, speed, power, reaction time).[9] The maximum physical effort is evaluated in relation to its intensity and duration. Intensity can be measured in units of power (W) or as energy expenditure measured as VO_2 during exercise (l/min). In the case of electrocardiographic exercise tests conducted on a treadmill, exercise intensity is evaluated with metabolic equivalents of task (MET), which are calculated with the equations proposed by the American College of Sports Medicine based on the treadmill speed and incline.[20] One MET corresponds to the consumption of 3.5 ml of oxygen/min/kg of body weight. That value was determined based on the VO_2 at rest of a 40-year-old man with a body weight of 70 kilograms. An estimated capacity evaluation with MET based on the treadmill speed and incline can lead to an overestimated capacity rate. Ades et al[21] demonstrated that capacity values were overestimated by 30% in men and 23% in women when VO_2 was calculated from MET, when compared with a direct measurement of VO_{2peak}.

Physical capacity depends on age, sex, as well as body weight and body composition. It is assumed that human aerobic physical capacity increases up to 20 years of age, then it is stabilized between 20 and 25 years of age, and after 25 years of age it regularly declines on average by 10% per each decade of life. Fleg et al[22] demonstrated that physical capacity decreases by 3% to 6% per every 10 years in young (20–30 years of age) and by up to >20% in older (>70 years of age) healthy people. At every age, physical capacity of women is 10% to 20% lower than that of men. This is related to their lower muscle mass, lower hemoglobin concentration, and smaller SV.[18] The age-dependent decrease in physical capacity is associated with a progressive reduction in muscle mass, SV, and maximum achievable HR. Reduction in SV results from the decreasing contractility of muscle fibers and their defective relaxation. Regular physical activity may slow this process down.[23]

Factors underlying capability for aerobic physical exercise are as follows:

1 Effectiveness of functions that jointly facilitate oxygen transport to the tissues (maximum cardiac output, arterial-mixed venous oxygen content difference, hemoglobin level, diffusing capacity of the lung, maximum lung ventilation)
2 Age, sex, genetic factors
3 Physical training, daily physical activity
4 Thermoregulatory effectiveness
5 The efficiency of systemic mechanisms controlling metabolism, including the capacity of buffer systems reducing acidosis and processing lactate
6 Tolerance of fatigue changes (mental factors, tolerance of hypoglycemia)
7 Musculoskeletal system characteristics.

Direct measurement of VO_2, with its value compared with the norms for a population (relative capacity) considering race, sex, age, and body composition, is considered the reference parameter for evaluation of physical capacity.

Indications and contraindications Indications for CPET in cardiology are as follows[1,2,5,11,24-27]:

1 Identifying causes of exercise intolerance and dyspnea
2 Diagnostic workup as well as the evaluation of the disease progression, exercise capacity, and prognosis in: heart failure, hypertrophic cardiomyopathy (HCM), pulmonary hypertension (PH), suspected ischemic heart disease, suspected mitochondrial myopathy, unexplained exertional dyspnea, chronic obstructive pulmonary disease (COPD) or interstitial lung disease, pre- and postoperative evaluation and evaluation of long-term prognosis, valvular diseases
3 Evaluation of physical capacity in apparently healthy people
4 Choice of training, monitoring, and evaluation of results in cardiac rehabilitation
5 Evaluation of treatment effectiveness.

Contraindications to CPET as well as absolute and relative indications to stop the testing are the same as for electrocardiographic exercise testing, and are described elsewhere.[28]

Technical conditions and preparation of testing equipment Technical conditions, equipment, and safety requirements to be met by the CPET laboratory do not differ significantly from those specified for electrocardiographic exercise testing and are described elsewhere.[28] Additionally, the laboratory should be equipped with a hygrometer and an indoor thermometer. Moreover, the system for exercise testing should be additionally equipped with a gas analyzer and a set of face masks (of various sizes

to fit the patient's face tightly). Optionally, appropriate mouthpieces and a nose clip can be used instead of a mask.

Before the testing, the apparatus must be calibrated, considering current environmental conditions, as specified in the instructions provided by the manufacturer. Volumetric calibration with a standard 2 to 3 l syringe (depending on the recommendations of the manufacturer) needs to be adjusted to body temperature, pressure, and saturated with water vapor conditions – temperature of 36.8°C, ambient atmospheric pressure, 100% humidity. Gaseous calibration should be performed using a standard gas mixture containing 15% of oxygen, 6% of carbon dioxide, and 79% of nitrogen. Gaseous parameters should be adjusted to standard temperature, pressure, and dry conditions – temperature of 0°C, pressure of 1013 hPa, 0% humidity.

Supervising personnel CPET should be supervised and interpreted by a physician with experience in exercise testing, specified elsewhere.[28] Additionally, the person performing the test should have knowledge and experience in performing cardiopulmonary tests as well as interpreting the results.[1]

Conducting the test **Aims of the test** The aim for the test should be established before CPET, based on the referral and medical history.

Patient medical history The patient should be interviewed with regard to symptoms from the week preceding the test and their intensity (eg, increasing coronary pain, significant abrupt drop in the exercise capacity, syncope at rest and on exertion) as well as relevant past medical history (eg, recent or existing infections, orthopedic and neurological disorders, or mental diseases, such as depression or anxiety). Patient's exercise capacity based on the daily activity and ability to perform physical exercise (for instance according to NYHA class) should be assessed before the test. Names and doses of cardiac medications, as well as the time of the last dose taken on the day of the test should also be noted.

Patient data and protocol selection In accordance to the rules for electrocardiographic exercise testing, described elsewhere.[28]

Information about the test and written consent Before the test, the patient should be informed about the aim and the course of the test, and about possible inconveniences and complications related to the test. Written consent must be obtained.

Patient preparation The patient should come in for the test about 3 hours after a light meal in comfortable, loose clothing and sports footwear enabling walking on a treadmill or riding an exercise bike. For up to 6 hours before the test, the patient should avoid intense physical exercise and should not drink strong tea, coffee, or any other energy drinks, or smoke cigarettes. On the day of the test, the patient should take their standard medications. The way of expressing fatigue, any undesirable symptoms, and the need to stop exercise should be discussed with the patient before the test.

Skin preparation and placement of leads Skin preparation and placement of leads was described previously elsewhere.[28]

Conducting the test **Test stages, loading protocols** Before the exercise is started, it is recommended to perform spirometry at rest, and in the majority of CPET devices it is necessary.

The CPET stage should include: warming up (2–3 minutes), exercise (about 8–12 minutes), recovery phase (5 minutes or to resolution of electrocardiographic changes and / or clinical symptoms).

For CPET, ramp and customized protocols are recommended. A detailed description of available protocols and methods for customized protocols were described in recommendations for electrocardiographic exercise testing.[28]

Variables measured during cardiopulmonary exercise testing During CPET and immediately after its completion, all parameters evaluated during electrocardiographic exercise testing (clinical, hemodynamic, and electrocardiographic), as well as ventilatory and gas exchange variables should be assessed and are presented below. Parameters evaluated in electrocardiographic exercise testing are described elsewhere.[28]

Ventilatory parameters to be assessed on CPET:

1. VE, l/min
2. VT, l
3. BF, l/min
4. Breath reserve (BR), %
5. Dead space (VD) to VT ratio (VD/VT)
6. Ventilatory efficiency (VE) versus carbon dioxide slope (VCO_{2slope})

Gas exchange parameters to be assessed on CPET:

1. VO_{2peak}, ml/kg/min, l/min; percent of predicted VO_{2peak} ($\%VO_{2pred}$), %
2. VO_2 at AT (VO_2-AT), ml/kg/min, l/min
3. Oxygen pulse (O_{2pulse}), ml/beat; percent of predicted O_{2pulse}, %
4. VO_2 plotted against work rate (WR) increase
5. O_{2pulse} plotted against WR increase
6. VCO_2 at peak exercise, l/min
7. RER
8. Ventilatory equivalent for oxygen
9. Ventilatory equivalent for carbon dioxide
10. End-tidal oxygen partial pressure ($PETO_2$), mm Hg

11 End-tidal carbon dioxide partial pressure ($PETCO_2$), mm Hg
12 VO_2 efficiency slope.

Parameters of cardiopulmonary exercise testing and their interpretation

Oxygen uptake VO_2 during physical exercise is a measure of aerobic capacity. VO_2 depends on the cellular oxygen demand and the ability to transport oxygen to tissues. Oxygen availability for tissues is influenced by: gas exchange at the alveolar level (structure and function of the respiratory system), ability of the blood to transport oxygen (hemoglobin concentration, arterial blood saturation, hemoglobin dissociation curve, carbon dioxide content, pH of blood), heart function (HR, SV), peripheral blood redistribution, oxygen extraction by tissues (capillary thickness, mitochondrial density and function, perfusion, tissue function).

VO_2 is defined as the product of the SV and the arterial-mixed venous oxygen content difference, calculated using the following formula: $VO_2 = HR \times SV \times [C(a-v)O_2]$, where $C(a-v)O_2$ is the arterial-mixed venous oxygen content difference (ml of oxygen/dl of blood).

During exercise, the arterial-mixed venous oxygen content difference is linearly correlated with VO_2 and achieves a physiological limit of 12 to 16 ml oxygen/dl of blood depending on the hemoglobin concentration (12–16 g/dl). Therefore, VO_{2peak} exercise depends mainly on the SV.[29-31]

Oxygen consumption during exercise with an increased load rises slowly until it reaches a plateau. VO_2 may increase 15-fold from rest values of 3.5 ml/kg/min, to 30 to 50 ml/kg/min. In well-trained people, VO_2 may be even 20-fold higher and reach 94 ml/kg/min.[1,2]

VO_{2peak} may be expressed as VO_{2max} or VO_{2peak}. VO_{2max} represents the amount of oxygen uptake during maximum physical effort and is defined as lack of increase in VO_2 (plateau) despite the increasing load at maximum fatigue. VO_{2max} is achieved in healthy people who can perform maximum effort. The time to achieving VO_{2max} depends on the dynamics of the load increase (protocol). The more the load increases in time, the sooner VO_{2max} is achieved. However, in each case, the VO_{2max} value is the same. In healthy people, VO_2 increase versus load increase ($\Delta VO2/\Delta WR$) is 10 ml/min/W, on average.[31] In obese patients, the relation between VO_2 to WR is shifted to a higher level, without a change in the VO_2 increase rate. VO_2 course versus WR is steeper in athletic individuals, and flatter in those with cardiovascular diseases.[32]

In patients with cardiovascular or respiratory diseases, reaching VO_{2max} is impossible (and may be dangerous); therefore, in this group, VO_{2peak} evaluation is used instead. It represents oxygen uptake at the peak of the exercise, usually at fatigue level of 15 to 16 points on the 20-point Borg scale (or 5–6 points on the 10-point Borg scale). VO_{2max} or VO_{2peak} should be presented as absolute (ml/min, l/min) and relative values, calculated per kilogram of the patient's body weight (ml/kg/min) values. Lower VO_{2peak} may reflect problems with oxygen transport (SV, ability of the blood to bind and transport oxygen), lung function (obturation, restriction, gas exchange), oxygen extraction at the tissue level (tissue perfusion and diffusion), neuromuscular and skeletal muscle disorders, and insufficient physical exercise.

Maximum test criteria There is no gold standard for the evaluation of maximum physical exercise. The presence of 1 or more of the following criteria is considered as a feature of maximum effort during CPET[2,33,34]:

1 Reaching plateau of VO_2 and/or HR despite continued load increase
2 Peak RER of 1.10 or higher
3 Postexercise lactate concentration of 8 mmol/l or higher
4 Perceived exertion, 18 or more points on the 20-point Borg scale or 8 or more points on the 10-point Borg scale
5 Exhaustion.

Predicted oxygen uptake To reduce interindividual variations, VO_{2peak} should be expressed as $\%VO_{2pred}$. VO_2 depends on the study population, age, sex, body size, fat-free body mass, level of daily physical activity, and the loading conditions. The physical capacity of a person undergoing the test may differ from the calculated predicted value because of the above factors. To calculate the predicted oxygen uptake value (VO_{2pred}), it is recommended to use the Wasserman and Hansen equation by the American Thoracic Society/American College of Chest Physicians and the European Association for Cardiovascular Prevention and Rehabilitation/American Heart Association.[1,5,35]

The calculation of VO_{2pred} in men is presented in TABLE 1 and in women in TABLE 2.[27,35,36]

Carbon dioxide output VCO_2 during exercise depends on SV, blood ability to transport carbon dioxide, and tissue exchange. As carbon dioxide is 20-fold more soluble in blood than oxygen, VCO_2 measured at the mouth level depends on ventilation to a greater extent than VO_2. Additionally, the body uses carbon dioxide production to compensate for metabolic acidosis. Therefore, VCO_2 increases significantly when the AT is exceeded.

