Cardiopulmonary Exercise Testing: Methodology, Interpretation, and Role in Exercise Prescription for Cardiac Rehabilitation

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Abstract

Cardiopulmonary exercise testing (CPET) is a crucial tool for assessing cardiorespiratory function, providing invaluable insights into individual physiological capacities. This review explores the clinical indications of CPET, its contraindications, as well as a comprehensive protocol for its execution. Additionally, it highlights key parameters measured during CPET and their interpretation, as well as the role of CPET in the prescription of aerobic training in cardiac rehabilitation. This review aims to provide a comprehensive, up-to-date synthesis of advances in the field of CPET and their clinical implications.

Keywords

Cardiopulmonary exercise testing, exercise intensity prescription, cardiac rehabilitation

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Cardiopulmonary exercise testing (CPET) represents a cornerstone in the comprehensive management of individuals with cardiovascular conditions, particularly within the context of cardiac rehabilitation (CR). This sophisticated diagnostic tool not only objectively measures patients' cardiorespiratory capacities, but also plays a pivotal role in shaping tailored exercise prescriptions. The significance of CPET stems from its integrated assessment approach, where multiple physiological systems are evaluated simultaneously under the stress of incrementally increased physical activity, taking the patient to their tolerance limit.

At its core, CPET involves a detailed analysis of exhaled respiratory gases alongside conventional exercise test monitoring methods, such as electrocardiography and hemodynamic assessments.[1] This combination allows for a holistic view of how the cardiovascular, respiratory, and musculoskeletal systems respond to exercise.[2,3] The data collected, ranging from oxygen uptake (VO_2) and carbon dioxide production to heart rate (HR) and blood pressure (BP), provide a multidimensional snapshot of a patient's physiological status during exercise. This comprehensive data collection is essential for determining the patient's exercise capacity and identifying any underlying limitations in physical functioning.

Widely recognized as the gold standard for evaluating cardiorespiratory fitness, CPET serves a broader purpose beyond assessment.[3,4] In CR, it plays an essential role in selecting personalized exercise training programs that are safe and effective. By using precise data on an individual's cardiovascular and pulmonary responses to exercise, healthcare professionals can customize rehabilitation strategies to optimally align with each patient's unique health profile.

Moreover, CPET is of inestimable value for the ongoing monitoring and adjustment of exercise programs. It allows clinicians to track improvements in exercise tolerance and cardiorespiratory health over time, facilitating timely modifications to the rehabilitation regimen. This adaptability not only enhances the effectiveness of CR but also ensures that patients remain at an appropriate level of exertion, maximizing their recovery potential and improving overall outcomes.

This literature review aims to examine the operational mechanics and interpretative frameworks of CPET, highlighting how these elements contribute to the prescription of exercise regimens in CR. By synthesizing recent research, this article aims to provide a comprehensive understanding of CPET and its role in optimizing CR protocols.

Indications for CPET

CPET holds significant clinical value across various medical conditions, offering insights into diagnosis, risk stratification, prognosis, exercise prescription, and therapeutic efficacy.[3,5] It is recommended in multiple situations, including assessing impairment and disability, as well as monitoring responses to different treatment modalities.[2]

In heart failure (HF), CPET is crucial for evaluating functional capacity and determining the need for ventricular assistance or heart transplantation (class I recommendation, level of evidence [LoE] C).[3,6] In valvular heart diseases, particularly for asymptomatic patients with severe aortic stenosis, CPET may guide therapeutic decisions when specific abnormalities are present, such as reduced peak VO_c, exertional angina, significant changes in systolic BP, or ventricular arrhythmias (class IIa

recommendation, LoE B).[7,8] Moreover, CPET plays an important role in tailoring exercise prescriptions for patients with coronary artery disease (class I recommendation, LoE A).[9]

CPET is also indicated for conditions, such as hypertrophic cardiomyopathy, unexplained exertional dyspnea, suspected or confirmed pulmonary arterial hypertension, secondary pulmonary hypertension, suspected myocardial ischemia, and suspected mitochondrial myopathy.[3,10,11]

Moreover, CPET plays a crucial role in CR. It serves multiple purposes, including assessing the effectiveness of exercise training, stratifying risks to determine appropriate levels of supervision and monitoring, and tailoring individualized exercise prescriptions.[2,12–15]

Contraindications for CPET

Before performing CPET, it is crucial to assess any potential contraindications.[16,17]

Absolute contraindications for CPET include:

- recent acute myocardial infarction (within 3–5 days);
- unstable angina;
- uncontrolled arrhythmias causing symptoms or hemodynamic instability;
- active endocarditis;
- acute myocarditis or pericarditis;
- symptomatic severe aortic stenosis;
- decompensated HF;
- acute aortic dissection;
- uncontrolled asthma;
- acute pulmonary embolism;
- arterial desaturation at rest in room air (less than 85%); and
- physical disabilities that prevent safe and adequate testing.

Relative contraindications include:

- untreated left main coronary artery stenosis or its equivalent;
- asymptomatic severe aortic stenosis;
- severe untreated hypertension at rest (systolic BP >200 mmHg; diastolic BP >110 mmHg);
- significant tachyarrhythmias;
- high-degree atrioventricular block or other significant bradyarrhythmias;
- untreated lower limb thrombosis;
- severe abdominal aortic aneurysm;
- recent stroke or transient ischemic attack;
- advanced or complicated pregnancy;
- psychiatric or mental impairments that prevent cooperation; and
- uncorrected medical conditions such as significant anemia, major electrolyte imbalances, and hyperthyroidism.

