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# Cardiopulmonary exercise testing in pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension

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Cardiopulmonary exercise testing allows for a comprehensive assessment of the mechanism of exercise limitation in pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. Competitive pathophysiologic mechanisms may affect the clinical interpretation of cardiopulmonary disease as they relate to dyspnea, leg fatigue, and exercise intolerance.

## KEYWORDS

pulmonary hypertension, chronic thromboembolic pulmonary disease, chronic thromboembolic pulmonary hypertension, cardiopulmonary exercise testing, pulmonary embolism

## 1 Introduction

Cardiopulmonary exercise testing (CPET) is a diagnostic tool used to investigate functional capacity and characterize exercise limitations related to circulatory impairment and ventilatory inefficiency (1, 2). It is a durable and versatile test that provides invaluable information on a patient's cardiovascular and pulmonary disease. Traditionally the 6 min walk distance is routinely used to assess the functional capacity of patients with PH for risk stratification, but can lack cardiopulmonary specificity. Therefore current ESC/ERS guidelines (3) recommend CPET for further evaluation in symptomatic patients with intermediate echocardiographic findings of pulmonary hypertension (PH), therefore we will try to provide key parameters to understand and interpret those findings. CPET allows the analysis of gas exchange at rest as well as during exercise and recovery, using breath-by-breath analysis of oxygen uptake ( $V_{O_2}$ ), carbon dioxide output ( $V_{CO_2}$ ), and ventilation ( $V_E$ ). This data is integrated with measurements of symptoms, heart rate, blood pressure, work rate, and electrocardiographic findings.

The definition of PH was recently updated to emphasize early disease detection in the guidelines from the World Health Organization (WHO) -European Society of Cardiology (3). Currently, PH is defined as a mean pulmonary artery pressure (mPAP) of greater than 20 mmHg and pulmonary vascular resistance (PVR) of greater than 2 Wood Units. There are 5 clinical categories based on the etiology of PH, and we will focus on pulmonary arterial hypertension (PAH)- WHO Group 1, and chronic thromboembolic pulmonary hypertension (CTEPH)- WHO Group 4.

PAH is precapillary PH characterized by endothelial dysfunction leading to increased pulmonary vascular resistance (3). It can be idiopathic, hereditary, or associated with predisposing diseases. CTEPH is an uncommon complication of pulmonary embolism (PE) defined by the presence of precapillary PH with angiographic evidence (i.e., computed tomography of the chest, magnetic resonance imaging of the pulmonary arteries, catheter-based pulmonary angiography) of organized thrombotic residua within the pulmonary arteries that are present in spite of at least 3 months of anticoagulation therapy. For those with imaging evidence of chronic PE in the absence of rest-hemodynamic evidence of PH, the diagnosis of chronic thromboembolic disease (CTED), or most recently the proposed designation, chronic thromboembolic pulmonary disease (CTEPD), is suggested.

In both PAH and CTEPH, there are multiple variables affecting cardiac function and pulmonary gas exchange leading to exercise intolerance and exertional dyspnea. These changes reflect the underlying exercise pathophysiology and can be evaluated via CPET. This review summarizes the developments and evidence on the application of CPET in PH.

## 2 Practical considerations and key parameters of cardiopulmonary exercise testing

The usefulness of the CPET depends on an individual's capacity to perform physical exercise, evaluating the ability of the pulmonary system's ability to clear CO<sub>2</sub> and the cardiovascular system's ability to supply oxygen to the muscles. There is a close evaluation of the delivery and removal systems (i.e., ventilation, diffusion, transport of O<sub>2</sub> and CO<sub>2</sub> in the blood, and capillary gas exchange). The increase in oxygen uptake by the peripheral muscles is a response to an increase in cardiac output (CO = heart rate × stroke volume), which increases 6 times with exercise. The cardiac output is distributed to skeletal muscles and shunted away from the non-active tissues (e.g., splanchnic circulation). There is an increase in blood flow to the lung in addition to vasodilation of the pulmonary vessel, with increased extraction of O<sub>2</sub> from the blood to the muscles, resulting in an increased arteriovenous oxygen difference. Ventilation (V<sub>E</sub>) increases proportionally with the work rate. When inhalation takes place, the air in the alveoli, known as the tidal volume (V<sub>t</sub>), accounts for the gas exchange. The air not participating in this exchange, is known as the dead space (V<sub>d</sub>). During exercise, both dilation of the respiratory passages and the effective areas of gas exchange (tidal volume) increase, therefore gas exchange remains intact. The increase in V<sub>E</sub> should be matched with an increase in blood flow, hence an appropriate cardiac output is important to maintain gas exchange. The point at which oxygen uptake is unable to increase adequately for peripheral oxygen demand marks the aerobic-anaerobic transition at which lactic acidosis will begin to occur. This is called the anaerobic threshold. If at any point there is a mismatch in this supply-demand chain there will be a clinical symptom.