Respiratory exchange ratio The relationship between VCO_2 and VO_2 is called RER. It is calculated as a ratio between VCO_2 and VO_2 (VCO_2/VO_2). VCO_2 and VO_2 increase at the same rate to RER (= 1.00). Above that value, VCO_2 is additionally

TABLE 1 Calculation of predicted oxygen uptake in men expressed as ml/min according to Wasserman and Hansen[35]

Step 1: Calculate
Cycle factor = 50.72 – 0.372 × age (y)
Ideal weight (kg) = 0.79 × height (cm) – 60.7
Step 2: Classify body weight
Actual weight < / = / > ideal weight
Step 3: Select an equation
Actual weight < ideal weight
VO_2 = ([ideal weight + actual weight]/2) × *cycle factor*
Actual weight = ideal weight
VO_2 = actual weight × *cycle factor*
Actual weight > ideal weight
VO_2 = (ideal weight × *cycle factor*) + 6 × (actual weight – ideal weight)
Step 4: Include the load type
For exercise bicycle ergometer
VO_2 calculated in step 3 is equal to VO_{2pred} depending on the body weight
For treadmill
VO_{2pred} is equal to VO_2 from step 3 × 1.11
Example: a 55-year-old man with a body mass of 78 kg and height of 170 cm achieved the VO_{2peak} 2600 ml/min during the CPET on treadmill
Ideal weight 74 kg; cycle factor 30.26; VO_{2pred} 2501.4 ml/min (this is the minimum predicted value below which impairment of aerobic exercise capacity can be recognized)
Relative capacity $\%VO_{2pred}$ = 100 × 2600 / 2501.4 = 103.9%
Calculation result: good exercise capacity $\%VO_{2pred} \geq 100\%$

Abbreviations: CPET, cardiopulmonary exercise testing; VO_2, oxygen uptake; VO_{2peak}, oxygen uptake at peak exercise; VO_{2pred}, predicted oxygen uptake

TABLE 2 Calculation of predicted oxygen uptake in women expressed as ml/min according to Wasserman and Hansen[35]

Step 1: Calculate
Cycle factor = 22.78 – 0.17 × age (y)
Ideal weight (kg) = 0.65 × height (cm) – 42.8
Step 2: Classify body weight
Actual weight < / = / > ideal weight
Step 3: Select an equation
Actual weight < ideal weight
VO_2 = ([ideal weight + actual weight + 86]/2) × *cycle factor*
Actual weight = ideal weight
VO_2 = (actual weight + 43) × *cycle factor*
Actual weight > ideal weight
VO_2 = (ideal weight + 43) × *cycle factor* + 6 × (actual weight – ideal weight)
Step 4: Include the load type
For exercise bicycle ergometer
VO_2 calculated in step 3 is equal to VO_{2pred} depending on the body weight
For treadmill
VO_{2pred} is equal to VO_2 from step 3 × 1.11

Abbreviations: see TABLE 1

increased by an elevation in carbon dioxide production due to lactate compensation and hyperventilation. RER of 1.10 or more at peak exercise is a generally accepted indicator of sufficient fatigue during the test; however, exceeding this value is not an indication for discontinuing the exercise. Reaching RER of less than 1.00 at the peak of the exercise reflects submaximal exercise, and can also be observed in some pulmonary restrictions of exercise tolerance.[25]

Anaerobic threshold AT represents a level of exercise above which aerobic production of energy is supported by anaerobic processes and is reflected in an increase in lactate levels in tissues and in peripheral blood. AT can be defined physiologically as VO_2 above which aerobic ATP production in muscles is supplemented by anaerobic processes. VO_2-AT is expressed as a percentage of VO_{2pred} and as a percentage of VO_{2peak}.[5,35] The mean value of VO_2-AT in people who do not train and lead a sedentary lifestyle, is within the range of 50% to 60% VO_{2pred}. In the general population of healthy people, VO_2-AT is within an extensive range of 35% to 85% and depends on age, exercise type, and load protocol. VO_2-AT is independent of the patient's motivation to exercise. The metabolism of muscles taking part in an activity influences the time at which AT occurs. Reduction in VO_2-AT can be caused by the same disorders that cause reduction in VO_{2peak}.

Determination of the anaerobic threshold Both invasive and noninvasive methods are used to determine AT. In the invasive method, lactate levels in the peripheral blood are determined and the lactate thresholds are established – first at the lactic acid level of more than 2 mmol/l, and second at the lactic acid level of more than 4 mmol/l.

In CPET, AT is usually determined by a noninvasive method, by establishing the ventilatory thresholds VT1 (first ventilatory threshold) and VT2 (second ventilatory threshold), also called the respiratory compensation point (RCP). VT1 is usually determined by the V-slope method or by the ventilatory equivalents method, while the ventilatory equivalents method is used for VT2.

The V-slope method uses a curve of VCO_2 in relation to VO_2. An increase in the rise rate of VCO_2 versus VO_2 results in a steeper curve. AT is found at the curve bending point.

The ventilatory equivalents method uses the time course of ventilatory equivalents for oxygen (VE/VO_2) and carbon dioxide (VE/VCO_2) as well as $PETO_2$ and $PETCO_2$. AT is determined at the point at which VE/VO_2 and $PETO_2$ reach their minimum, and their steady increase begins, while VE/VCO_2 and $PETCO_2$ remain unchanged.

It is recommended to determine AT with the above methods, optimally applying both

methods simultaneously (dual methods approach), with simultaneous RER evaluation, which should be close to 1.0.

Oxygen pulse O_{2pulse} is a product of VO_2 and HR presenting the amount of oxygen inhaled in 1 heartbeat (ml/beat).

According to the Fick equation, VO_2 depends on SV and the arterial-mixed venous oxygen content difference. Therefore, changes in O_{2pulse} during exercise reflect changes in SV. $O_{2pulse} = SV \times [C(a - v)O_2]$, where $C(a - v)O_2$ indicates arterial-mixed venous oxygen content difference (ml of oxygen/dl of blood).

In normal conditions, O_{2pulse} increases during incremental load exercise, assuming the shape of hyperbola, with a fast increase at low exercise intensity and gradual flattening at peak exercise.

Low O_{2pulse}, unchanging despite the increase in load, may result from a reduced SV and/or tissue inability to further extract oxygen. Low O_{2pulse} may reflect poor physical fitness, cardiovascular diseases or reduced capacity caused by lung diseases.

Maximal voluntary ventilation Before the exercise testing, spirometry at rest should be performed to evaluate vital capacity and forced expiratory volume in 1 second (FEV_1). Spirometry at rest allows exclusion of significant restriction or obturation, which can result in exercise limitation. The spirometry result is used to calculate the MVV from the equation: $MVV = FEV_1 \times 40$.

Detailed description of spirometry lie beyond the scope of this paper.

Breathing reserve Exercise BR shows the extent to which the VE approaches MVV at peak exercise, and can be expressed as liters per minute (BR = MVV – VE peak) or as a percentage (BR = [(MVV – VE peak) / MVV]× 100%).

BR value of 15% represents the lower limit of normal in an average population of healthy people. Athletes (due to their high exercise capacity) and elderly people (due to low MVV) can have lower BR values, even when no disease is present.

Exercise BR can also be expressed as the product of peak ventilation multiplied by MVV at rest (VE peak/MVV) or its percentage ratio (100 × VE/MVV). Predicted values of these parameters are 0.8 and below, and 80% and below, respectively.[1,5] In healthy people, VE at peak exercise is within the range of 50% to 80% MVV.

Breathing frequency BF represents the number of breaths per minute. In the majority of people, BF is increased 2- to 3-fold, and in healthy people it does not exceed 50 to 60 breaths per minute.

Tidal volume VT represents the volume of 1 breath. During exercise, VT is 3- to 4-fold increased in younger, and 2- to 4-fold in older people.

Minute ventilation VE is the product of VT and BF, as in the following equation: VE = VT × BF. VE rises progressively during exercise, initially because VT increases to 60% to 70% of the maximum load, and then mainly due to an increase in BF. In patients with heart failure, the VE versus load curve may oscillate.

Exercise oscillatory ventilation Exercise oscillatory ventilation (EOV) means alternate hyper- and hypoventilation. The diagnosis is based on determining parameters of oscillatory ventilation for at least 60% of the exercise duration, of amplitude of 15% or more of the average VE value at rest.[26]

Ventilatory equivalent for oxygen VE/VO_2 is the VE to VO_2 ratio. It represents the volume of VE required to uptake 1 liter of oxygen. This parameter is nonlinear. Its value is influenced by intensified ventilation, increased VD, and oscillatory breathing.

Ventilatory equivalent for carbon dioxide VE/VCO_2 is the VE to VCO_2 ratio. It represents the volume of VE required to output 1 liter of carbon dioxide. This parameter rises during hyperventilation and when the VD increases. Physiologically, 23 to 25 l of VE are required to output 1 l of carbon dioxide. The mutual relation of VE/VO_2 and VE/VCO_2 curves allow differentiation of the cause of intensified ventilation (metabolic acidosis, psychiatric disorders, anxiety).

Oxygen and carbon dioxide end-tidal partial pressure $PETO_2$ and $PETCO_2$ are measured at the end of spontaneous exhalation. These parameters depend on hyperventilation and VD. During exercise, initially, $PETO_2$ decreases and $PETCO_2$ increases. With further load, $PETO_2$ decreases, reaching the lower turning point (nadir), and $PETCO_2$ remains unchanged (AT, simultaneous increase in VE/VO_2). During further loading, $PETO_2$ continues to rise, and $PETCO_2$ starts to decrease (with a simultaneous increase in VE/VCO_2), indicating that the RCP has been reached.

Ratio of physiological dead space to tidal volume The physiological VD to VT ratio indicates a fraction of each breath that corresponds to VD – both anatomical (oral cavity, larynx, bronchi) and alveolar (poorly perfused alveoli). VD/VT reflects a disrupted balance between ventilation and perfusion. In healthy people, VD/VT is about 0.34 and decreases by 0.1 during exercise. In patients with lung diseases or PH caused by diseases of the left heart, this parameter is higher and does not decrease

during exercise. Calculation of this parameter requires an invasive measurement of carbon dioxide partial pressure in the arterial blood and calculation of $PETCO_2$ as well as consideration of the VD of the apparatus. The use of a non-invasive method for VD/VT calculation, based on the estimation of carbon dioxide partial pressure in the arterial blood in reference to normal ratios of expiratory gases during exercise in healthy people,[37] may be a source of error in the diagnostic workup of the significantly disrupted rate of ventilation to perfusion in patients with such diseases.[1]

Ventilatory efficiency Ventilatory efficiency is measured as VE versus VCO_2 slope. It represents a relationship between VE and VCO_2 expressed as the slope of the straight line calculated using a simple linear regression equation.[38] In patients with heart failure, who have increased ventilation, VE vs VCO_2 slope is steeper than in healthy people. Normal values are within the range of 20 to 30.

TABLE 3 Normal values and normal responses to exercise for key cardiopulmonary exercise testing variables[5,31]

Parameter	Normal values / responses
VO_{2peak}, ml/kg/min	Wide range depending on age, sex, physical activity, 15–80 ml/kg bw/min
$\%VO_{2pred}$, %	≥100%
VO_2-AT, ml/kg bw/min	≥40–50% VO_{2pred} (age dependent)
RER at peak exercise	≥1.10 (indicates excellent exercise effort)
VE versus VCO_2 slope	<30 considered as normal; possible slight increase with age
$PETCO_2$, mm Hg	36–42 mm Hg at rest
	an increase of 3–8 mm Hg during exercise up to AT
	decrease following AT according to increased ventilation
VE/VO_2 at peak exercise	≤40; upper limit of normal response, 50
BR at peak exercise	>15%
VE at peak exercise/MVV	≤0.8
$\Delta VO_2/\Delta WR$, ml/min/W	An increase of 8.4–11.0 ml/min/W
HR during exercise, bpm	An increase of 10 bpm per 3.5 ml/kg bw/min increase in VO_2
HR recovery at 1 min standing, bpm	>12
Blood pressure	SBP increase 10 mm Hg per 3.5 ml/kg bw/min increase in VO_2, up to 210 mm Hg (men) and 190 mm Hg (women); DBP, unchanged or slight decreased
SpO_2, %	≥95% at rest and during exercise; should not decrease >5% (absolute value)

Abbreviations: $\%VO_{2pred}$, percent predicted oxygen uptake; AT, anaerobic threshold; BR, breath reserve; DBP, diastolic blood pressure; HR, heart rate; MVV, maximal voluntary ventilation; $PETCO_2$, end-tidal carbon dioxide partial pressure; RER, respiratory exchange ratio; SBP, systolic blood pressure; SpO_2, oxygen saturation by pulse oximetry; VE, minute ventilation; VE versus VCO_2 slope, minute ventilation versus carbon dioxide slope; VO_2-AT, oxygen uptake at anaerobic threshold; others, see TABLE 1

Oxygen uptake efficiency slope Oxygen uptake efficiency slope describes the respiratory response to physical exercise. It represents an absolute increase in VO_2 related to the 10-fold increase in ventilation. It is presented as a linear relationship between VO_2 and VE decimal logarithm.

Interpretation of the results, final report, and conclusions The interpretation of the test results should be comprehensive and integrated.

The following should be considered while evaluating the test:

1 Indication for the examination
2 Clinical details, results of additional tests, medications taken, level of physical activity
3 Comparison of the numerical test results to reference values
4 Graphic charts (eg, a 9-panel plot according to Wasserman)
5 Clinical presentation (chest pain, dyspnea, general fatigue, lower extremity muscle fatigue)
6 HR, blood pressure, and electrocardiographic changes
7 Perceived exertion
8 Reason for termination of the test.

Main parameters measured during CPET and criteria of a normal response to exercise are shown in TABLE 3.[5]

The charts proposed by Wasserman, the 9-panel plot, presenting relationships between parameters evaluated in CPET, are most commonly used.

In the fifth edition of the textbook *Principles of Exercise Testing and Interpretation* published in 2012, the order of the panels and some parameters were changed. The aim of the graphic presentation of parameters is to facilitate the interpretation of the test result.[35,39]

A 9-panel plot according to Wasserman (of 2012) includes the following panels:

1 Panel 1: VO_2, VCO_2, WR (y-axis) against time (x-axis) and a line presenting VO_{2pred} and the predicted VO_2 increase against the WR increase
2 Panel 2: HR and O_{2pulse} (y-axis) against time (x-axis)
3 Panel 3: HR (y-axis) against VO_2 (x-axis), and VCO_2 (y-axis) against VO_2 (x-axis)
4 Panel 4: VE/VO_2 and VE/VCO_2 (y-axis) against time (x-axis)
5 Panel 5: VE (y-axis) against time (x-axis)
6 Panel 6: VE (y-axis) against time VCO_2 (x-axis), scale 30:1
7 Panel 7: $PETCO_2$, $PETO_2$, pulse oximetry arterial hemoglobin saturation (SpO_2) (y-axis) against time (x-axis)
8 Panel 8: RER (VCO_2/VO_2) (y-axis) against time (x-axis)
9 Panel 9: VT (y-axis) against VE (x-axis); VC and the inspiratory capacity (IC) are shown as horizontal lines. MVV is shown as a vertical line.