Implementation of Cardiopulmonary Exercise Test Facilities, Equipment and Staff

The CPET laboratory must be well equipped to deal with emergency situations and patient monitoring. Essential equipment includes an ergometer, an electrocardiograph, an emergency telephone, an oxygen source, a stadiometer, a scale, a skinfold calibrator, a BP monitor, and an emergency cart equipped with a defibrillator.[18,19] Resuscitation equipment should be accessible and subject to appropriate maintenance and use procedures. To ensure patient safety, tests should be carried out by healthcare professionals with expertise in exercise physiology, cardiology, pulmonology, or sports medicine, and in the presence of a physician. The environment should be controlled, maintaining a temperature between 16°C and 24°C and humidity between 30% and 60%.[20] The number of people present in the laboratory should be limited to the strict minimum needed to obtain measurements and ensure patient safety, and an emergency response plan must be part of the standard procedure.[5,21]

Preparation

Before CPET, patients should avoid eating and drinking coffee for two hours prior, wear comfortable clothing, refrain from smoking, and take regular medications as prescribed.[22] They should receive clear information about the procedure, benefits, and risks, and sign a consent form. Gestural communication for the test is agreed upon, and the importance of maximum effort is emphasized.[5] A comprehensive medical history and physical examination are conducted, including a resting ECG after proper skin preparation.[23] Spirometry is performed to evaluate ventilatory reserve and identify any limitation.[5,24] The CPET system must be calibrated according to the manufacturer's recommendations, accounting for ambient conditions. Calibration reports should be printed before each test, and if calibration fails, the test should not proceed.[2,5,25]

Selection of Exercise Protocol and Ergometer

Ergometer

When choosing between a treadmill and a stationary cycle ergometer for CPET, several factors are considered. The cycle ergometer is often preferred for its increased safety and suitability for patients with deconditioning, obesity, or joint issues. It produces less movement artifact and allows for precise measurement of external work rate, essential for assessing exercise capacity.[16,26] There are two types of cycle ergometers: electrically braked cycles, which offer precise work rate control; and mechanically braked cycles, which require a fixed pedaling cadence (60–70 cycles per minute) to stabilize the work rate.[27]

Treadmills are more familiar to most people and simulate natural activities like walking or running. They engage a larger muscle mass and typically result in a maximal oxygen consumption (VO_2max) 5–10% higher compared to cycle ergometers.[5,16,19,28] However, accurately quantifying the external work rate on a treadmill is challenging due to difficulties in estimating the relationship between speed, incline, and metabolic cost.[27] Patients often use handrails, reducing the metabolic cost of walking.[16]

Ergometer choice depends on the test's objectives and the patient's fitness level. For exercise prescription, it is beneficial to use the same type of exercise during testing as will be used in training sessions.

Exercise Protocol

CPET provides valuable assessment of cardiorespiratory function, and selecting the appropriate protocol is crucial for ensuring reliable results. Two main categories of protocols are commonly used: progressive (incremental) tests and constant load tests. In progressive tests, the workload is gradually increased either continuously (ramp) or in stages, often ranging from 5 to 25 W per minute on a cycle ergometer, or by gradually increasing speed and incline on a treadmill.[26]

Ramp protocols are characterized by a gradual increase in workload, evenly distributed throughout each minute of the exercise phase.[29] For example, on a cycle ergometer, a ramp protocol of 15 W per minute,

commonly used in clinical settings, increases workload by approximately 1.5 W every 6 seconds. These ramp protocols are preferred over step protocols as they avoid the abrupt increases typical of step protocols (e.g. 25 W every 3 minutes).[25] Additionally, they allow for a linear increase in VO_2, thereby improving accuracy in determining VO_2max and ventilatory thresholds (VTs).[21]

Conversely, constant load protocols involve maintaining a constant workload for a defined period, typically used for specific studies such as exercise-induced bronchospasm diagnosis or metabolic threshold evaluation.[21,30] Ideally, the duration of progressive exercise is 10 ± 2 minutes, ensuring maximal physiological stress without excessive hyperventilation or premature cessation due to lactic acidosis.[26,31]

Cardiopulmonary Exercise Test Steps

Every cardiopulmonary exercise test should be divided into four stages: the initial phase, the warm-up phase, the incremental exercise phase, and the recovery phase.

Initial Phase

Lasting 2–3 minutes, the initial stage allows patients to familiarize themselves with the equipment and for resting measurements to be taken.[22] Stable resting values include VO_2 below 5 ml/minute/kg, respiratory exchange ratio (RER) below 0.85, and minute ventilation (VE) between 6 and 12 l/minute.[23,32] Deviations from these values may indicate issues, such as voluntary or anticipatory hyperventilation, equipment malfunction, or mask leaks.[33]

Warm-up Phase

A warm-up of around 3 minutes is recommended, during which the patient pedals or walks without resistance.[22] For cycle ergometer tests, it is advised to keep the workload below 15 W, with a pedaling cadence between 55–70 revolutions per minute.[18] For treadmill tests, selecting the lowest speed, such as between 1.0 and 1.6 km/hour, is recommended.[22]

Incremental Exercise Phase

Lasting 10 ± 2 minutes, this phase involves gradually increasing exercise intensity. Before reaching the first ventilatory threshold (VT1), it is advisable to ensure that measured VO_2 values closely match theoretical values, with an approximate increase of 10 ml/minute/W in VO_2 per workload.[33] Differences exceeding 150 ml/minute may indicate a mask leak or other technical problem. At the end of each workload increment, it is recommended to measure parameters, such as ECG, BP, perceived sensations, and, if necessary, collect blood samples.[23]

Recovery Phase

This phase lasts at least 3 minutes, during which patients pedal without resistance at approximately 30 revolutions per minute or walk at a very slow pace.[22,23] This phase helps return the body to a resting state safely, avoiding abrupt exertion cessation.

Key Cardiopulmonary Exercise Testing Parameters to Interpret

CPET aims to detect exercise intolerance and, if present, to define the contributing mechanisms. The interpretation of CPET relies on several variables, some of which are more clinically relevant:

Oxygen Consumption

VO_2 is a key measure of cardiorespiratory fitness, calculated using the equation $VO_2 = VI \times FIO_2 - VE \times FEO_2$, where VI and VE are inspired and expired air volumes, and FIO_2 and FEO_2 are oxygen concentrations in the inspired and expired air, respectively.[26,34,35] VO_2 can be expressed in ml/minute or ml/kg/minute and is influenced by cardiovascular and respiratory function, hemoglobin concentration, and mitochondrial efficiency.[18] During exercise, VO_2 increases with workload until it plateaus at VO_2max. In some patients, especially those with certain pathologies, this plateau may not be observed; maximal oxygen consumption (VO_2peak) is instead measured.