The assessment of exercise capacity can be performed via a treadmill or stationary cycle ergometer. The selection of the exercise modality will depend on the patient and center's availability. Treadmills are preferred. Meanwhile, cycle ergometers are preferred in cases of gait and balance instability, severe obesity, orthopedic limitations, or when simultaneous right heart catheterization or echocardiogram is planned. The Bal and Ware, Naughton, and individualized ramp protocol involve increments in work rate per stage. They are recommended, as they allow to establish relationships between measured V<sub>O<sub>2</sub></sub> and work rate. Individuals should be expected to exercise for 8–12 min (4). Table 1 summarizes the CPET variables that are measured and calculated during the study (1, 3). Normal values may be affected in some individuals depending on their age, gender, volitional effort, and comorbidities.

## 3 Physiology of exercise in PAH and CTEPH

During exercise, peripheral muscles have increased oxygen demand that is achieved by peripheral vasodilation and increased oxygen extraction. When the normal individual exercises, the cardiac output should increase to match this oxygen delivery for the increasing demand of peripheral muscles (10). In the lungs increased tidal volume and pulmonary blood flow (achieved via vasodilation and pulmonary capillary recruitment) allows for a proportional increase in alveolar oxygen uptake. The maximal achievable oxygen uptake is labeled as the peak O<sub>2</sub> (peak V<sub>O<sub>2</sub></sub>) (5). In the alveoli, the carbon dioxide is cleared by a corresponding increase in minute ventilation (V<sub>E</sub> = V<sub>t</sub> × respiratory rate). The point at which oxygen uptake is unable to increase adequately for peripheral oxygen demand marks the aerobic-anaerobic transition at which lactic acidosis will begin to occur. This point is called the anaerobic threshold.

The physiological derangements in PH originate from obliteration and obstruction of pulmonary arteries (Figure 1). In PAH, vascular inflammation, remodeling, and endothelial dysfunction precipitate an increase in pulmonary vascular resistance. There is an imbalance in the production of pulmonary vasodilators and vasoconstrictors, abnormal proliferation of cells in the walls of the pulmonary arteries and arterioles, and intraluminal thrombus (11, 12). In CTEPH, residual thrombotic material causes pulmonary arterial obstruction, hindering pulmonary vasodilation and increasing dead space ventilation. In PAH and CTEPH, there is a decrease in the vasodilatory capacity, as well as in the distensibility and patency of the pulmonary vasculature. This hypoperfusion to ventilated lung regions is reflected as low P<sub>ETCO<sub>2</sub></sub>. In both entities, PAH and CTEPH, there is an increase in afterload, or pulmonary vascular resistance, which limits the increased stroke volume needed for effective circulation at the time of exercise (10, 13, 14). The pulmonary vascular bed of PH patients is unable to be recruited and distended, leading to increased pulmonary artery pressures (10). The sustained increased afterload causes adaptive myocardial hypertrophy, which is initially reflected by RV wall

TABLE 1 Cardiopulmonary exercise test variables.