First, the patient is evaluated for limitations in physical capacity on the basis of VO_{2peak} (panel 1). When VO_{2peak} is lower, the cause is determined – whether it is cardiac (panels 1, 2, and 3), or respiratory (panels 1, 5, 7, and 9), or related to disrupted ventilation to perfusion rate (panels 1, 4, 6, and 7), or to metabolic disorders (panels 1 and 8).

The evaluation of results should help answer a number of questions presented in TABLE 4.[31]

Methods used to diagnose the causes of limited exercise tolerance caused by cardiovascular or respiratory diseases are based on algorithms. Algorithms proposed by Wasserman[40] are most commonly used. A simplified diagnostic algorithm is shown in FIGURE 1.[27,40] Colored algorithms proposed by Guazzi et al,[5,26] separate for individual diseases or syndromes, are useful in practice during the evaluation of the disease stage and prognosis.

A final report should include:

1 Patient details, age, body weight, height
2 Test date
3 Indications for the test
4 Initial diagnosis and treatment
5 Type of equipment / apparatus used in the test (treadmill, bicycle ergometer), loading protocol
6 Perceived exertion (Borg scale)
7 Reason for termination of the test
8 HR and blood pressure responses to the load, and electrocardiographic changes
9 Main parameters of spirometry at rest
10 Graphical data display
11 Numerical data (initial, at peak exercise, at AT, and at RCP [when determined], and % of predicted values)
12 Descriptive results interpretation: presence, degree, and possible cause of the capacity limitation
13 Comparison with previous results (when available).

Clinical applications and interpretation of cardiopulmonary exercise testing

Distinguishing between cardiac and pulmonary causes in patients with exertional dyspnea Cardiovascular and respiratory diseases are the most common causes of exertional dyspnea and limited exercise tolerance. CPET allows an integrated evaluation of the response of the respiratory and circulatory systems to exercise. Evaluation of exertional dyspnea of unspecified origin is one of the elementary indications for CPET. Differentiation of the symptoms is challenging, especially when the disorders are not advanced, are caused by heart failure with preserved ejection fraction (HFpEF), or – even more difficult scenario – when heart failure is accompanied by COPD. It is estimated that up to 40% of patients with heart failure have COPD and approximately 30% of patients with COPD have heart failure.[5,25,27]

The main parameters evaluated in the differential diagnosis of dyspnea are: VE versus VCO_2 slope, $\%VO_{2pred}$, $PETCO_2$, and BR. Spirometry should be performed both before and after CPET (particularly, in evaluation of exercise-induced asthma), with an evaluation of FEV_1 and the peak expiratory flow. SpO_2 on pulse oximetry should also be monitored.

To detect exercise induced bronchospasm, usually intensified during the first several

TABLE 4 Questions useful in cardiopulmonary exercise testing assessment according to Wasserman et al[31]

Question	Pathology	Markers of abnormality (numbers of panels according to Wasserman 9-panel plot)
Is exercise capacity reduced?	Any disorder	VO_{2peak} (panel 1)
Is the metabolic requirement increased?	Obesity	VO_2-WR relationship (panel 1)
Is oxygen uptake impaired?	Ischemia, myopathies, valvular diseases, congenital heart diseases, pulmonary vascular diseases, peripheral artery diseases, anemia, hypoxemia, elevated carboxyhemoglobin content	ECG; $\Delta VO_2/\Delta WR$; VO_2/HR (panels 1, 2, 3) $\Delta VO_2/\Delta WR$; AT; VO_2/HR; VE/VCO_2 (panels 1, 2, 3, 4, 6) blood pressure; $\Delta VO_2/\Delta WR$; $\Delta VCO_2/\Delta WR$ (panels 1, 5) VO_2/HR (panels 1, 2, 3, 7)
Is ventilatory capacity reduced?	Pulmonary diseases, chest wall diseases	BR; ventilatory response (panels 1, 4, 7, 9)
Is there ventilation-perfusion mismatch?	Pulmonary diseases, pulmonary vascular diseases, heart failure	$P(A\text{-}a)O_2$; $P(a\text{-}ET)CO_2$; VD/VT; VE/VCO_2 at (panels 4, 6, 7)
Are there defects of muscle oxygen utilization?	Muscle glycolytic or mitochondrial enzyme defect	AT; RER; VCO_2; HR vs VO_2; lactate concentration (panels 1, 2, 3, 8)
Are there any behavioral problems?	Psychogenic dyspnea	Breathing pattern (panels 1, 7, 8, 9)
Is the effort sufficient enough?	Poor effort	Increased HR reserve; increased BR; RER at peak exercise <1.0; normal AT $P(A\text{-}a)O_2$; $P(a\text{-}ET)CO_2$ (panels 1, 2, 3, 8, 9)

Abbreviations: $P(A\text{-}a)O_2$ alveolar to arterial oxygen partial pressure difference; $P(a\text{-}ET)CO_2$, arterial to end-tidal carbon dioxide partial pressure difference; VCO_2, carbon dioxide output; VD, dead space; VT, tidal volume; WR, work rate; others, see TABLES 1 and 3

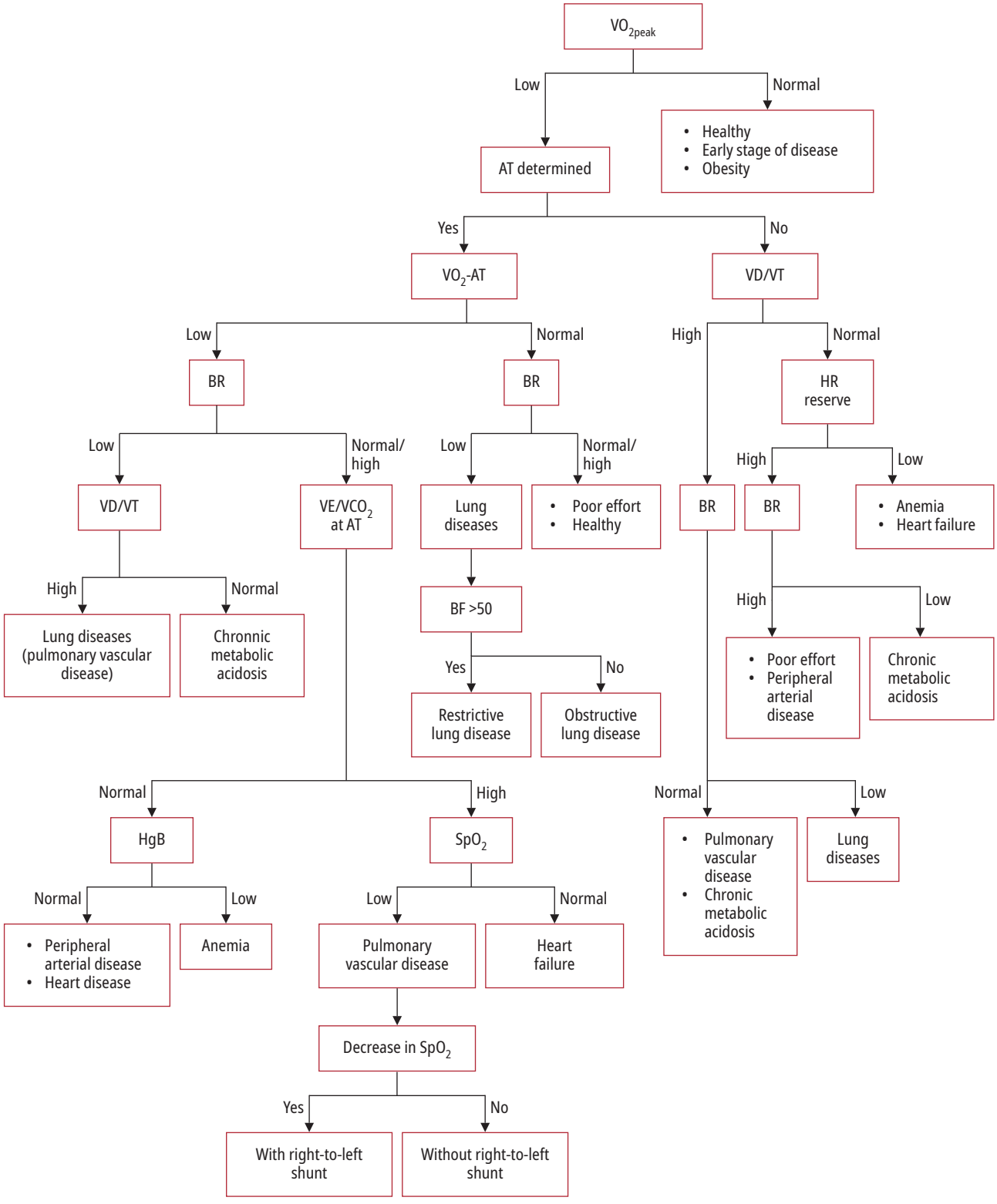

FIGURE 1 Algorithm for the differential diagnosis of the cause of exercise limitation (modified from Wasserman[40])
Abbreviations: Hgb, hemoglobin concentration; others, see TABLES 1, 3, and 4

minutes after exercise, FEV_1 and peak expiratory flow measurements should be taken 1, 3, 5, 7, 10, 15, and 20 minutes after CPET completion. Reduction in FEV_1 of more than 15% after exercise is a diagnostic criterion for exercise induced bronchospasm. Anomalies in VE versus VCO_2 slope and $PETCO_2$ indicate impaired ventilation and perfusion in the pulmonary vascular bed, which may be related to pulmonary vasculopathies. The mismatch between pulmonary perfusion and ventilation results in an increase in VE/VCO_2 and hypoxemia, that is, reduction in SpO_2 is observed (see Pulmonary hypertension).

TABLE 5 Cardiopulmonary exercise testing parameters useful in differentiation between cardiac and pulmonary causes of exertional dyspnea

Parameter	Cardiac disease	Pulmonary disease
VO_{2peak}	Reduced	Reduced
VO_2-AT	Reduced	Normal or reduced
$\Delta VO_2/\Delta WR$	Often reduced	Normal
HR at peak exercise	Can be reduced	Can be reduced
O_{2pulse} at peak exercise	Often reduced	Can be reduced
BR	>20%	<15%
FEV_1 at recovery	As before exercise	Can be reduced
PaO_2 or SaO_2	Normal	Often reduced
VD/VT	Can be increased	Often increased
VE vs VCO_2 slope	Often increased	Can be increased

Abbreviations: FEV_1, forced expiratory volume at 1 second; O_{2pulse}, oxygen pulse; PaO_2, atrial pressure of oxygen in arterial blood; SaO_2, arterial oxygen saturation by gasometry; others see TABLES 1, 3, and 4

TABLE 6 Weber classification of functional limitation in heart failure

Class	Severity of functional impairment	VO_{2peak}, ml/kg bw/min
A	Little or no impairment	>20
B	Mild to moderate	16–20
C	Moderate to severe	10–15.9
D	Severe	<10

Abbreviations: see TABLE 1

TABLE 7 Ventilatory classification system in patients with heart failure

Class	VE versus VCO_2 slope
I	<30.0
II	30.0–35.9
III	36.0–44.9
IV	≥45.0

Abbreviations: see TABLE 3

VE/MVV, FEV_1, and peak expiratory flow disorders occur in patients with dyspnea of pulmonary origin. Ventilatory limitations in exercise tolerance are usually diagnosed in the event of reduction in BR of less than 15% to 20%. In an isolated lung disease, VO_{2peak} is lower due to limited ventilatory capacity. This may also cause a reduction in HR peak. AT may be normal when the patient reaches the required level of exercise. In lung diseases, both of obstructive and of restrictive nature, a characteristic course of the VT versus VE and of the VE/VCO_2 relationship curves is observed.

Cardiovascular diseases are characterized by compromised ability to supply oxygen in response to demand. VO_{2peak} and VO_2-AT, as well as the ratio of oxygen consumption to the work performed ($\Delta VO_2/\Delta WR$) are reduced. O_{2pulse} values, representing indirect measurements of the SV, are lower.

CPET parameters useful for differentiation between cardiac and pulmonary causes of exertional dyspnea are presented in TABLE 5.

The response of the above-mentioned parameters to exercise is not always unambiguous. When cardiovascular and lung diseases concur, the dominant cause of dyspnea can be indicated only after consideration of the clinical context.

Cardiopulmonary exercise testing in differentiation of exertional dyspnea: summary

1 Indications: exertional dyspnea, differentiation between cardiac and respiratory causes.
2 Main parameters: VE versus VCO_2 slope, $\%VO_{2pred}$, $PETCO_2$, and BR.
3 Notes: spirometry at rest should be performed before CPET. SpO_2 monitoring during the test is recommended.

Heart failure Heart failure is a complex pathophysiological process, in which hematologic, metabolic, endocrine imbalances, and sympathetic activation result from a defective heart function. CPET holds a well-established position and is a test recommended in patients with heart failure.[24,34,41-49] According to the current European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic heart failure, CPET[41]:

1 Is recommended as a part of the evaluation for heart transplantation and/or mechanical circulatory support (class I recommendation, level of evidence C).
2 Should be considered to optimize exercise training (IIa/C).
3 Should be considered to identify the cause of unexplained dyspnea (IIa/C).
4 May be considered to detect reversible myocardial ischemia (IIb/C).

Individually selected protocols with gradually increasing workload are recommended (Naughton protocol, ramp-type protocols). CPET can be conducted on a treadmill or a bicycle ergometer.