The prediction of VO_2peak during cardiopulmonary exercise testing is crucial for accurate assessment of maximal aerobic capacity. This prediction is generally based on regression equations that take into account factors, such as age, sex, height, and weight. Among the most frequently used are the equations developed by Hansen, Sue, and Wasserman, often referred to as the "Wasserman equations."[36]

For practical application of this equation when using a cycle ergometer, VO_2peak (l/min) is predicted based on body composition and age as follows:[37]

For Men

Ideal weight (kg) = 0.79 × height (cm) − 60.7

If actual weight equals or exceeds ideal weight:

Peak VO_2 = 0.0337 × height − 0.000165 × age × height − 1.963 + 0.006 × (actual weight − ideal weight)

If actual weight is less than ideal weight:

Peak VO_2 = 0.0337 × height − 0.000165 × age × height − 1.963 + 0.014 × (actual weight − ideal weight)

Use an age of 30 years for adults younger than 30 years.

For Women

Ideal weight (kg) = 0.65 × height (cm) − 42.8

VO_2peak = 0.001 × height × (14.783 − 0.11 × age) + 0.006 × (actual weight − ideal weight)

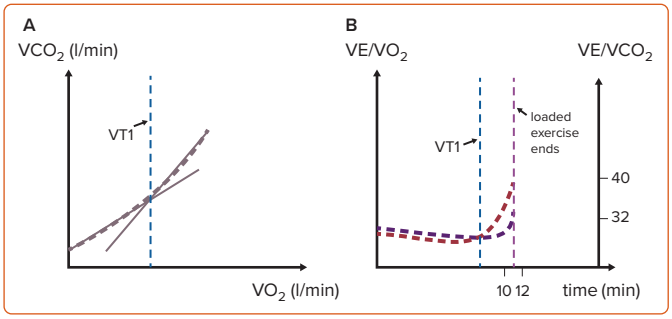
Use an age of 30 years for adults younger than 30 years.

These equations are used to estimate an individual's maximum aerobic capacity, which is then compared with results measured during a cardiopulmonary exercise test. A measured VO_2peak of less than 80% of the predicted value is often a sign of functional limitation due to cardiac, pulmonary, or muscular issues.[23]

Ventilatory Thresholds

VTs are critical metabolic transition points during exercise, expressed as a percentage of VO_2max or in l/minute. The anaerobic threshold (VT1; also called first ventilatory threshold) occurs when ventilation increases more rapidly than VO_2, indicating the onset of a mixed aerobic-anaerobic metabolism[18] with rising lactate and decreasing pH.[38] The respiratory compensation point (VT2; also called second ventilatory threshold, critical power, or lactate threshold) indicates the point at which lactate buffering becomes insufficient.[39] Direct measurement requires arterial lactate sampling, but graphical methods can also define these thresholds. *Figure 1* illustrates the V-slope method (Beaver method) and the respiratory

Figure 1: Determination of the First Ventilatory Threshold



A: V-slope method for determining VT1. This method plots the relationship between VO_2 and VCO_2. The inflection point where the slope of the curve changes indicates VT1, marking the transition to a disproportionate increase in VCO_2 relative to VO_2. B: Respiratory equivalents method for determining the VT1. This method uses the respiratory equivalents of oxygen (VE/VO_2) and carbon dioxide (VE/VCO_2). VT1 is identified at the point where VE/VO_2 begins to increase without a concomitant increase in VE/VCO_2, indicating an increase in ventilation relative to oxygen consumption in response to lactate accumulation. VCO_2 = carbon dioxide production; VE = minute ventilation; VO_2 = oxygen consumption; VT1 = first ventilatory threshold.

equivalents method (VE/VO_2 and VE/VCO_2; where VCO_2 represents carbon dioxide production), which are often used to determine VT1. [25,37,40–42]

Oxygen Pulse

The oxygen pulse (O_2 pulse; VO_2/HR) is an indirect indicator of oxygen transport in the cardiopulmonary system, reflecting myocardial contractility, blood oxygen supply, and muscle oxygen extraction.[43] During exercise, it initially rises rapidly due to increases in stroke volume (SV) and arteriovenous oxygen difference ($C(a\text{-}v)O_2$), then slows after VT1.[23] β-blockers can increase the VO_2/HR by reducing HR.[26] Abnormal variations, such as early flattening or a decrease, may indicate issues like reduced SV from myocardial ischemia, left ventricular outflow obstruction, or abnormal muscle oxygen extraction.[27,43,44]

The maximum VO_2/HR is considered normal when it exceeds 80% of the maximum predicted value, which generally corresponds to around 15 ml/beat in men and 10 ml/beat in women.[45]

The predicted maximum VO_2/HR is usually calculated by dividing the predicted maximal VO_2 by the predicted maximal HR. However, due to the variety of reference equations available for these measurements, some researchers choose to use regression equations specifically tailored to maximal VO_2/HR.[37] For example, the SHIP study provides specific equations for this parameter:[46]

For Women

Predicted maximum VO_2/HR (ml/beat) = −3.7 − 0.004 × age + 0.056 × height (cm) + 0.075 × weight (kg) + 0.42 × β-blocker use (coded as 0 for no and 1 for yes)

For Men

Predicted maximum VO_2/HR (ml/beat) = −0.7 − 0.044 × age + 0.064 × height (cm) + 0.086 × weight (kg) − 0.62 × current smoking status (coded as 0 for no and 1 for yes)+ 1.73 × β-blocker use (coded as 0 for no and 1 for yes)

The Respiratory Exchange Ratio

The respiratory exchange ratio (RER) is a key indicator of energy substrate metabolism, calculated as VCO_2/VO_2. During exercise, RER increases due to lactic acidosis or hyperventilation, signaling the activation of anaerobic metabolism.[2,26] At peak effort, an RER above 1.10 signifies maximal effort, while lower values indicate submaximal effort.[2,18,47–49] Achieving a high RER indicates bodily stress but does not necessitate test termination.