Nomenclature	Definition	Normal values
<b>Metabolic and cardiovascular</b>		
Peak $V_{O_2}$	Aerobic capacity	$\geq 85\%$ based on predicted $V_{O_2}$ or $\geq 20$ mL $O_2$ /min/kg (5) $\geq 10$ mL $\cdot$ kg $^{-1}$ $\cdot$ min $^{-1}$ if treated with $\beta$ -blockade $\geq 14$ mL $\cdot$ kg $^{-1}$ $\cdot$ min $^{-1}$ if not treated with $\beta$ -blockade
$V_{O_2}$ at AT	Oxygen consumption at the onset of metabolic acidosis	$\geq 40\%$ – $80\%$ predicted $V_{O_2}$ (5)
$V_{O_2}/WR$	Dependence on anaerobic metabolism due to cardiac output and impaired peripheral muscle oxygen use	$\geq 10$ mL/min/W
Peak HR	Chronotropic response to exercise	220-age ( $>85\%$ predicted)
$O_2$ pulse	( $V_{O_2}/HR$ ) Stroke volume recruitment and correlation between an increasing cardiac output on heart rate	$\geq 80\%$ (5)
Heart rate recovery	Onset of parasympathetic tone and withdrawal of sympathetic tone (Maximum HR - HR one minute post exercise)	$\geq 18$ beats/min in the first minute post exercise
OUES	Oxygen uptake efficiency slope: ability to increase $V_{O_2}$ per 10-fold rise in ventilation	In men, OUES (L/min) = $[1,320 - (26.7 \times \text{age}) + (1,394 \times \text{body surface area})]/1,000$ . In women, OUES (L/min) = $[1,175 - (15.8 \times \text{age}) + (841 \times \text{body surface area})]/1,000$ (6, 7)
<b>Ventilation and mechanics</b>		
Peak $V_E$	Maximal ventilation achieved during exercise	
Breathing reserve	$(1 - V_E/MVV) \cdot 100 < 20\%$ and abnormally reduced	15%–20% (or $\geq 11$ –15 L/min) (5)
Dynamic hyperinflation	Increase in air trapping during exercise secondary to a shorter expiratory time	Decrease in inspiratory capacity $< 140$ mL (8)
<b>Gas exchange</b>		
$V_E/V_{CO_2}$ slope	Ventilatory efficiency	$< 30$
$V_E/V_{O_2}$ at AT	Ventilatory equivalent of $O_2$ , which is lowest near AT and then increases once compensatory hyperventilation takes place	$< 30$ (9)
$P_{ETCO_2}$	Efficacy of $CO_2$ delivery to alveoli ( $PACO_2 - PaCO_2$ )	$> 28$ mmHg
Saturation of $O_2$	Oxygen saturation	$> 95\%$
$P(A-a)O_2$	Efficacy of $O_2$ uptake	10–20 at rest, 15–30 at peak
$V_d/V_t$	Ratio of physiologic dead space to tidal volume	0.25–0.35 at rest (should decrease with exercise) (1)

hypertrophy, and later on by RV dilation (15, 16). There can be RV ischemia related to imbalanced oxygen supply and demand associated with hypertrophy, increased RV workload, and metabolic demands, without an increase in blood supply or microcirculation (17). In addition, there is uncoupling between the pulmonary vascular bed and the right ventricle, leading to right heart failure at peak exercise and inability to augment CO. In addition, elevated right ventricular pressure and dilation can cause interventricular septal shifting, which further reduces the pulmonary venous return to the left atrium, thereby decreasing left ventricular diastolic filling, systemic cardiac output, and tissue oxygen delivery (18–20).