Patients with advanced heart failure limit their daily physical activity, and therefore are very reluctant to undergo symptom-limited CPET. According to the latest guidelines, maximal CPET is understood as reaching RER of more than 1.05 and achieving AT during the optimum pharmacotherapy (I/B).[42] However, not all patients with heart failure are able to achieve the optimal RER during symptom-limited CPET. It is caused by skeletal muscle disorders (morphological, structural, functional, and metabolic), fatigue of respiratory muscles leading to abnormal ventilation, adverse effects of medications, or significant fatigue preventing continuation of the test.[43,44]

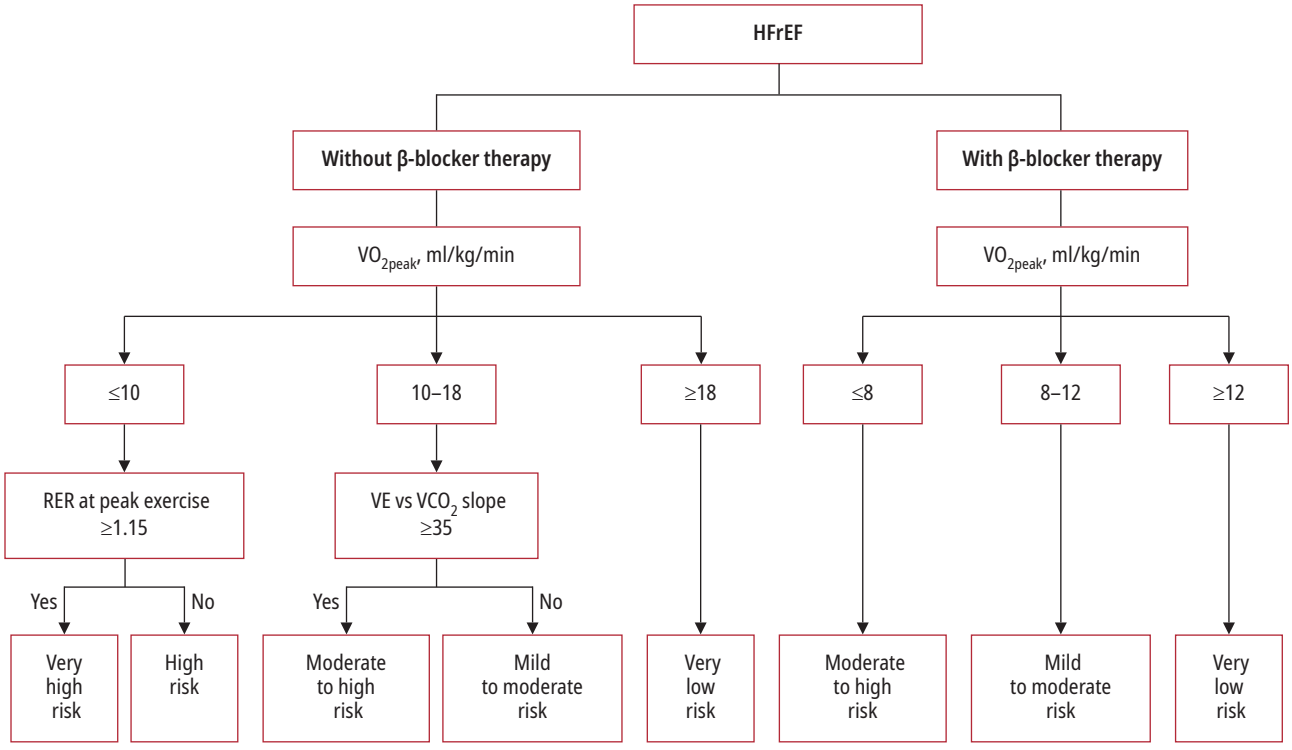

FIGURE 2 The algorithm based on cardiopulmonary exercise tests results, for risk stratification in patients with heart failure with reduced ejection fraction modified from The Committee on Exercise Physiology and Training of the Heart Failure Association of the European Society of Cardiology[41]
Abbreviations: HFrEF, heart failure with reduced ejection fraction; others, see TABLES 1 and 3

Evaluation of heart failure progress Traditional evaluation of heart failure progress is based on the Weber classification presented in TABLE 6.[7] Parameters describing ventilation effectiveness (VE vs VCO_2 slope, $PETCO_2$, EOV) are also increasingly often used to assess heart failure progress.[5] The ventilatory classification is shown in TABLE 7.[50]

Prognosis in heart failure CPET for evaluation of prognosis is performed at least 1 month after an episode of acute decompensated heart failure in patients in a stable clinical condition with established pharmacotherapy, which is defined as the lack of changes in the NYHA class and treatment, and no need for hospitalization during the last 4 weeks.[43,44] There are indications that the patient's ability to perform the test can itself be considered a predictor of a better prognosis.[43] According to the literature, patients with low VO_{2peak} (≤10 ml/kg/min) and RER of 1.15 or more have the worst prognosis.[43]

Risk stratification algorithms in heart failure based on cardiopulmonary exercise testing The Committee on Exercise Physiology and Training of the Heart Failure Association of the European Society of Cardiology published a proposal for CPET-based risk stratification of patients with heart failure.[43] The patients were divided according to "nonstandard" or "standard" criteria of a referral for the test.

The nonstandard group, requiring individual specialized interpretation of results, included patients over 70 years of age, women, patients with atrial fibrillation or comorbidities affecting exercise tolerance, patients with an implanted left ventricular assist device, patients who could only perform submaximal CPET (ie, achieved RER <1.0), patients with indications for end-point evaluation or serial CPETs (a repeated test is suggested in patients with peak oxygen uptake <14 ml/kg/min and if there is disproportion between patient symptoms and results of other tests).

The standard group included all other patients with heart failure with a reduced left ventricular ejection fraction. The algorithm for CPET risk assessment in this group of patients is shown in FIGURE 2. When EOV occurs during the test, the risk is increased by 1 level in all patient subgroups.

Risk assessment in patients with HFpEF was based on $\%VO_{2pred}$. Patients who achieved VO_{2pred} below 50% were considered mild to moderate risk, and the remaining patients with 50% or higher VO_{2pred} were considered very low risk.[43,44,47-49]

Certain CPET parameters were included in multiparameter prognostic factors developed for patients with chronic heart failure. For example, the Metabolic Exercise test data combined with Cardiac and Kidney Indexes (MECKI) score is based on $\%VO_{2pred}$ and VE versus VCO_2 slope, as well as other values.[45]

Cardiopulmonary exercise testing in patients with chronic heart failure: summary

1 Indications: evaluation of the stage of congestive heart failure (qualification for a heart transplantation and / or mechanical circulatory support), optimization of exercise training program, evaluation of dyspnea of unspecified origin, evaluation of ischemia.

2 Main parameters: VO_{2peak} (at RER >1.05), $\%VO_{2pred}$, VO_2 at AT, VE versus VCO_2 slope, PET-CO_2, EOV, degree of HR decrease during rest, arrythmias, blood pressure.

Adults with congenital heart diseases CPET is a necessary parameter for monitoring patients with adult congenital heart disease (ACHD). The main evaluated parameters include: VO_{2peak}, ventilation efficiency (VE vs VCO_2 slope), chronotropic response, HR disorders triggered by physical exercise, and blood pressure response to exercise. CPET result (as well as VO_{2peak}) correlates with the number of hospitalizations and mortality rate in several ACHDs.[51] Regularly repeated CPET helps decide on the necessity and timing of potential intervention.

CPET in patients with ACHD can be performed on a bicycle ergometer or on a treadmill.[52-54] During the test, close monitoring of electrocardiogram is necessary due to frequent occurrence of arrythmias, particularly in patients with tetralogy of Fallot and in patients with transposition of the great arteries (TGA). When evaluation of the myocardial ischemia is necessary (eg, aortic stenosis, coronary artery anomalies), a test on bicycle ergometer is preferred, due to a lower number of movement artefacts in the electrocardiogram. Blood pressure measurements during the test are particularly important in patients with aortic coarctation (CoA) or arterial stenosis. Monitoring of arterial blood oxygen saturation by pulse oximetry throughout the test is also recommended (also during the initial stage, for assessment of initial saturation). In patients with cyanotic defects or with PH, pulse oximetry ensures safe performance of the test.

For assessment of patients with ACHD, ramp-type and customized protocols are recommended.[55-59]

Indications for cardiopulmonary exercise testing in patients with adult congenital heart disease Indications for CPET in ACHD include:

1 The need for precise and reliable evaluation of exercise tolerance in patients with ACHD as part of regular evaluation in specialized healthcare centers (in particular patients after repair procedures such as repaired tetralogy of Fallot, TGA, Fontan procedure as well as patients with Eisenmenger syndrome)[60]

2 Initial symptom evaluation (eg, in patients with bicuspid aortic valve and aortic valve stenosis, or who underwent heart defect surgery as a child)

3 Evaluation of chronotropism, presence of atrioventricular blocks before pacemaker implantation

4 Evaluation of pharmacotherapy

5 Evaluation of cardiac rehabilitation results

6 Evaluation of surgery results.

Contraindications to cardiopulmonary exercise testing in patients with adult congenital heart disease Contraindications do not differ from those specified for electrocardiographic exercise testing. Additionally, the following should be considered (as relative contraindications):

1 Severe aortic / pulmonary / mitral stenosis

2 Significant right or left ventricular outflow tract obstruction (LVOTO)

3 Arterial anomalies requiring surgical treatment

4 Severe PH.

The most important cardiopulmonary exercise testing parameters in patients with adult congenital heart disease VO_{2peak} is the best individual indicator for exercise tolerance, risk of hospitalization, and death. Women reach 65% to 75% of VO_{2peak} achieved by men (excluding patients with Eisenmenger syndrome).[61] The lowest VO_{2peak} values are observed in patients with Eisenmenger syndrome, those with cyanotic heart defects, those after Fontan procedure, those with corrected TGA (with accompanying defects, eg, ventricular septal defect and pulmonary valve stenosis) or with TGA after physiological corrections, for example, after Mustard / Senning repair. The highest VO_{2peak} is observed in patients with TGA after anatomical correction, in patients with valvular defects, and after surgical repair of CoA. Patients with cyanotic heart defects have the worst exercise tolerance amongst all patients with ACHD.[62]

VE versus VCO_2 slope is the best mortality predictor in noncyanotic patients.[63] The highest values are observed in PH patients in the course of congenital heart disease, with complex heart defects, with cyanotic heart defects with a right--to-left shunt, and the lowest in patients with TGA after anatomical correction and in patients with CoA.[63,64]

AT is frequently not achieved in patients with cyanotic heart defects, with complex heart defects and with the weakening of skeletal muscles.

HR reserve depends on the exercise level. It is an independent predictor of death in patients with ACHD, also in patients treated with negative chronotropic medications.[64]

The analysis of the most important CPET parameters in the selected ACHDs is shown in TABLE 8.

Application of cardiopulmonary exercise testing in selected adult congenital heart diseases Patients with ACHD, due to long-term adaptation to the disease, even when asymptomatic, can have

significantly lowered VO_{2peak}. In these patients, many factors contribute to the etiology of lower exercise tolerance. Patients with simple noncyanotic defects not accompanied by PH have higher exercise tolerance than those with complex cyanotic defects or with PH. CPET results allow deciding to modify pharmacotherapy and determine timing of cardiac intervention, especially in patients with tetralogy of Fallot after surgical correction, Ebstein anomaly, or after Fontan procedure. In patients with repaired tetralogy of Fallot, significant pulmonary valve insufficiency develops in the course of the disease, as well as dilation and impaired function of the right ventricle. Reduced VO_{2peak} indicates lack of cardiac and circulatory reserves to adequately increase SV during exercise. The accompanying deterioration in the right ventricular function in echocardiography supports the decision to replace the pulmonary valve. CPET is also a well established tool for monitoring patients with a pulmonary valve dysfunction in many heart defects after percutaneous pulmonary valve implantation.[65] Reduced exercise tolerance recorded in CPET in patients with Ebstein anomaly and significant tricuspid valve insufficiency is a generally recognized indication for a valve repair (class IC recommendation according to ESC).[60,66]

The range of normal values to be used for the interpretation of CPET results in patients with ACHD remains a controversy. It is not recommended to compare the exercise capacity of patients with ACHD with that of healthy people, as in this group of patients exercise tolerance differs depending on the type of heart defect or even on the repair procedure performed. Patients with TGA after physiological repair procedures can serve as an example here, as their capacity is significantly lower than that of patients with TGA after anatomical corrections. Another example are patients after the Fontan procedure who, depending on the operation method (standard surgery – aortopulmonary collaterals vs total cavopulmonary connection) can have an entirely different exercise capacity. The best solution to this problem would be individual databases with reference values for particular heart defects created by each center providing care to patients with ACHD.[62]

Cardiopulmonary exercise testing in patients with adult congenital heart disease: summary

1 Indications: an objective assessment of exercise tolerance in patient after repair procedures, evaluation of symptoms related to exercise, evaluation of chronotropic response, evaluation of pharmacotherapy and/or surgery outcomes, and evaluation of the rehabilitation progress.