VO_2/Work Rate Slope

The VO_2/work rate slope reveals the aerobic energy cost per watt and is of paramount importance in assessing physical performance. It is initially linear before VT1; beyond this point, the slope decreases as some of the oxygen uptake is redirected toward physiological functions other than physical effort.[23] Typically ranging between 9 and 11 ml/minute/W, values below this indicate issues in oxygen distribution, while a sudden drop may indicate the presence of cardiac ischemia or mitral insufficiency.[27,50] Thus, this parameter is influenced by the severity of pathologies, reflecting dysfunctions in cardiovascular, ventilatory, and metabolic systems.[23]

The Ventilation/Carbon Dioxide Slope

The ventilation/carbon dioxide slope (VE/VCO_2 slope) measures ventilatory efficiency during exercise.[5] The VE/VCO_2 slope initially decreases, then begins to rise after VT1 as ventilation increases in response to elevated CO_2 production. Analyzing this slope is crucial for assessing conditions like pulmonary hypertension and HF.[51,52] The reference value for the VE/VCO_2 slope is calculated using the equation:

34.4 − 0.0723 × height (cm) + 0.082 × age (years)

This formula applies to both sexes, with a SD of 3.0. The upper limit of normal is defined as the predicted mean plus 4.9, differentiating between normal and pathological states.[37,53]

Elevated VE/VCO_2 slope values (>40) indicate increased dead space and are an independent marker of poor prognosis.[2,54,55]

End-Tidal Partial Pressure of Carbon Dioxide

End-tidal partial pressure of carbon dioxide ($PETCO_2$) reflects the concentration of carbon dioxide in exhaled air at the end of expiration and provides crucial information on a patient's ventilatory efficiency and cardiac function.[56] In healthy subjects, $PETCO_2$ ranges typically between 36–42 mmHg, indicating efficient gas exchange and a normal ventilation-perfusion (V/Q) balance.[57] During exercise, $PETCO_2$ generally increases until VT1, then stabilizes until the respiratory compensation point, after which it begins to decrease.[27,47]

A $PETCO_2$ lower than normal during incremental exercise may indicate compromised lung function, reduced cardiac output, or ventilation-perfusion mismatch, which are common problems in patients with chronic cardiopulmonary disease.[58,59] These changes may reflect the severity of pathologies such as hypertrophic cardiomyopathy, HF, pulmonary hypertension, restrictive lung diseases, and chronic obstructive pulmonary disease.[60]

Minute Ventilation

Minute ventilation measures the volume of air expelled from the lungs in 1 minute. During exercise, VE initially increases due to the expansion of tidal volume (VT), which can reach up to 60% of vital capacity, followed by an increase in respiratory frequency as VT stabilizes.[26,61] This respiratory frequency can reach up to 30–40 breaths per minute in younger individuals. Maximum ventilation (VEmax) obtained during exercise represents maximum ventilatory demand.[62] Abnormalities in VEmax, such as a respiratory frequency exceeding 55 breaths per minute or insufficient increase in tidal volume, may suggest pulmonary limitation.[63] Peak

exercise ventilation (peak VE) can be estimated using the following equation:[37,64]

$$\text{Peak VE (l/min)} = 17.32 - 28.33 \times \text{sex} - 0.79 \times \text{age (years)} + 0.728 \times \text{height (cm)}$$

In this equation, sex is coded as 0 for men and 1 for women.

Adequate Patient Effort

Ensuring adequate effort during CPET is crucial for reliable results. Key indicators of effort include: achieving a RER of around 1.05 for individuals with health issues or about 1.1 for healthy individuals; surpassing VO_2 at the anaerobic threshold (AT); and approaching predicted maximal values of VO_2, HR, and VE. Additionally, attainment of VO_2max, a VE/VO_2 exceeding 30–35, and a blood lactate concentration of 8 mmol/l all signify sufficient effort.[18,22] These parameters validate the test, which should continue unless exercise tolerance is poor or there is an indication for termination.[65]

The Effect of Pharmacotherapy on Cardiopulmonary Exercise Test Parameters

Analyzing the impact of pharmacological treatments on CPET parameters is essential for refining the interpretation of cardiopulmonary exercise test results in patients with cardiac limitations. By understanding how drugs, such as β-blockers and renin–angiotensin–aldosterone system (RAAS) inhibitors, influence these parameters, clinicians can improve the accuracy and relevance of their assessments.

β-blockers, widely used in the treatment of HF, neutralize sympathetic nervous system hyperactivity by blocking α-1, β-1, and/or β-2 adrenergic receptors.[66] While these drugs improve cardiac function, their effects on key CPET parameters, such as peak VO_2 and VE/VCO_2 slope, are mixed. Most studies report no significant change in peak VO_2 after β-blocker treatment, suggesting that benefits in terms of cardiac contractility (e.g. increased stroke ejection volume) are counterbalanced by a reduced HR, which may limit aerobic capacity.[67–71] However, one study showed that bisoprolol significantly increased peak VO_2 compared with carvedilol, although the absence of a baseline CPET limits the strength of this result.[72] In terms of VE/VCO_2 slope, results are variable. Some studies showed significant improvements, particularly in patients with higher brain natriuretic peptide levels at baseline,[71,73] while others found no change.[68,72,74] Other CPET variables, such as $PETCO_2$ and oxygen uptake kinetics, also showed improvements with β-blockers, though the exact mechanisms and the degree of influence on exercise capacity require further investigation.[69,75]

Regarding RAAS inhibitors, these drugs—including angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs)—play a crucial role in the management of HF, improving cardiac function by reducing preload and afterload and improving myocardial contractility.[66,76] Studies of RAAS inhibitors consistently demonstrate significant improvements in peak VO_2, particularly when ACE inhibitors and ARBs are used in combination.[77–80] This combined approach probably results in a greater reduction in angiotensin II production. However, the impact on VE/VCO_2 slope is less consistent, with ACE inhibitors generally showing more positive results than ARBs, while aldosterone antagonists such as spironolactone have minimal effects.[81–84]

In addition to β-blockers and RAAS inhibitors, phosphodiesterase-5 inhibitors, principally sildenafil, have been shown to improve endothelial function and vascular tone by increasing the availability of nitric oxide, which is often reduced in patients with HF.[85] Studies consistently demonstrate that sildenafil significantly improves both peak VO_2 and VE/VCO_2 slope, whether treatment is acute or chronic.[85–87]

Interpretation of Cardiopulmonary Exercise Testing

The data from CPET are organized into a nine-panel plot as described by Wasserman et al., which helps visualize and interpret the diverse physiological responses to exercise.[37] *Figure 2* illustrates the nine-panel Wasserman trace in a healthy subject and a subject with cardiac limitation.