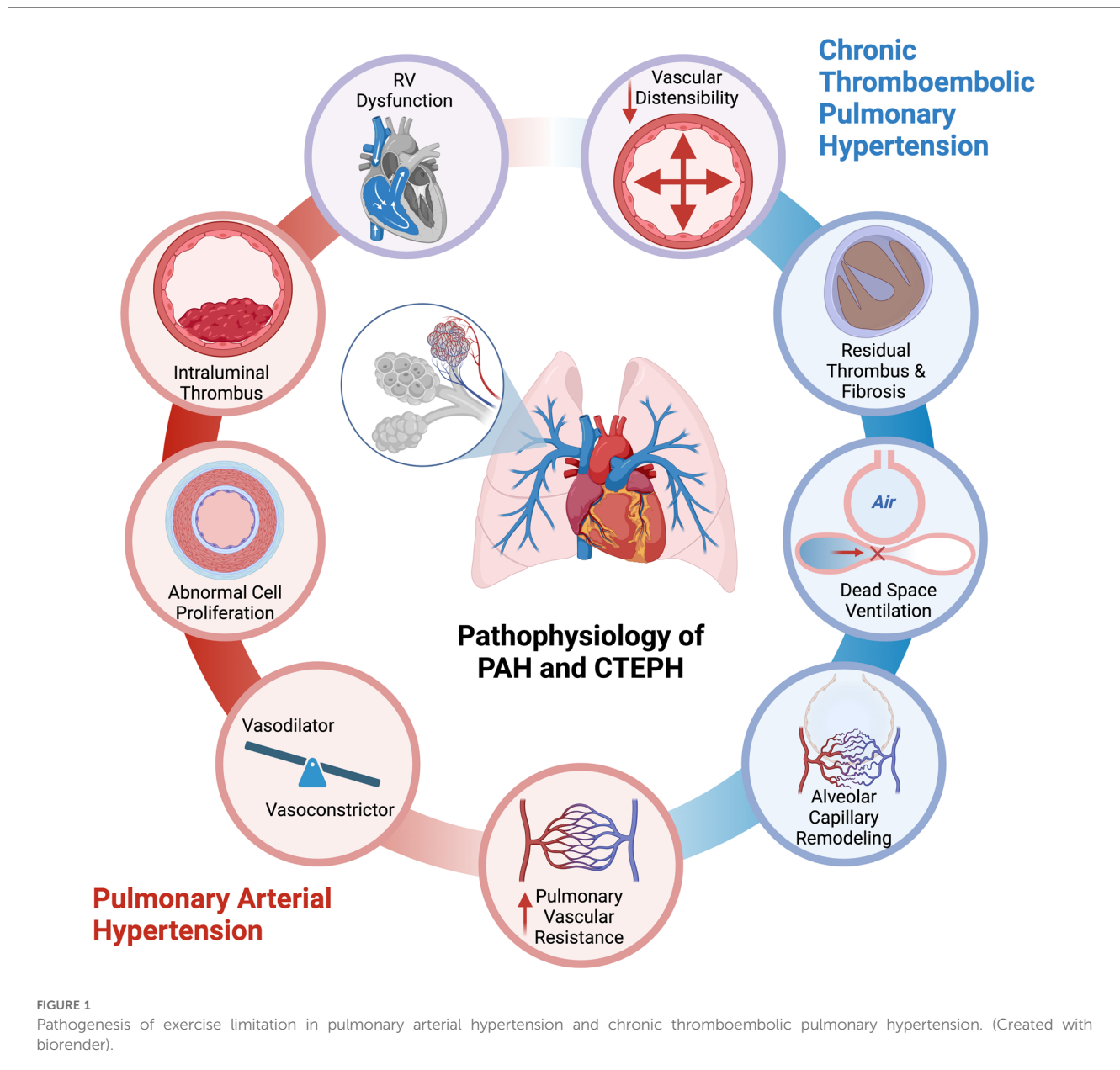
The resulting hypoxia leads to vasoconstriction and impaired tissue oxygen delivery to peripheral muscles, causing lactic acidosis, lowered peak  $V_{O_2}$ , and a reduction in the anaerobic threshold. This leads to the production of  $V_{CO_2}$  and an excessive increase in ventilation during exercise (increased  $V_E/V_{CO_2}$ ). This results in the characteristic CPET pattern of PH with low  $P_{ETCO_2}$ , high ventilatory equivalent for carbon dioxide ( $V_E/V_{CO_2}$ ), and low peak  $O_2$  uptake (peak  $V_{O_2}$ ).

### 3.1 Indications and contraindications for CPET

Patients with PH can have nonspecific symptoms, such as fatigue, dyspnea, and exercise intolerance. CPET can help

identify the source of exercise intolerance, monitoring disease progression or treatment response, and aiding in prognosis. Ultimately, CPET allows for physiologic risk stratification. Table 2 includes the absolute and relative contraindications. CPET can provide reproducible cardiovascular-specific information as you can record heart rate, electrocardiogram, blood pressure, and gas exchange patterns. The primary measurements made are respiratory rate, end-tidal  $pO_2$ , and  $pCO_2$ . Other parameters, such as  $O_2$  pulse, and ventilatory equivalents for  $O_2$  and  $CO_2$  are also obtained. Individuals should reach an RER  $> 1.05$ . There are some limitations with the interpretation of the data depending on the volitional effort of the individual, but the interpretation can be done in the context of the maximum HR and RER achieved. The patient does not require prior training to achieve better performance. CPET can rule out other factors affecting the ability to exercise, such as anemia, pulmonary mechanical pathology, or skeletal muscle myopathy. CPET in patients with PH is highly reproducible and provide robust endpoints to assess exercise capacity (21).

Although CPET is generally well-tolerated, contraindications include physical barriers to exercise or decompensated disease state including but not limited to active myocardial ischemia, uncontrolled arrhythmia, severe aortic stenosis, COPD exacerbation, uncontrolled asthma, or other acute respiratory failure (22). Barriers for implementation can be related to confidence in interpreting results and lack of equipment or trained technicians.



### 3.2 Cardiopulmonary exercise testing in pulmonary arterial hypertension

The goal of CPET in PAH is to provide an early diagnosis, help stratify individuals with intermediate risk PH, identify peripheral muscle abnormalities related to PAH, and prognosticate and evaluate the efficacy of therapeutic interventions (23, 24) (Figure 2). The use of CPET in PAH was derived from its use in left heart failure (25). The mechanisms that impair exercise in PAH are: (1) inability to vasodilate the pulmonary vascular bed (i.e., impaired distensibility and vasodilation and smaller vessels) (26); (2) reduction in the RV contractility (19); (3) chronotropic impairment (27); (4) abnormal gas exchange and hypoxemia; (5) chemoreceptor activation; (6) endothelial dysfunction; and (7) skeletal muscle myopathy. All of these are measurable with