2 Main parameters: VO_{2peak}, VE vs VCO_2slope, chronotropic response, HR reserve, arrhythmias, and blood pressure.

Hypertrophic cardiomyopathy The recommendations of American Heart Association regarding exercise stress tests list HCM with LVOTO and significant gradient as a relative contraindication to an exercise stress test.[3] However, recent data[67,68] suggest that exercise stress tests in patients with HCM are not only safe, but can also be an important part of a comprehensive evaluation. CPET, according to ESC guidelines, is recommended to evaluate the progression and mechanism of exercise tolerance, and to evaluate changes in SBP during exercise (IIa/B).[69] CPET does not replace stress echocardiography but is its a valuable supplement.[70]

TABLE 8 Analysis of the most important cardiopulmonary exercise testing parameters in the selected congenital heart diseases in adults

ACHD	VO_{2peak}	VE vs VCO_{2slope}	VO_2-AT	HR max	O_2 pulse	Comments
rToF	↓↓↓	↑↑↑	↓↓	↓↓	↓↓↓	Most common in patients with pulmonary regurgitation
Ebstein anomaly	↓↓↓	↑↑	↓↓	↓↓	↓↓↓	–
TGA after M/S procedure	↓↓↓	↑↑	↓↓	↓↓	↓↓↓	See comment on the bottom
CoA	↓↓	↑	↓↓↓	↓	↓↓	Hypertensive SBP response to exercise has prognostic value
Fontan circulation	↓↓↓↓	↑↑↑↑	↓↓↓	↓↓↓	↓↓↓↓	Patients after TCPC have better exercise capacity than after APC
Eisenmenger syndrome	↓↓↓↓	↑↑↑↑	↓↓↓↓	↓	↓↓↓↓	Drop in SaO_2 Often do not achieve VT

Patients with TGA after anatomical correction (arterial switch; Jatene procedure) are usually asymptomatic; signs of ischemia can be present during CPET

↑, occasionally elevated; ↑↑, sometimes elevated; ↑↑↑, often elevated; ↑↑↑↑, most often elevated; ↓, occasionally decreased; ↓↓, sometimes decreased; ↓↓↓, often decreased; ↓↓↓↓, most often decreased

Abbreviations: APC, atriopulmonary connection; CoA, coarctation of the aorta; M/S, Mustard/Senning repair; rToF, repaired tetralogy of Fallot; TGA, transposition of the great arteries; TCPC, total cavopulmonary connection; others, see TABLES 1, 3, 4, and 5

Electrocardiographic evaluation during exercise In an electrocardiogram of HCM patients, the most commonly observed signs are left ventricular hypertrophy with ST segment depression and pathological Q waves. In an apical HCM, deep inverted T waves are observed in precordial leads. In many patients with HCM, conduction disturbances are observed, especially left bundle branch block.[71] The presence of the above changes prevents reliable evaluation of ischemia during exercise. In 45% of patients with HCM, arrhythmia may occur during exercise: atrial fibrillation in 2%, nonsustained ventricular tachycardia in 1.2%, and single ventricular ectopic beats in 33%.[72]

Blood pressure profile evaluation Four types of blood pressure response to exercise can be observed in patients with HCM: 1) hypotensive response with a continuous drop in SBP from the start of exercise; 2) hypotensive response in the form of a sudden drop in SBP from the maximum value; 3) normal SBP response during exercise, but an initial rapid drop at the early stage of recovery, and then a gradual increase by 10 mm Hg from the minimum value; 4) normal blood pressure response.

Inadequate blood pressure response to exercise in HCM is usually defined as SBP drop or increase by less than 20 mm Hg versus initial values and is observed in 20% to 40% of patients. Abnormal blood pressure response provides prognostic information and is considered one of the markers for the risk of death in patients with HCM.[73-76] Inadequate blood pressure response to exercise has low positive and high negative predictive value, thus it is the most useful for the identification of patients with a lower risk of death.[74] Therefore, patients with an abnormal blood pressure response require other additional tests to stratify the risk of death.

Differential diagnosis CPET is a useful supplementary tool in the differentiation of HCM and athletic heart, especially in patients with unclear echocardiographic images (the so-called grey zone wall thickness). In patients with HCM, a reduction in VO_{2peak} and in VO_2-AT is to be expected, but in people with athletic heart, VO_{2peak} should reach values of more than 50 ml/kg/min (or >20% above the predicted value).[77]

Prognostic value Numerous studies demonstrated that VO_{2peak} is correlated with many clinically significant variables, for example, degree of diastolic dysfunction or quality of life.[78,79] Furthermore, a reverse correlation with the pressure gradient in the left ventricular outflow tract was also identified, while myectomy and alcohol ablation procedures aiming at a reduction in LVOTO cause an increase in VO_{2peak}.[80,81] In a study conducted at Mayo Clinic on a group of 182 patients with HCM and LVOTO, with or without mild symptoms, lower $\%VO_{2pred}$ values were associated with a higher risk of a composite endpoint defined as an all-cause mortality rate and progression to advanced heart failure.[82]

It was proven several times that low VO_{2peak} is an independent predictor of serious adverse events in HCM.[67,68] In another large study including 1898 patients with HCM (62% with LVOTO), VO_{2peak}, VO_2-AT, and VE versus VCO_2 slope were predictors of all cause mortality and heart transplantation.[83]

In the assessment of the eligibility for transplantation, a value of VO_{2peak} of 14 ml/kg/min or less (or <50% VO_{2pred}) is considered one of the qualifying criteria.[84] CPET is recommended in patients with severe clinical symptoms, left ventricular systolic and/or diastolic dysfunction as part of evaluation for heart transplantation or for the left ventricular assist device implantation (I/B).[69]

Qualification for alcohol ablation and myectomy According to ESC guidelines,[69] CPET should be considered in symptomatic patients who are referred for septal myectomy or alcohol ablation to evaluate exercise tolerance (IIa/C). There are no data available indicating specific values for VO_{2peak} that would support a decision for earlier myectomy or alcohol ablation in patients with LVOTO with mild symptoms, or for delaying the procedure in patients with significant LVOTO but normal values of CPET parameters.[85]

Follow-up and risk stratification CPET can provide objective evidence for disease progression, but the frequency of performance of the follow-up CPET is not extensively supported by scientific evidence, and according to ESC guidelines this test can be considered every 2 to 3 years in patients in a stable clinical condition or every year in patients whose symptoms are progressive (IIb/C).[69]

There are several risk models described in the literature which are based on echocardiography and CPET. In the Hypertrophic Exercise-derived Risk HF model for the evaluation of a composite endpoint (death due to heart failure, heart transplantation, progression of heart failure to NYHA class III–IV, exacerbation of heart failure requiring hospitalization, septal myectomy, and alcohol ablation procedures), the peak circulatory power (a product of VO_{2peak} and peak SBP), VE vs VCO_2 slope, and left atrium dimension (in a parasternal long-axis view) were independently related to the composite endpoint.[68]

Finocchiaro et al[86] demonstrated that reduced physical capacity (<80% VO_{2pred}), VE vs VCO_2 slope higher than 34, and the left atrial volume index higher than 40 ml/m^2 were independent predictors of the composite endpoint (procedures of intraventricular septum reduction,

heart transplant, and cardiac death). Similarly, in a large study including 1005 patients with HCM, lower absolute and percentage predicted VO_{2peak}, inadequate chronotropic response, and a lower left ventricular ejection fraction were independent predictors of the composite endpoint (adequate discharges of a cardioverter-defibrillator, resuscitation, stroke, heart failure, and death).[67]

Cardiopulmonary exercise test in patients with hypertrophic cardiomyopathy: summary

1 Indications: assessment of progression and mechanism of exercise intolerance, assessment of changes in SBP during exercise.

2 Main parameters: VO_{2peak}, $\%VO_{2pred}$, VE versus VCO_2 slope, $PETCO_2$, SBP, arrhythmias, ST-segment and T-wave changes.

Pulmonary hypertension CPET is performed in patients with PH in evaluation of disease progression, presence of patent foramen ovale with a right-to-left shunt, and evaluation of prognosis, treatment response, and indications for heart and lung transplant.[5,25,27,87-89] Contraindications to CPET include syncope, significant arrhythmia, and acute right ventricular heart failure.

In patients with pulmonary arterial hypertension (PAH), ESC proposed complex prognostic evaluation, which includes 2 CPET parameters: VO_{2peak} and VE versus VCO_2 slope.[88]

In patients with PH, both primary and secondary, the evaluation of VO_{2peak}, VE versus VCO_2 slope, and $PETCO_2$ during exercise is useful, as changes in these parameters are related to mismatch between pulmonary perfusion and ventilation.[87]

TABLE 9 Changes in ventilation parameters in pulmonary arterial hypertension

Parameter	Change
$PETCO_2$ at rest	Reduced
$PETCO_2$ at AT	Markedly reduced
VD/VT during exercise	Increased
VE vs VCO_2 slope during exercise	Markedly increased
SpO_2 during exercise	Reduced

Abbreviations: see TABLES 3 and 4

TABLE 10 Cardiopulmonary exercise testing parameters in the evaluation of 1-year mortality risk in pulmonary arterial hypertension

Risk	VO_{2peak}	VE versus VCO_2 slope
Low (<5%)	>15 ml/kg bw/min	<36
Moderate (5–10%)	11–15 ml/kg bw/min	36–44.9
High (>10%)	<11 ml/kg bw/min	≥45

Abbreviations: see TABLES 1 and 3

Changes in VE/VCO_2 and $PETCO_2$ in patients with PAH will be different as compared with patients with PH caused by left heart disease or related to lung diseases and/or hypoxia. These parameters are the basis for differential diagnosis of etiologies of PH.[90]

CPET result in patients with PH is characterized by low $PETCO_2$, high VE versus VCO_2 slope, low O_{2pulse}, and low VO_{2peak}.[91] Regardless of the etiology of PH, VO_{2peak} is reduced proportionally to the disease severity, depends on the level of pulmonary vascular resistance and reduced SV. In young people, $\%VO_{2pred}$ appears to be more appropriate, and in this respect CPET has an advantage over the 6-minute walk test. On the basis of high VE versus VCO_2 slope or VE/VCO_2 values, and low $PETCO_2$ values (decreasing during exercise), conclusions can be drawn on the progress of anomalies in the hemodynamic parameters of pulmonary circulation and a poor prognosis for patients.[90]

In many patients with PAH, chronic thromboembolic PH, and PH associated with lung disease/hypoxia, SpO_2 drops during CPET. TABLE 9 presents changes in ventilation parameters in PAH.

In patients with PAH, CPET can reveal the presence of a right-to-left shunt on the atrial level, as a consequence of an increase in right atrial pressure exceeding left atrial pressure during exercise. The criteria for shunt diagnosis include low $PETCO_2$ at rest, with a drop at the beginning of exercise with a simultaneous sudden increase in $PETO_2$, VE/O_2, and RER, and with an accompanying drop in SpO_2.

CPET is recommended for a periodic assessment of patients with PAH every 6 to 12 months, and additionally, in case of clinical exacerbation.[88] TABLE 10 demonstrates the use of CPET parameters for the evaluation of a 1-year mortality risk in PAH.

Cardiopulmonary exercise testing in pulmonary hypertension: summary

1 Indications: evaluation of disease progression, presence of patent foramen ovale with a right-to-left shunt, and the evaluation of prognosis, treatment results, and indications for heart and lung transplants

2 Main parameters: VO_{2peak}, VE versus VCO_2 slope, $\%VO_{2pred}$, $PETCO_2$, SpO_2, SBP, arrhythmias

Coronary artery disease CPET improves diagnostic, prognostic and monitoring possibilities of the electrocardiographic exercise test in coronary artery disease (CAD).[92,93] Sensitivity and specificity of CPET in CAD diagnostic workup are higher than those of the electrocardiographic exercise test (87% vs 46% and 74% vs 66%, respectively). This enables diagnosis in patients who previously had electrocardiographic exercise test determined as negative.[92] The main advantage of CPET over other diagnostic methods

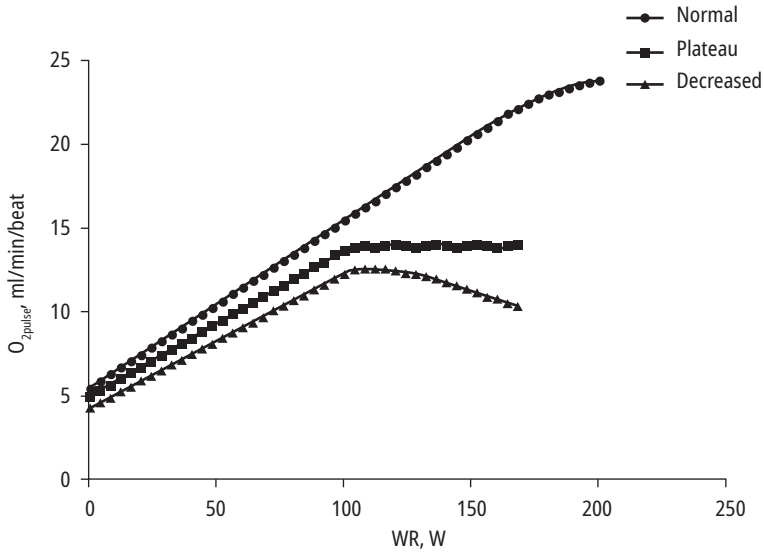

FIGURE 3 Normal and pathological courses of oxygen pulse versus work rate

Abbreviations: see TABLES 4 and 5

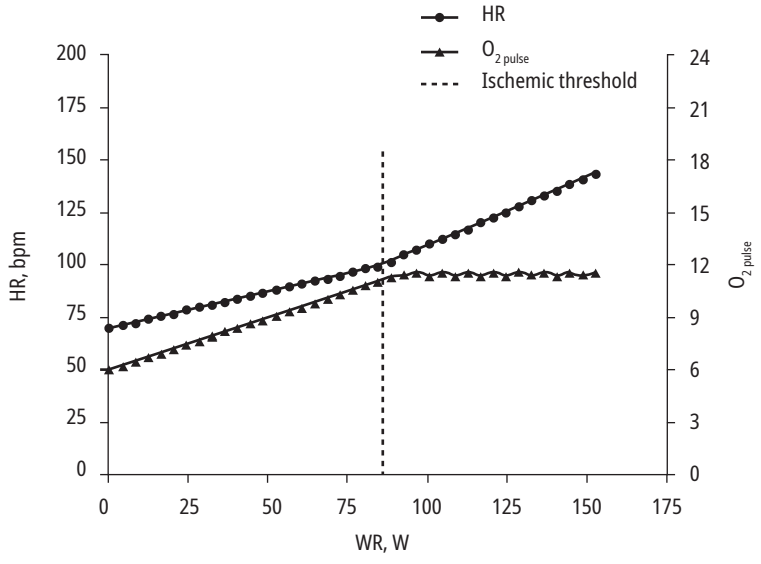

FIGURE 4 Trends of heart rate (y1-axis) and oxygen (y2-axis) in relation to work rate (x-axis) in a patient with exertional myocardial ischemia

Abbreviations: see TABLES 3, 4 and 5

used to diagnose CAD is the possibility to find and evaluate quantitatively functional hemodynamic disturbances induced by ischemia.[94,95] In a cascade of ischemic changes caused by progressively increasing exercise, these hemodynamic disturbances precede electrocardiographic (ST depression/elevation) and clinical (chest pain) signs of ischemia. This is of particular clinical importance for the identification of the early stages of ischemic heart disease without significant coronary stenosis.[96] This clinical form of CAD, symptomatic or presenting as atypical picture, affects women more frequently than men, and is characterized by an increased risk of acute coronary syndromes.[97] Its early diagnosis enables the initiation of complex management including reduction of modifiable risk and pharmacotherapy.