Panel 1: Minute Ventilation versus Time

This panel shows the progressive increase in minute ventilation (VE) during exercise. Initially, ventilation increases proportionally to workload through both respiratory rate and tidal volume. After VT1, the increase is mainly due to respiratory rate. At the end of exercise in a healthy subject (dotted grey line), VE plateaus below maximum voluntary ventilation (MVV), indicating adequate ventilatory reserve. Ventilation anomalies include reduced efficiency in VE for patients with cardiac limitations (solid grey line), characterized by an early increase in respiratory rate and reaching maximum ventilation sooner.

Panel 2: Oxygen Pulse versus Time and Heart Rate versus Time

This panel shows the progression of VO_2/HR and HR during exercise. In healthy individuals (dotted red line), HR increases linearly with workload or VO_2 until it plateaus near the age-predicted maximum. In cardiac patients (solid red line), HR is higher for a given workload or VO_2, indicating decreased SV, and HR peaks below the age-predicted maximum.

VO_2/HR in healthy individuals (dotted orange line) increases linearly with exercise intensity due to rising SV and improved muscle oxygen extraction, plateauing at peak exercise. In cardiac patients (solid orange line), the VO_2/HR increases less regularly and plateaus at a lower level due to reduced SV from conditions like HF or chronotropic incompetence.

Panel 3: VO_2 versus Time and VCO_2 versus Time

This panel schematically illustrates the VO_2-work relationship. In a healthy individual, oxygen consumption (dotted red line) increases in parallel with the increase in work (dotted black line). However, in an individual with cardiac limitations, this relationship is abnormal: the increase in VO_2 (solid red line) is minimal and does not parallel the increase in work. This indicates a reduced capacity to increase oxygen consumption in response to an increased workload, reflecting significant cardiac limitations.

Panel 4: VE versus VCO_2

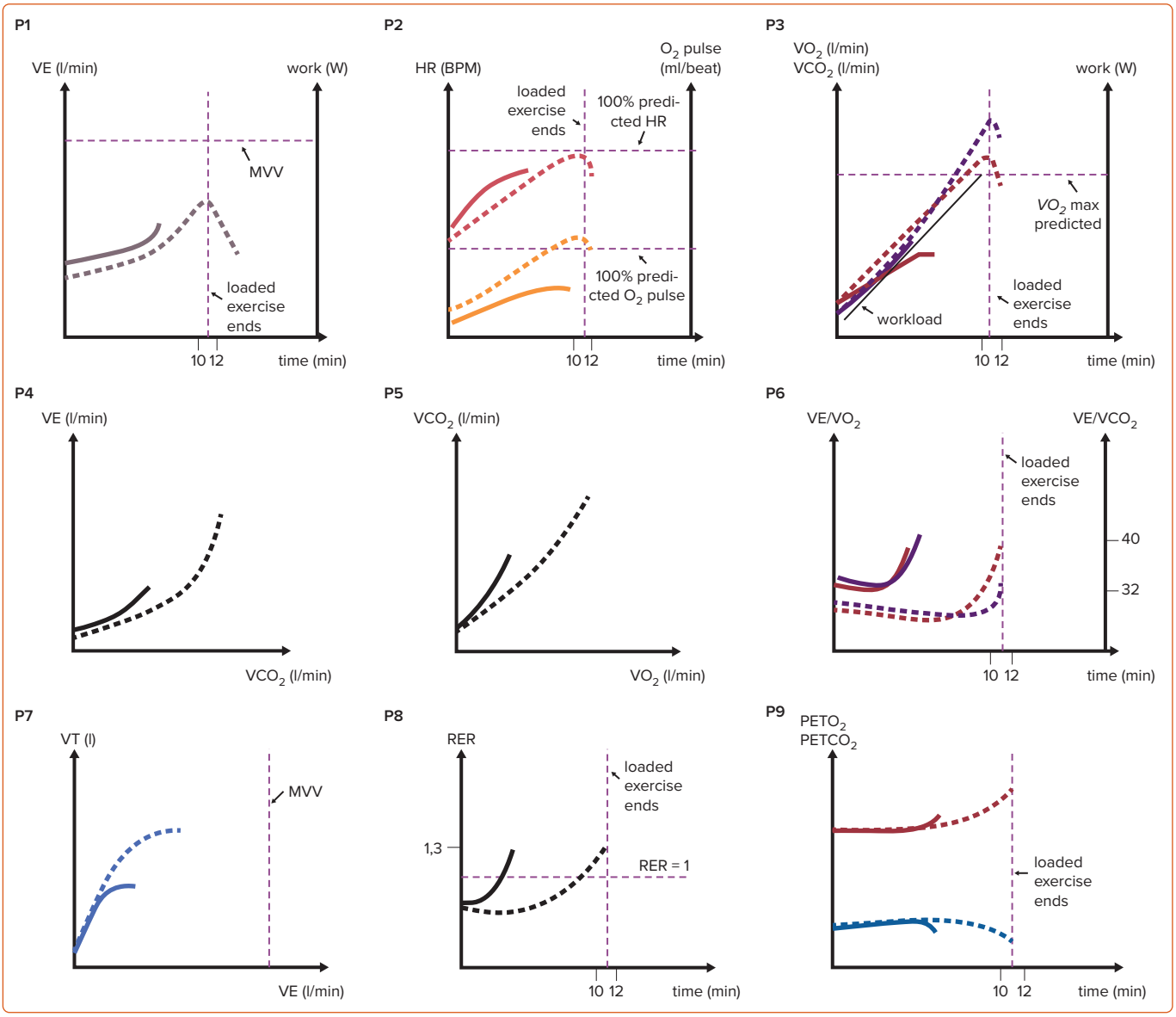
This panel schematically illustrates the progression of VE with VCO_2. In healthy individuals (dotted black line), VE increases linearly with VCO_2, reflecting adequate CO_2 elimination. At the VT, VE increases disproportionately due to lactic acid accumulation and continues to rise, peaking at maximal effort.

In individuals with cardiac limitations (solid black curve), VE also rises with VCO_2, but due to limited cardiac output, oxygen delivery and CO_2 elimination are compromised. Consequently, VE increases disproportionately at lower exercise levels and reaches a lower, earlier peak.

Panel 5: VO_2/VCO_2 Relationship (V-Slope Method)

This panel shows the kinetics of VCO_2 relative to VO_2. In healthy individuals (dotted black line), VCO_2 increases linearly with VO_2 until VT1. Beyond this

Figure 2: Expected Changes in Physiological Response to Exercise



Expected changes in physiological response to exercise in patients with cardiac limitation (solid lines) compared with normal individuals (dotted lines), presented in nine panels (P1–P9). HR = heart rate (beats/min); MVV = maximum voluntary ventilation; $PETO_2$ = end-tidal partial pressure of O_2 (mmHg); $PETCO_2$ = end-tidal partial pressure of CO_2 (mmHg); RER = respiratory exchange ratio (VCO_2/VO_2); VCO_2 = carbon dioxide production (l/min); VE = minute ventilation (l/min); VE/VCO_2 = carbon dioxide respiratory equivalent; VE/VO_2 = respiratory oxygen equivalent; VO_2 = oxygen consumption (l/min); VO_2/HR = oxygen pulse (ml/beat); Vt = tidal volume.

point, VCO_2 rises more rapidly due to lactic acid buffering, peaking at maximum CO_2 elimination capacity.

In individuals with cardiac limitations (solid black line), VCO_2 also rises with VO_2, but limited cardiac output causes an earlier shift to anaerobic metabolism. The VCO_2 curve peaks earlier and at a lower value compared to healthy individuals.

Panel 6: VE/VO_2 versus VE/VCO_2

This panel illustrates the evolution of VE/VO_2 and VE/VCO_2 in a healthy subject and a subject with cardiac limitations.

In a healthy subject at rest, VE/VO_2 decreases at the beginning of exercise because oxygen consumption increases more rapidly than ventilation. During moderate exercise, this ratio stabilizes, indicating proportional increases in ventilation and oxygen consumption. As exercise intensity approaches the AT, VE/VO_2 increases due to the need to expel more CO_2 produced by anaerobic metabolism, and continues to rise at maximal intensity to meet high metabolic demands and buffer lactic acid (dotted red line). Similarly, VE/VCO_2 stabilizes or slightly decreases during moderate exercise, indicating efficient matching of ventilation to CO_2 production. Near the AT, this ratio increases significantly as the body expels excess CO_2 generated by lactic acid buffering, and continues to rise at maximal exercise, reflecting the body's efforts to manage the acidosis resulting from intense anaerobic metabolism (dotted blue line).

However, in patients with cardiac limitations, VE/VO_2 decreases less rapidly at the beginning of exercise due to the heart's limited capacity to increase cardiac output. During moderate exercise, this ratio may stabilize at a higher level or continue to increase slowly, indicating ventilatory inefficiency. As exercise intensity approaches the AT, this ratio increases more rapidly because ventilation increases disproportionately to oxygen consumption due to the early onset of anaerobic metabolism. At maximal exercise, VE/VO_2 may not reach the levels observed in healthy individuals,

reflecting a limited capacity to tolerate exercise (solid red line). Similarly, VE/VCO_2 does not decrease as much during moderate exercise, indicating inefficient ventilation relative to CO_2 production. Near the AT, this ratio increases rapidly, marking an early transition to anaerobic metabolism, and at maximal exercise, it peaks earlier and at a higher value than in healthy individuals, indicating excessive but less effective ventilation in managing metabolic acidosis (solid blue line).

Panel 7: Tidal Volume versus Minute Ventilation

This panel shows the relationship between VT and VE during exercise. In healthy individuals, VT initially increases significantly with small increases in VE. VT then rises more slowly, plateauing at higher exercise levels, with further VE increases due to higher breathing frequency (dotted blue curve). In patients with cardiac limitations, VT may plateau earlier due to cardiopulmonary limitations, causing VE increases to rely more on breathing frequency (solid blue curve). Typically, VE during exercise does not exceed 80% of MVV, indicating sufficient ventilatory reserve for both healthy subjects and those with cardiac limitations.

Panel 8: Respiratory Exchange Ratio

This panel illustrates the RER during a cardiopulmonary exercise test. In healthy individuals (dotted black curve), the RER starts below 1, gradually approaches 1 with increasing exercise intensity, and exceeds 1 at higher intensities, indicating a shift to anaerobic metabolism. In cardiac-limited patients (solid black curve), the RER rises more rapidly, exceeding 1 at lower workloads, indicating an earlier onset of anaerobic metabolism even at lower exercise intensities.

Panel 9: End-Tidal Partial Pressures of O_2 and CO_2

This panel shows the evolution of end-tidal partial pressure of oxygen ($PETO_2$) and $PETCO_2$ during exercise. In healthy individuals, $PETO_2$ increases slightly at first and then rises more after VT1, reflecting adequate oxygen supply and increased ventilation (dotted red curve). $PETCO_2$ remains stable or increases slightly, then decreases after VT1 due to hyperventilation (dotted blue curve). In cardiac-limited patients, $PETO_2$ may not rise as expected, indicating inadequate oxygenation (solid red curve). $PETCO_2$ may not decrease as expected at higher exercise levels, suggesting ineffective ventilation and CO_2 elimination (solid blue curve).