Hemodynamic and electrocardiographic anomalies secondary to ischemia are analyzed in CPET on the basis of[5,92-96]:

1 Trend in O_{2pulse} vs WR: the course of the O_{2pulse} curve in relation to WR
2 Trend in VO_2 vs WR: the course of the VO_2 curve in relation to WR
3 Hemodynamic response to exercise (trend in HR vs WR: the course of the HR curve in relation to WR, SBP)
4 Relative capacity ($\%VO_{2pred}$)
5 Electrocardiographic evaluation
6 Reason for termination of the test.

O_{2pulse} and VO_2 are parameters reflecting SV and cardiac output.[98] The course of O_{2pulse} trend versus WR, which is a straight line in healthy people, is flattened (plateau) or even reduced when systolic dysfunction occurs due to cardiac ischemia. FIGURE 3 is a schematic representation of normal and pathological courses of O_{2pulse} versus WR.

In normal conditions, the straight-line HR growth rate is observed in relation to the increasing load. In patients with a normal chronotropic response to exercise and ischemia induced by exercise with an accompanying drop in SV, a compensating higher HR increase occurs when compared during the initial period of exercise, below VT1. A schematic representation of HR and O_{2pulse} trends in relation to the load is shown in FIGURE 4.

In patients with impaired chronotropic response to exercise due to pathological or iatrogenic causes, the impaired SV resulting from cardiac ischemia induced by exercise is manifested as a clearly disrupted course of the VO_2 versus WR curve, analogically as the O_{2pulse} versus WR trend (FIGURE 5).

In the final CPET report, the character of the O_{2pulse} versus WR and VO_2 versus WR trends ought to be described as: ongoing increase with a rising load; early, maintained plateau; early plateau and a reduction during exercise.[5]

Relative capacity, calculated as $\%VO_{2pred}$, relates to ischemic disease progression, although it is not a specific parameter.[5] $\%VO_{2pred}$ values in successively repeated CPET have a great prognostic importance, also confirming the effectiveness of treatment.[94,96]

Diagnostic stratification of patients with suspected myocardial ischemia based on CPET is shown in TABLE 11.[5,95,96]

Cardiopulmonary exercise testing in coronary artery disease: summary

1 Indications: diagnostic workup of ischemia.
2 Main parameters: O_2 pulse versus WR trend, VO_2 versus WR trend, HR versus WR trend, SBP, $\%VO_{2pred}$, ST-segment and T-wave changes, arrhythmias, reason for termination of the test (lower extremity muscle fatigue, angina, dyspnea).

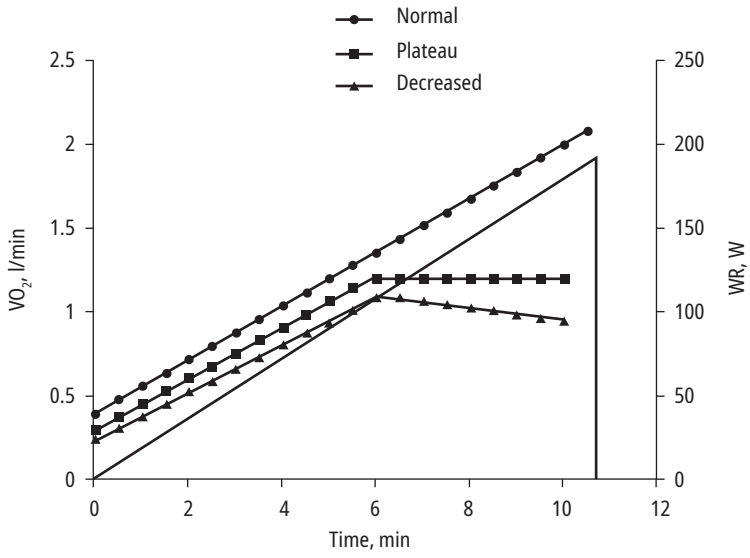

FIGURE 5 Normal and pathological courses of oxygen uptake (y1-axis) in relation to work rate – solid line (y2-axis)

Abbreviations: see TABLES 1 and 5

Patients with implantable devices CPET is increasingly used in the evaluation of patients with cardiac implantable electronic devices (CIEDs): pacemakers, implantable cardioverter-defibrillators, and cardiac resynchronization devices (CRT). The most common CPET application in patients with CIEDs is patient evaluation before and after CRT implantation, evaluation of chronotropic capacity, and optimization of stimulation thresholds.

The most important CPET parameters in patients with CIEDs are: VO_{2peak}, ventilation efficiency (VE vs VCO_2 slope), chronotropic response (particularly in heart failure patients), evaluation of stimulation effectiveness during exercise (important in patients with CRT), and heart rhythm disorders caused by exercise.

Test methods and protocol selection In patients with CIED, treadmill is the preferred device because of higher VO_{2peak} obtained and a better chronotropic response in patients with a rate-responsive function activated.[52,53,99] The evaluation of myocardial ischemia in an electrocardiogram is difficult in patients with a stimulated ventricular rhythm. The same load protocols are applied as in patients without CIED. In patients with CRT, protocols used for the evaluation of patients with heart failure are preferred.[55] Before a patient with CIED undergoes a test, it is necessary to determine the device settings, especially its base stimulation rate, maximum tracking rate, atrioventricular delay, thresholds for detecting arrhythmias in patients with implantable cardioverter-defibrillators and CRT defibrillator (so-called ventricular tachycardia/ventricular fibrillation detection zones), and a programmed algorithm for ventricular tachycardia/ventricular fibrillation termination with antitachycardia pacing or defibrillation. The target HR during exercise should be 10 to 20 bpm lower than the detection threshold for arrhythmia. The device can also be reprogrammed, for example, with therapy deactivated in the ventricular tachycardia zone, by increasing ventricular fibrillation detection threshold to more than 220 bpm, or by increasing arrhythmia detection threshold above maximum HR.[27] In such situation, the person programming the device should be present during the test. In pacemaker-dependent patients and in patients with CRT, attention should be paid to the HR value at which 1:1 conduction is maintained. Exceeding this value may cause a sudden slowing of the frequency of the stimulated ventricular rhythm, a drop in SV, and hemodynamic symptoms. The frequent occurrence of such symptoms requires the reprogramming of the device, particularly, in young patients with good physical exercise tolerance,

TABLE 11 Diagnostic stratification of patients with suspected myocardial ischemia (modified from Guzzi et al[5])

Data from CPET	Risk of ischemic heart disease		
Parameter	Low	Moderate	High
O_{2pulse} vs WR trajectory	Continual rise	Early and sustained plateau	Early plateau and drop during exercise
VO_2 vs WR trajectory	Continual rise	Early and sustained plateau	Early plateau and drop during exercise
$\%VO_{2pred}$	≥100%	99–75% 74–50%	<50%
HR vs WR trajectory	Linear rise HR vs WR with possible flattening only at peak exercise		Higher HR increase after AT
Blood pressure	Rise	Flat response	Drop
ECG	Absence of arrythmia, conduction disturbances, ST changes	Arrythmia, conduction disturbances, ST changes not lead to test termination	Arrythmia, conduction disturbances, ST changes lead to test termination
Patient reason for test termination	Muscle fatigue	Angina	Dyspnea

Abbreviations: ECG, electrocardiogram; O2pulse, oxygen pulse; others, see TABLES 1, 3, and 4

in whom an increase in the maximum tracking rate is recommended.[100]

Indications and contraindications to cardiopulmonary exercise testing in patients with cardiac implantable electronic devices Indications for CPET in patients with CIEDs include: 1) evaluation before CRT implantation and evaluation of the response to CRT, 2) evaluation of the chronotropic response and settings of the rate-responsive pacing, 3) optimization of atrioventricular delay in patients with sequential stimulation, 4) evaluation prior to rehabilitation and qualification for training, 5) evaluation of rehabilitation results.

Absolute contraindications include: hemodynamically significant arrhythmias, electrical storm, pacing and sensing disturbances.

Current and potential cardiopulmonary exercise testing applications in patients with cardiac implantable electronic devices CPET is used as a reference method for the evaluation of heart failure patients to qualify patients for CRT and objectively evaluate the resynchronization therapy.[101,102] VO_{2peak} improvement is commonly accepted as one of the criteria of response to CRT.[103-105] The volume of data indicating that initial VO_{2peak} might predict a response to CRT is increasing.[106-109]

CPET is also used for the optimization of stimulation program (eg, a reduction in excessive stimulation by elongating the atrioventricular interval) and in the selection of an appropriate simulating program for patients with chronotropic incompetence.[110,111] Chronotropic incompetence, frequently occurring in patients with congestive heart failure, limits exercise tolerance and can be reduced by the appropriate programming of the device, and evaluation with CPET is useful in that respect.[112-114]

However, further multicenter studies on the role of CPET in patients with CIEDs, especially with CRT, are necessary to establish the role of that test in that group of patients.

Cardiopulmonary exercise testing in patients with cardiac implantable electronic devices: summary

1 Indications: patient evaluation before and after CRT implantation, evaluation of chronotropic capacity and optimization of stimulation thresholds, evaluation before planned rehabilitation.
2 Main parameters: VO_{2peak}, VE versus VCO_2 slope, chronotropic response, stimulation effectiveness during exercise, arrhythmias caused by exercise.
3 Notes: before starting the test, it is necessary to become acquainted with the setting of the implanted device.

Chronic pulmonary diseases CPET is a useful tool in evaluation of respiratory diseases. Its performance is especially warranted in the context of symptoms related to exercise. CPET should be considered in the following clinical scenarios: exertional dyspnea, concurrent pulmonary and nonpulmonary causes of exertional dyspnea, subclinical forms of pulmonary disorders, basic diagnostic methods resulting in an ambiguous diagnosis, or prognosis assessment in chronic disorders.[115,116] Each CPET should be preceded by spirometry at rest, which is one of the basic diagnostic tools in respiratory disorders.

Diagnostic value of cardiopulmonary testing in obstructive lung diseases In accordance with the recommendations of the Global Initiative for Asthma, bronchial asthma can be diagnosed on the basis of spirometry at rest, when the FEV_1 to forced vital capacity ratio drops below 0.75 to 0.8 of the predicted values.[115] The guidelines of the Global Initiative for Chronic Obstructive Lung Disease specify the FEV_1 to forced vital capacity ratio value below 0.70 after inhalation of bronchodilator as a cutoff value for COPD diagnosis.[116] CPET may prove to be an indispensable tool in the case of exercise-induced bronchial obstruction. To document its occurrence, it is recommended to record the flow-volume loop before exercise, at its peak and during the post-exercise phase.[26,117-119] Diseases accompanied by bronchial obstruction change the shape of this curve (FIGURE 6).

CPET also enables the evaluation of mechanisms underlying exertional dyspnea. An increase in VE versus VCO_2 slope and VE/VCO_2 nadir indicates that the physiological VD is increased, while an abnormal shape of the flow-volume curve reflects the magnitude of exertional obstruction. Low (<20% of predicted value) BR value at the peak exercise may suggest a ventilation-related cause of reduced exercise tolerance.[120]

Prognostic value of cardiopulmonary exercise testing in obstructive lung diseases In COPD, the prognostic value was proven for VE versus VCO_2 slope (poorer 4-year prognosis for the result >30.0, with subsequent cutoff points for 35.9 and 44.9), $PETCO_2$ (poorer prognosis for the at-rest value <33.0 mm Hg and the exercise-related increase <3 mm Hg), and for VO_{2peak} (poorer prognosis in Weber classes >A).[5] VO_{2peak} can be taken into account if exercise was terminated with RER higher than 1.0 or due to electrocardiographic abnormalities or pathological hemodynamic response.[26]

Diagnostic value of cardiopulmonary testing in restrictive lung disease CPET changes specific for restrictive lung diseases are: lower VO_{2peak} and an increase in parameters related to the enlarged physiological VD. As similar anomalies can also occur in obstructive disease, spirometry at rest and the flow-volume loop during and after exercise should also be evaluated. BR evaluation may also be useful (usually >50% at peak exercise in restrictive disorders).[32]

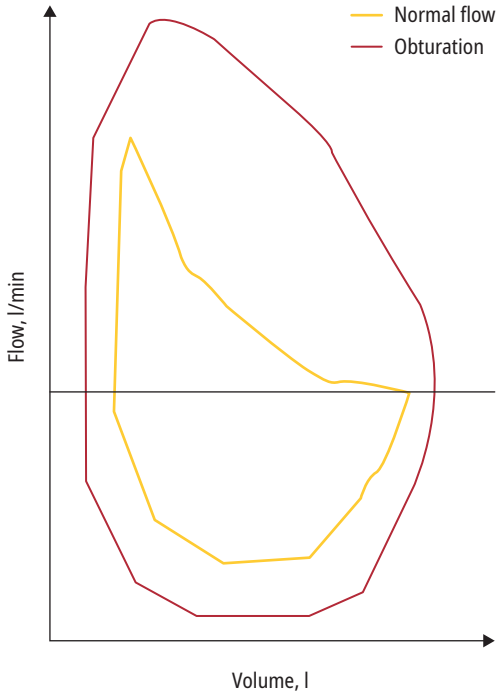

FIGURE 6 Flow–volume loop

Prognostic value of cardiopulmonary exercise testing in restrictive lung disease CPET parameters used in the prognostic evaluation are analogous to those used in obstructive lung diseases.[26,116]

Chest wall pathologies Patients with disorders affecting the chest wall such as chest deformations, muscle disorders, and severe obesity present a reduced VO_{2peak}. CPET allows to establish whether exertional dyspnea is masking comorbidities, and this is of particular importance for obese people. Chest wall disorders as a basic mechanism of exertional dyspnea may be suspected in the case of high BF accompanied by their low volume and a high VT/IC ratio.[40]

Preoperative evaluation In the case of patients with planned pulmonectomy or lobectomy, values of VO_{2peak} higher than 15 ml/kg/min are associated with a better prognosis, even in patients with worse lung function in spirometry. The values lower than 10 ml/kg/min are associated with a poorer prognosis.[25,121,122] Prognosis is also negatively affected by exercise-related abnormalities in the electrocardiogram and by specified symptoms of CAD.[26]

Cardiopulmonary exercise testing in chronic lung diseases: summary

1 Indications: exertional dyspnea, suspected exertional obstruction, subclinical forms of pulmonary disorders, prognosis evaluation in chronic diseases, preoperative evaluation.