Key Questions for Interpreting a Cardiopulmonary Exercise Test

To properly interpret a CPET, it is important to ask these nine fundamental questions:[63]

1. Is the effort exerted during the test maximal?
- Did the patient achieve more than 80% of the predicted work (panel 3)?
- Did they exceed 80% of the predicted maximum heart rate (panel 2)?
- Did they attain a VCO_2/VO_2 of more than 1.15 (panel 8)?
2. What is the value of peak VO_2 (panel 3)?
3. Is the relationship between VO_2 and effort normal?
- Is the increase in VO_2 proportional to the increase in workload (panel 3)?
4. Is it possible to determine VT1?
- Is there a point where VCO_2 increases disproportionately compared to VO2 (panel 5)?
- Is there a point where VE/VO_2 begins to increase while VE/VCO_2 remains stable or slightly decreases (panel 6)?
- In up to 10% of tests, determining the AT may be difficult.
5. If yes, what is the value of VO_2 at VT1 (panels 5 and 6)?
6. Was the HR response normal (panel 2)?
- Did HR increase linearly with increasing exercise intensity?
- Did HR decrease rapidly during recovery (more than 12 beats in the first minute)?
- Did any medications, such as β-blockers, affect HR response?
7. Did VO_2/HR increase with exercise (panel 2)?
8. Is there any ventilatory limitation (panel 7)?
- Does VEmax exceed 80% of the MVV?
9. Were there any ECG changes?

CPET for Exercise Intensity Prescription

Appropriate exercise prescription is crucial for enhancing the safety and efficacy of CR. There's no one-size-fits-all approach to training due to variations in physiology, comorbidities, medications, and prior exercise experience. This variability means individuals may have differing tolerances to specific exercise intensities, influenced by factors such as underlying health conditions and medication effects. Among intensity prescription methods, CPET is widely recognized as the most accurate and effective for assessing aerobic exercise intensity.[60,88] It is endorsed by many health organizations including the American College of Sports Medicine, the American Heart Association, the American Thoracic Society, the American College of Chest Physicians, the European Society of Cardiology, and the European Association of Preventive Cardiology.[89–91] Unlike the traditional use of predicted maximum HR (220 − age) to design exercise programs, CPET offers a more precise evaluation by considering individual exertion capacity. The principles of exercise prescription, encapsulated in the FITT (Frequency, Intensity, Time, and Type) framework, are crucial for designing and monitoring exercise programs.[65,90] While frequency, duration, and type of exercise can often be determined without resorting to exercise testing, intensity depends on each individual's exertion capacity and considered the most crucial variable in enhancing cardiorespiratory fitness during CR for the majority of patients.[14,92] By analyzing CPET data, clinicians can determine the optimal intensity domain that corresponds to each patient's functional capacity and goals, ensuring that the prescribed exercise program is sufficiently challenging to induce physiological adaptations, but not excessively taxing to jeopardize the individual's health.

Key CPET Parameters for Determining Exercise Intensity

Cardiopulmonary exercise testing provides us with objective tools for accurately determining exercise intensity. These objective methods include the use of indices such as peak exercise capacity indices, VTs, and the myocardial ischemia threshold. This approach enables a comprehensive assessment of the patient's exercise capacity and physiological responses. As a result, we can tailor exercise intensity to each individual, optimizing clinical benefits while minimizing potential risks.

Peak Exercise Capacity Indices

Exercise prescription in CR typically relies on several indices of peak exercise capacity including: the percentage of peak workload, indicating the maximum amount of work achieved; the percentage of peak HR, reflecting the maximum elevation of HR; the percentage of peak oxygen uptake, assessing the maximum amount of oxygen used during exercise; the percentage of oxygen uptake reserve, representing the difference between maximal oxygen consumption during exercise and at rest; and the percentage of HR reserve, measuring the difference between maximal HR and resting HR, evaluating the heart's capacity to increase its rate during exercise.[65,93,94]

However, the use of these indices may be limited by several factors. Up to 15% of the outpatient CR population patients may struggle to achieve

maximal effort (RER ≥1.10) during exercise tests, complicating the precise assessment of their capacities.[95] Additionally, changes in medication dosage and timing for HR control medications can disrupt the HR response to exercise intensity, complicating the precise prescription of exercise intensity. [93,96]

The ramp rate during exercise testing can also significantly influence peak VO_2 or peak workload values, potentially distorting results and making exercise prescription less accurate.[97,98] Another drawback is that when exercise intensity is determined based on peak workload, it does not automatically adjust to changes in an individual's exercise capacity, unlike HR.[93] For example, if a person's exercise capacity increases over time through a CR program, the same workload may no longer induce the same exercise intensity. Thus, arbitrary increases in workload may be necessary to maintain effective exercise intensity.

Given these limitations, relying solely on these indices may not be sufficient to guarantee optimal exercise intensity for all patients. This underlines the need to use alternative methods to prescribe the most appropriate intensity possible.

Ventilatory Threshold

An alternative approach to determining exercise intensity, rather than relying solely on indices of peak exercise capacity, is to associate it with VT1 and VT2. This approach, more commonly used in European CR programs, requires analysis of cardiopulmonary gases. By identifying these thresholds, training zones can be established, with light intensity below VT1, moderate intensity between VT1 and VT2, and high intensity above VT2.[93]

VT1 is typically achieved at around 50–60% of peak VO_2 or 60–70% of peak HR.[99,100] VT2 is usually reached at approximately 70–80% of peak VO_2 and 80–90% of peak HR during incremental exercise, potentially related to the "critical power."[101]

Despite its potential advantages, this approach presents notable challenges. Variability among subjects in consecutive tests, discrepancies between observers and sites, and the low reproducibility of VT2 in patients with cardiovascular diseases (CVD) are among these challenges.[93,102,103] Moreover, translating VTs to constant-load exercise is complex due to the slow kinetics of oxygen consumption, particularly pronounced in patients with CVD and HF.[31,93,104,105] In this regard, Mezzani et al. proposed an empirical rule recommending that the prescribed power for constant-load exercise should be 10 W lower than the maximal power achieved during the initial incremental test in patients with CVD.[106] Despite these limitations, using VT1 and VT2 to define exercise intensity could prove more effective in improving VO_2max compared to percentage-based prescriptions.[107] This observation, validated in healthy subjects, warrants further investigation in patients with CVD.[108]

Myocardial Ischemia Threshold

The myocardial ischemia threshold (MIT) is the HR or workload level at which a 1 mm horizontal or downward sloping ST segment depression begins to appear during incremental exercise testing.[109] Generally it is recommended that patients with residual ischemia keep their exercise below the MIT to avoid complications.[106] However, methods for precisely determining the MIT and prescribing exercise intensity remain subject to further research for effective standardization. Lacking a precise determination of the MIT, clinicians may opt for alternative methods, such as using percentages of maximum power or maximum HR to prescribe exercise intensity more conveniently.[93] This often involves choosing lower percentages of maximum power or maximum HR to avoid placing excessive strain on the heart. In the case of ischemia symptoms during exercise, such as chest pain or electrocardiographic abnormalities, exercise intensity percentages should be adjusted to even lower levels to ensure patient safety.

CPET Limitations

Although CPET is an indispensable tool for assessing cardiorespiratory fitness and prescribing exercise in CR, it is crucial to recognize its limitations.

Averaging Respiratory Data

The methods used to average respiratory data, in particular the length of averaging intervals, can have a significant impact on measurements of VO_2max. Shorter averaging intervals often result in artificially high peak values, which can lead to misinterpretation of a patient's aerobic capacity, particularly if baseline conditions are not clearly established or documented. Unfortunately, existing guidelines do not provide consistent recommendations on the optimal method for averaging respiratory data. In clinical practice, it is most common to use averaging periods ranging from 10 to 60 seconds. This variability underscores the need for clear documentation and justification of the chosen interval in the assessment of aerobic capacity.[110]

Inter-Observer Variability

Subjectivity in the interpretation of VTs by different observers can also compromise the reproducibility of results. Although modern software provides automated interpretation tools, visual confirmation by experienced observers is still required, introducing a risk of inter-observer variability.[103]

Variability in Test Implementation

The way in which CPET is performed can vary considerably, impacting the consistency of results. Correct equipment calibration, standardized patient encouragement, and consistent exercise protocols are essential to ensure reliable and comparable results.

Impact of Drugs and Medical Devices

Patients taking HR-modulating drugs or equipped with devices such as pacemakers may show altered responses during CPET. In particular, these interventions may influence parameters such as VO_2/HR, complicating the assessment of cardiovascular function during exercise. It is essential to take these factors into account when analyzing CPET results to ensure accurate interpretation and facilitate reliable comparisons between different tests or patients.[111]

Integration with Other Clinical Parameters

The integration of CPET results with other clinical parameters represents a multidimensional challenge that requires particular attention in clinical practice. CPET provides comprehensive data on cardiorespiratory function during exercise. However, to take full advantage of this information, it needs to be effectively integrated with other clinical data, such as imaging results, laboratory analyses, and physical examinations. This integration faces several obstacles. Firstly, the complexity and volume of CPET data require specific expertise for correct interpretation, often at the intersection of different medical specialties, such as pulmonology, cardiology, and sports medicine. Secondly, the lack of standardized protocols for correlating CPET data with other clinical tests can hamper accurate diagnosis and treatment planning. Thirdly, currently available software for the analysis of CPET data is not always designed for

seamless integration with other clinical parameters, which may limit its usefulness in a holistic diagnostic framework.

Practical Recommendations to Overcome the Limitations of CPET

To address the challenges and limitations of CPET, we propose practical recommendations to improve the reproducibility, interpretation, and clinical integration of results:

- Implement comprehensive training programs for all healthcare professionals performing CPET to improve and standardize its interpretation.
- Formulate clear, standardized guidelines on the optimal averaging intervals for respiratory data, supported by clinical research, to reduce variability and the risk of misinterpretation.
- Ensure thorough documentation of the chosen averaging intervals and provide a rationale based on patient-specific conditions and baseline measurements.
- Promote the use of automated interpretation tools, while maintaining the requirement for verification by experienced observers to minimize subjectivity.
- Ensure that the same exercise mode and protocol are used for serial CPET tests.
- Maintain strict protocols for calibration and maintenance of CPET equipment. Regular checks can ensure data accuracy and reliability, particularly for VT2, which is difficult to reproduce in CVD patients.
- To reduce variability due to disparities between the two observers in the determination of VT1 and VT2, it is important to involve a third observer to assess differences between the two evaluators.
- Develop and follow a standardized script to encourage patients during CPET to maintain consistency of effort stimulation between tests.
- Conduct a thorough pre-test assessment to identify any medications or devices that may affect CPET outcomes and adjust protocols accordingly.
- Foster a collaborative approach involving specialists from cardiology, pulmonology, and sports medicine to integrate CPET data effectively with other clinical findings.
- Establish correlation protocols between CPET results and other diagnostic tests, to ensure a comprehensive approach to diagnosis and treatment planning.

By implementing these recommendations, clinicians can enhance the utility, accuracy, and clinical relevance of CPET, leading to better patient outcomes and more effective management of cardiovascular and respiratory conditions.

Conclusion

CPET is an essential tool in patient evaluation. CPET allows for a precise and comprehensive assessment of cardiorespiratory capacity, facilitating the customization of aerobic training programs in CR. This optimization enhances therapeutic benefits while minimizing risks.

However, to fully exploit its potential, it is essential to develop standardized protocols that improve reproducibility and comparability of results across different centers and patient populations. In addition, the integration of CPET with other diagnostic modalities, such as cardiac imaging or pulmonary function assessment, offers a promising avenue for a more comprehensive approach to patient management. This would enable us not only to refine diagnoses, but also to tailor treatments more closely to patients' specific needs. Finally, future research should also focus on exploiting emerging technologies, such as artificial intelligence, to optimize the interpretation of CPET data and improve clinical decision-making. ❑

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