2 Main parameters: VO_{2peak}, VE versus VCO_2 slope, $PETCO_2$, BR, SpO_2, and a flow-volume loop.

3 Note: exercise testing should be preceded by resting spirometry, exercise induced bronchospasm may also occur after cessation of exercise.

Clinical oncology This subchapter discusses the role of CPET in patient evaluation during oncologic treatment or follow-up in cancer survivors. Risk stratification with the CPET before surgeries in patients with cancer is discussed in section Pre- and postoperative assessment below.

Differential diagnostics of dyspnea in oncology Cardiopulmonary capacity, and thus patient functional performance, belong to the most important clinical criteria for cancer treatment eligibility. An objective evaluation can be difficult in certain populations, such as elderly people, patients with obesity or metabolic disorders, cancer of the respiratory system, and abnormal echocardiography results before they are qualified for potentially cardiotoxic chemotherapy.[122-125] CPET is recommended in patients with cancer, because it enables an objective evaluation of their physical capacity (VO_{2peak} measurements) and differential evaluation of comorbidities limiting exercise capacity.[126] This test remains reliable, regardless of the patient's motivation to make the maximum effort and this may be of importance in those with depression, which is common in oncology patients. Considering that a large percentage of patients with cancer have at least 1 important comorbidity, often cardiovascular, CPET becomes a valuable tool for the objective evaluation of functional performance prior to cancer therapy.[127] The usefulness of VO_{2peak} measurement in oncology was proven in many clinical situations.[128,129] The evaluation of ventilation parameters, such as VE, VT, and BF, is particularly useful in patients with lung cancer, advanced cancer with lungs metastases, and with lung comorbidities.

Evaluation during or after anticancer therapy Cancer therapy (radiotherapy, chemotherapy, molecularly targeted therapy, immunotherapy) and supportive treatment used in oncology (eg, glucocorticoids) may cause heart perfusion anomalies, symptomatic or asymptomatic decrease of left ventricular ejection volume, as well as anemia, autonomic dysfunction, lung fibrosis, pulmonary dysfunctions, endothelial dysfunction, and myopathies.[130-139] In consequence, cancer treatment, both previous, and current, in combination with cancer disease progression, particularly at the metastatic stage, negatively affects aerobic metabolism during exercise by changing the activity and number of red blood cells (anemia), disrupting lung diffusion (damaged alveolar-capillary barrier in lungs), deteriorating ventilation response during exercise, causing changes in oxygen transport (changes in the function of capillaries), and disrupting the respiratory chain (mitochondrial damage).[140]

One of the most important problems in modern clinical oncology is cancer-related fatigue, associated with cancer disease itself, and with its treatment. One of the meta-analyses establishes the influence of various forms of recommended exercise during cancer therapy on the subjective feeling of fatigue.[141] Eighteen studies with randomization (12 on breast cancer, 4 on prostate cancer, 2 on other cancers) were analyzed. In patients with breast cancer, only controlled aerobic exercise led to a significant reduction in cancer-related fatigue. Another meta-analysis focused on whether physical activity is appropriate and effective in patients during and after cancer therapy.[142] After analyzing 82 studies, it was demonstrated that physical activity is advantageous for muscle strength, symptoms of fatigue, self-esteem, anxiety, functional condition, and quality of life. CPET seems to be an ideal test for the objective evaluation of the sense of fatigue related to cancer treatment, as well as for excluding the progress of concurrent heart failure and encouraging the patient to initiate physical training, even as a form of recreation.

Patients who underwent cancer therapy have lower physical capacity, which, to some extent, must be associated with adverse effects of chemo- and radiotherapy.[143] Even athletes have significant changes in VO_2-AT during exercise after chemotherapy for Hodgkin lymphoma.[144] CPET can, in a simple way, demonstrate a significant difference in deterioration in physical capacity between healthy people and patients who underwent cancer therapy.[145,126]

People who underwent cancer therapy in childhood experience premature complications of cardiovascular and other systems (respiratory, neuroendocrine, etc.), which may significantly reduce their physical capacity.[146] In an age-independent analysis, it was demonstrated that VO_{2peak} is lower in these patients, when compared with healthy peers: in men, 28.53 versus 30.90 ml/kg/min (P = 0.08), and in women 19.81 versus 23.40 ml/kg/min (P = 0.03). Furthermore, in men, older age (P = 0.01), higher content of fat (P <0.001), high or low left ventricular mass (P = 0.03) were predictors of lower VO_{2peak}, while in women lower VO_{2peak} was predicted by older age (P <0.001), methotrexate treatment (P = 0.01), and left ventricular contractility abnormalities (P = 0.02). In conclusion, it was stated that these patients should train regularly with a well-designed plan and appropriate monitoring.

Similarly, young adults who underwent therapy for acute lymphoblastic leukemia are at a higher risk for delayed cardiotoxicity caused by anthracyclines.[147] It was demonstrated that reduced VO_{2peak} (ml/kg/min) might affect 47% of patients, more often those after anthracycline therapy than those undergoing other regimens (56% vs 17%, P <0.001). In a multivariate analysis, anthracycline therapy was negatively correlated with VO_{2peak} (ml/kg/min), while in echocardiography, parameter e' was the best predictor for VO_{2peak} (ml/kg/min). In conclusion, it was emphasized that myocardial contractile dysfunction was correlated with exercise intolerance, particularly, in patients previously treated with anthracyclines.

Evaluation of training results in patients with cancer ESC Position Paper[148] describes aerobic physical exercise as a promising nonpharmacological strategy for the prevention and/or treatment of chemotherapy-induced cardiotoxicity. The listed results included improved cardiopulmonary capacity and cardiovascular function, an increase in the percentage of patients who reach the planned end of chemotherapy, reduced frequency and intensity of adverse effects, such as nausea, fatigability, and pain.

There is an increasing need for a practical use of CPET in patients with cancer to plan their physical training.[127,149,150] Initial CPET not only allows to establish exercise capacity and optimally plan the training intensity, but most importantly, identifies people with contraindications to physical exercise.[151]

Increasingly more patients with cancer want to remain physically active both during cancer treatment and after its completion.[152,153] A normal CPET result can be maintained in these patients if they follow an appropriate training plan and maintain physical activity, regardless of electrocardiographic and echocardiographic abnormalities. This is true even in patients with lung cancer in whom underlying disease reduces lung capacity during exercise.[154,155] After 8 to 12 weeks of training based on HR at AT, a 10% to 12% improvement in VO_{2peak} can be achieved both in healthy people and in patients after cancer therapy.[156] Patients with breast cancer who train regularly during cancer therapy do not experience a decrease in aerobic metabolism during exercise and maintain normal body weight during and post chemo- and radiotherapy.[157] Even patients post bone marrow transplant, training on the basis of AT determined during CPET, improve their ventilation capacity by approximately 28% and reduce their subjective sense of fatigue.[158]

Cardiopulmonary exercise testing in oncology: summary

1 Indications: differential diagnostics of dyspnea, evaluation during or after cancer treatment, qualification for cardiac rehabilitation and evaluation of its results, risk stratification before surgery.

2 Main parameters: VO_{2peak}, VO_2-AT, VE, VT, BF

Pre- and postoperative assessment A trend for the use of preoperative CPET to evaluate the risk of adverse perioperative events and to

plan appropriate perioperative care in patients undergoing surgery is rising globally, particularly in the United Kingdom. However, in Poland the use of CPET for this purpose seems to be significantly limited.

The extensive literature data suggest the use of CPET to predict risk during major surgery, especially major abdominal, colon, urological, liver and bile ducts, liver transplantation, vascular, and chest surgery.[159-169] The importance of patient evaluation after neoadjuvant chemotherapy and radiotherapy preceding oncologic surgery has been demonstrated.[170] CPET may also be useful when referring patients for rehabilitation to improve their capacity before or after surgery.[171]

Indications for preoperative cardiopulmonary exercise testing Indications for preoperative CPET include[172]:

1 Assessment of perioperative morbidity and mortality
2 Obtaining additional information to support cross-disciplinary decision-making processes (eg, organ transplant qualification procedures)
3 Supporting the choice of the best perioperative care (intensive care, high dependency care, or a general ward)
4 Supporting a decision about possible preoperative interventions, that is, expanded evaluation and treatment of comorbidities
5 Assessment of newly diagnosed comorbidities
6 As a part of the qualification for pre- and postoperative rehabilitation program
7 Obtaining additional information before deciding about the type of anesthesia used for the surgery.

Contraindications to cardiopulmonary exercise testing Contraindications to CPET are the same as in other populations (in accordance with the American Thoracic Society guidelines).[1] It should be noted that patients before vascular surgery can undergo CPET, as the abdominal aortic aneurysm of more than 8 cm in diameter is only a relative contraindication to exercise testing. Care should be taken in patients with cancer because of thromboembolic complications common in this group. Although asymptomatic severe aortic stenosis is a relative contraindication to exercise testing, CPET may help decide about the order of procedures in comorbidities.

Prognostic value of cardiopulmonary exercise testing CPET allows the assessment of peri- and postoperative prognosis in numerous types of surgeries. However, unambiguous and final recommendations based on specific parameters cannot be made. The following CPET parameters of were found to have prognostic value: VO_{2peak}, VO_2-AT, VE/VCO_2 at AT.

An attempt can be made to sum up and specify cutoff points for individual parameters in specific types of surgery:

1 Liver transplantation: 90-day survival, VO_2-AT 9 ml/kg/min; 3-year survival, VO_2-AT 11.5 ml/kg/min; and admittance to an intensive care unit, VO_2-AT of less than 9.9 to 11 ml/kg/min
2 Vascular surgery for abdominal aortic aneurysm: 90-day survival, VO_{2peak} 15 ml/kg/min
3 Pancreatic surgery: hospitalization length, VO_2-AT 10–10.1 ml/kg/min
4 Other surgeries within the abdominal cavity: mortality, VO_2-AT 10.9 ml/kg/min.

Data from published studies on hospital, short- and long-term mortality, and hospitalization length postsurgery is shown in Supplementary material, *Table S1*.

Key components of preoperative cardiopulmonary exercise testing interpretation A test report should include parameters of a predictive value for peri- and postoperative risk, that is, VO_{2peak}, VO_2-AT, VE versus VCO_2 slope, and VE/VCO_2 at AT. The reason of limited exercise tolerance should be identified. It is also suggested to include a conclusion about perioperative risk the report, as well as implications concerning further preoperative tests and interventions.

2014 ESC/European Society of Anaesthesiology guidelines do not recommend a routine CPET assessment before noncardiac surgery.[173] Nevertheless, it seems that CPET may be a valuable tool for perioperative risk stratification and for planning of postoperative care. In conclusion, VO_2-AT is an optimal predictor of prognosis for liver, pancreas, and other abdominal surgeries, and VO_{2peak} remains the best prognostic parameter for the abdominal aortic aneurysm.

Cardiopulmonary exercise testing in pre- and postoperative evaluation: summary

1 Indications: pre- and perioperative risk assessment, diagnosis of comorbidities, qualification for pre- and postoperative rehabilitation programs.
2 Main parameters: VO_{2peak}, $\%VO_{2pred}$, VO_2-AT, VE versus VCO_2 slope, VE/VCO_2 at AT.

Cardiac rehabilitation According to the definition by the World Health Organization, cardiac rehabilitation is the sum of activities required to provide the patients with the best possible physical, mental, and social conditions so that they may, by their own efforts, preserve or resume as normal a place as possible in the community.[174] In recent decades, cardiac rehabilitation has evolved from traditional programs based mainly on physical activity towards complex activities covering optimal pharmacotherapy and invasive treatment to reduce clinical symptoms and improve prognosis, modification

of cardiovascular risk factors, physical training, and education, together with psychological support, and social and occupational rehabilitation.

Aims of CPET in cardiac rehabilitation[26,27]:

1 Evaluation of physical exercise tolerance (gold standard); VO_{2max} or VO_{2peak} measurement, and VCO_2
2 Differential diagnosis of dyspnea of unspecified origin
3 Demonstration of disease symptoms that do not occur at rest, including rhythm and conduction disturbances, myocardial ischemia, etc.
4 Stratification of cardiovascular risk related to physical exercise
5 Determination of physical training intensity: loads and HR
6 Evaluation of cardiac rehabilitation results
7 Evaluation of prognosis
8 For the needs of occupational therapy

The preparation of an individual aerobic physical training plan is based on 2 methods:

1 VO_2-AT evaluation (example: when a patient with heart failure achieves VO_{2peak} of 16 ml/kg/min, and VO_2-AT of 12 ml/kg/min at HR of 105 bpm during CPET with a load protocol ramp 10 W/min, then the recommended training HR will be approximately 105 bpm
2 Calculation of training VO_2 on the basis of VO_2 reserve, using an equation proposed by Karvonen et al[175]: T VO_2 = (VO_{2max} – VO_2 rest) (0.01 × training intensity as percentage) + VO_2 rest, where T VO_2 indicates training VO_2. Note that training intensity as percentage is recommended at 40% to 85%, depending on the cardiovascular risk and the level of physical fitness.

Planning of physical training intensity that corresponds to HR and load obtained at AT is considered an appropriate strategy to achieve expected results of motor rehabilitation. Training intensity should be within the range from the lowest load necessary to achieve metabolic effects to values below those provoking adverse clinical symptoms or changes on electrocardiogram (ischemia, rhythm or conduction disorders). Training HR should be 10 bpm below the value at which signs of ischemia occurred.[20] In patients with implantable cardioverter--defibrillators, HR during exercise should not exceed a value 20 bpm lower than the programmed device intervention threshold.

In practice, 3 training intensity ranges are used, and to determine them, VT1, VT2, and RCP should be identified during CPET:

1 Light to moderate training: exercise with oxygen demand below VT1 during which stable lactate concentration is maintained at the rest values or slightly above (1–2 mmol/l)
2 Moderate to intense training: called aerobic--anaerobic transition, limited by VT1 and RCP
3 Intense to maximum training: loads above RCP to VO_{2peak}, without achieving steady state, with lactate concentration rising fast to 8 mmol/l, used in, for example, loading cycles of high intensity interval trainings[59]

Cardiopulmonary exercise testing in evaluation of energy expenditure and nutrition status The amount of energy spent during CPET is calculated using an energy equivalent of oxygen consumption, which depends on RQ and is assessed in some approximation on the basis of RER (see section Physiology of exercise). For RER of 0.71, the energy equivalent is 4.68 kcal, while for RER 1.0, the energy equivalent is 5.05 kcal. Therefore, a caloric cost of given activity can be calculated based on the measurement of the oxygen cost, VO_2 (l/min or ml/kg/min), and the energy equivalent of oxygen consumption.[176]

Evaluation of cardiac rehabilitation results The most important effects of physical training in selected groups of patients undergoing cardiac rehabilitation[177]:

1 Improvement of exercise tolerance
2 Lower dyspnea in heart failure
3 Improvement in epithelial function, including epithelium-dependent vasodilation
4 Reduction of blood concentration of angiotensin II, aldosterone, and natriuretic peptides
5 Increase in diffusing lung capacity
6 Increase in "aerobic" regeneration ATP – lower lactate concentration at a given load
7 Improvement in metabolism and function of skeletal muscles
8 Lower rate of hospitalization for exacerbated heart failure
9 Decrease in all-cause mortality

Effects of physical training evaluated in CPET:

1 Increase in VO_{2peak} and $C(a-v)O_2$
2 Decrease in VO_2 when AT is exceeded
3 Increase in VO_2-AT – optimization of oxygen consumption in working muscles
4 Increase in oxygen uptake efficiency slope
5 Lower VE vs VCO_2slope
6 Drop in VE in relation to VCO_2 ("less linear" increase), most clearly visible post AT 7 Increase in HR reserve.

Cardiopulmonary exercise testing in cardiac rehabilitation: summary

1 Indications: evaluation of physical exercise tolerance, determination of physical training intensity, evaluation of rehabilitation results, occupational rehabilitation, prognostic evaluation.
2 Main parameters: VO_{2max} or VO_{2peak}, VO_2-AT, VCO_2, HR and WR at VT1, VT2.

Athletes and healthy people In the group of athletes and apparently healthy people, the primary reason for CPET is a quantitative evaluation of aerobic physical capacity.[5,26] The cardiovascular system is primarily responsible for exercise capacity in that group. Respiratory, musculoskeletal, and other systems play a secondary role.

Aerobic capacity is higher in endurance athletes (eg, long-distance running, cycling, rowing, cross-country skiing), than in strength athletes (eg, weightlifting). However, during the interpretation of exercise test results, it should be taken into consideration that in the training process of any sports discipline various types of exercise: dynamic, static, and resistance, are used simultaneously but in different proportions.

Aerobic physical capacity is well characterized by VO_{2max}. VO_{2max} can be measured in laboratories (systems working with cycle ergometers and treadmills) or in natural conditions (similar to the environment in which the examined person trains – portable systems).

Categories of aerobic capability characterized by VO_{2max} as ml/kg/min for healthy adults, depending on their sex and age, and according to various authors, are provided in Supplementary material, *Tables S2* and *S3*.

Physical capacity in athletes – professionals and amateurs – is expected to be at least in very good or good category. The highest VO_{2max} in athletes are approximately 7 l/min (absolute value) and 94 ml/kg/min (relative value).[2] However, usually these values are within the range of 40 to 85 ml/kg/min, depending on the discipline.[178]

An athlete's physical capacity, regardless of the discipline, is the basis on which technical skills are built. Aerobic physical capacity is used to qualify an athlete to a specific discipline. The "very good" category may be a precondition for achieving good results and good tolerance of endurance training in disciplines in which dynamic exercise prevails, while physical capacity in the "average" category may not be an obstacle to achieving very good results in other disciplines.

CPET results not only help to qualify people for the optimum type of training but also help to monitor training results. For this purpose, VO_2-AT (VT1 and VT2) is also used, beside VO_{2max}. Both thresholds are useful in the planning of physical training intensity. VT1 determines the intensity of exercise that can be performed for a long time, while VT2 represents a lower limit at which the ability to perform anaerobic exercise improves.

In physically untrained people, AT occurs at loads corresponding to 40% to 65% VO_{2max}, while in well-trained athletes of endurance disciplines it shifts to 80% to 90% VO_{2max}. The higher the AT, the higher the ability for this type of exercise. In well-trained athletes, the AT is shifted to higher values (with no changes in VO_{2max}), and this may indicate correctly and effectively conducted training.

Every CPET conducted in an athlete or an apparently healthy person consists of the initial determination of predicted values, maximum or peak parameters, and values characterizing AT.

In a group of adults who either train or plan to train recreationally, as well as in people of low and average physical activity, VO_{2max} value not only characterizes their ability for physical exercise, but also their health status and the risk of cardiovascular diseases. The lower the physical capacity, the lower the cardiovascular capacity and the higher the risk of chronic noninfectious diseases. People with maximum physical capacity above 7.9 METs are characterized by lower all-cause and cardiovascular mortality rates, when compared with other people.[179] Higher physical capacity in a group of apparently healthy men is associated with a reduction in cardiovascular and all-cause mortality rates regardless of other risk factors.[180]

In conclusion, it should be stated that the CPET can be used very extensively in the group of athletes and clinically healthy people, as shown in TABLE 12.

Cardiopulmonary exercise testing in the evaluation of athletes and healthy people: summary

1 Indications: qualification for optimal training, monitoring of training results.

2 Main parameters: VO_{2peak}, VO_{2max}, VO_2-AT (VT1 and VT2).

New applications CPET combined with imaging techniques is a relatively new and promising concept. It involves simultaneous performance of CPET and exercise stress echocardiography (SE). The simultaneous use of these 2 techniques allows to correlate functional changes evaluated in diagnostic imaging with exercise dynamics of electrocardiographic and CPET parameters.[181-183] This test can be performed in patients with limited exercise tolerance, including patients with both heart failure with reduced ejection fraction and HFpEF. It allows to determine the cause of exercise intolerance.[184] The evaluation of dynamics and the presence of flattening of the $\Delta VO_2/\Delta WR$ curve helps to identify patients with poor exercise tolerance, with an exercise-induced increase of pressure in the right ventricle, and patients with exercise-induced deteriorated function of the right ventricle.[182]

Until now, no standardized exercise test protocol was established for echocardiography during CPET. However, it seems that the semi-supine bicycle ergometer is the best option. When the test is performed in the semisupine position, echocardiographic parameters can be determined during exercise. Visualization depends on the acoustic window, respiratory movements of the chest, and body movements. The ramp protocol is recommended, with an increase in the load fitted to the patient's capacity (eg, 25 W/2 min or 12.5 W/2 min). Image acquisition every 2 minutes or at rest, with a low load, at peak exercise and at recovery is recommended.

TABLE 12 Indications for cardiopulmonary exercise testing in athletes and apparently healthy people

Aim	Athletes	Apparently healthy people
Quantitative assessment of exercise capacity: VO_{2max}	+	+
Assessment and application of training strategies: VO_2-AT	+	+ (optionally)
Monitoring of training results: VO_2-AT	+	+ (optionally)
Health status assessment		
– Cardiovascular system: HR, blood pressure, ECG	+	+
– Respiratory system: spirometry and ventilatory parameters	+	+
– Exercise metabolism assessment	+	+
Qualification for a chosen sport discipline	+	+ (optionally)
Cardiovascular risk factors evaluation: "low exercise capacity"		+

Abbreviations: VO_{2max}, maximal oxygen uptake; averaged value from 10–60 s according to protocol used; others, see TABLES 3 and 11

CPET-SE may be useful in diagnosis and evaluation of advancement of heart failure, valvular diseases, HCM, and PH.

Heart failure with reduced ejection fraction The test allows simultaneous evaluation of physical capacity, SV, left ventricular contractility and diastolic function, and right ventricular function exercise-induced mitral insufficiency, and exercise-induced PH.,[185-187] CPET has also a prognostic value. In patients with heart failure with reduced ejection fraction, the worst prognosis was found in those with the lowest tricuspid annular plane systolic excursion to pulmonary artery systolic pressure ratio and presence of EOV.[188]

Heart failure with preserved ejection fraction HFpEF still remains a diagnostic and therapeutic challenge. An advantage of CPET-SE is the possibility to simultaneously evaluate changes in the left ventricular filling pressure, using an early mitral flow-velocity to diastolic mitral annular velocity ratio (E/e'), and exercise-induced pressure in the right ventricle, with capacity parameters (VO_{2peak}, VO_2-AT, VE versus VCO_2 slope).[189] CPET enables early diagnosis and exclusion of other causes of exertional dyspnea.[190] It allows distinguishing patients with HFpEF depending on pulmonary pressure and the right ventricular function.[191] This test enables the determination of exercise intolerance mechanisms in patients with heart failure and borderline ejection fraction, and differentiation between cardiovascular diseases and deconditioning.[192,193]

Valvular diseases The determination of the progress of valvular disease is a recognized indication for SE. This test is recommended when there is a discrepancy between symptoms and valvular disease severity – the symptoms are present while the valvular disease is not severe, symptoms are not present or are ambiguous when severe valvular dysfunction is diagnosed, or when valvular disease coexists with left ventricular systolic dysfunction.[194,195] The primary goal of the stress test is to evaluate the valvular disease severity and its pathophysiological consequences (eg, pulmonary pressure increase, a transvalvular gradient increase, development or exacerbation of the left ventricular dysfunction).

There are strong theoretical indications for the use of CPET-SE in valvular defects; however, to this date the number of clinical studies confirming the usefulness of this method is insufficient.

Hypertrophic cardiomyopathy Hypertrophic cardiomyopathy (HCM) management is primarily focused on the prevention of sudden cardiac death and development of heart failure. The latest ESC guidelines concerning HCM management recommend functional evaluation using CPET in class I/B or IIa/B, depending on the presence or the lack of symptoms. Exercise SE is recommended in symptomatic patients when bedside maneuvers fail to induce the LVOTO gradient of 50 mm Hg or higher (I/B). On the other hand, in asymptomatic patients, exercise SE should be considered when a decision concerning modification of lifestyle or treatment is necessary (IIb/C).[69] A gradient of 50 mm Hg or higher, at rest or during provocation, is a cutoff point for surgical or procedural treatment, when the symptoms cannot be controlled by pharmacotherapy.[196,197] Although exercise-induced contractile disturbances may occur in patients with HCM, despite no changes in the coronary arteries. They can also be caused by significant coronary arteries stenosis.[198,199]

Parameters evaluated in CPET (VO_{2peak}, VO_2 at AT, VE versus VCO_2 slope) have a prognostic value in HCM.[83] Causes of exercise intolerance in HCM include pathologies occurring or exacerbated during exercise: LVOTO, mitral insufficiency, left ventricular dysfunction, and also chronotropic incompetence. Patients with HCM have a better prognosis when they achieve higher%VO_{2pred} with a lower LVOT gradient.[67] CPET-SE may provide complimentary information and allows the determination of the level and mechanism of exercise intolerance.[200,201]

Pulmonary hypertension Current ESC guidelines do not recommend a diagnosis of exercise-induced PH due to insufficient data; however, evaluation of exercise-induced changes in the right ventricular systolic pressure has a prognostic role in patients diagnosed with primary PH.[88] Pulmonary pressure may also rise in

many left-sided heart diseases, including valvular diseases and heart failure, and this may also be helpful in the evaluation of the disease progress. Both CPET and SE may be useful in diagnosing exercise-induced PH in patients with increased risk, for example, with systemic connective tissue disorders, particularly scleroderma.[202] Right ventricular dysfunction evaluated by systolic area change combined with low O_{2pulse} identifies high risk patients in idiopathic PAH.[203]

Combined cardiopulmonary exercise testing and cardiopulmonary exercise test: summary

1 Indications for the test: diagnostic workup and disease progression assessment in heart failure, valvular heart diseases, HCM, PH.

2 Main parameters: CPET (VO_{2peak}, VO_2 at AT, VE versus VCO_2 slope, arrhythmias, chronotropic competence, SBP), SE (global and regional contractility, valvular flow, LVOTO gradient).

Archiving of results Test results are issued to the patient as a hardcopy authorized by physicians monitoring and interpreting the test. The result report should include a title page with patient details and interpretation of the results, pages containing graphic and numeric representation of CPET results, and averaged 12-leads electrocardiogram from each test stage with marked changes in ST.

It is recommended to store the results in digital form in at least 2 copies (in case data is lost), in the memory of a computer used for exercise tests and a backup copy (external memory, server).

Test duration, financing CPET is an independent procedure and should be separately financed, considering work performed by a nurse / operator / physical therapist and a physician supervising and interpreting test results.

The time required to prepare the patient, perform the test, and interpret the results is at least 45 to 60 minutes.

Conclusions CPET is one of the essential tests of contemporary clinical practice. Its extensive diagnostic possibilities include not only patients with cardiovascular diseases but also those with respiratory and musculoskeletal diseases. CPET scope of application was recently expanded to patients with oncological diseases. This test not only helps to diagnose causes of exercise intolerance, but it also supports evaluation of the treatment, including planning and evaluation of cardiac rehabilitation. New opportunities are offered by combining CPET with imaging such as exercise stress echocardiography. These tests are complimentary and synergistic in their diagnostic and prognostic strength. The usefulness of the combination of these 2 methods has been demonstrated in recent studies, but still requires confirmation in daily clinical practice.

SUPPLEMENTARY MATERIAL

Supplementary material as well as references and the Polish version of the paper are available at www.mp.pl/kardiologiapolska.

ARTICLE INFORMATION

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For references, see Supplementary material at www.mp.pl/kardiologiapolska.