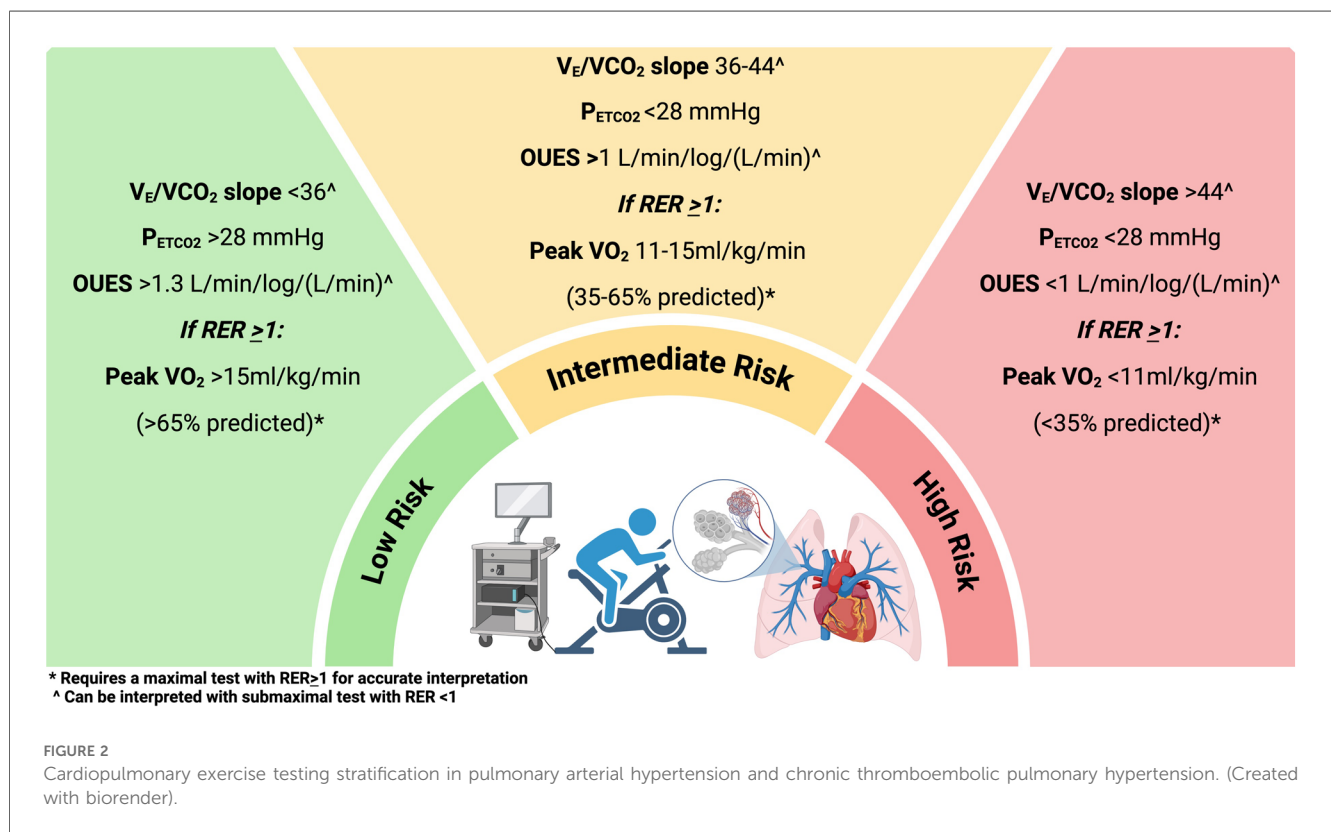
CPET. The main abnormalities recognized in PAH are called ventilatory inefficiencies and are determined by an abnormally high ratio of ventilation to  $\text{CO}_2$  production ( $V_E/V_{\text{CO}_2}$ ), as well as a low end-tidal  $\text{pCO}_2$  ( $P_{\text{ETCO}_2}$ ), and thus dead space ventilation, which in turn have proven to be reliable physiologic signatures of pulmonary vascular disease across a variety of PH conditions (28–31). Peak  $V_{\text{O}_2}$  is prognostic in PAH. Wensel et al. (32) first reported the prognostic capability of CPET in PAH showing that a low peak  $V_{\text{O}_2}$  of 10.4 mL/kg/min and a low peak exercise systolic blood pressure of less than 120 mmHg were associated with worse survival as compared to those with one or none of those factors.

Oxygen pulse reflects the capacity and efficiency of the heart to deliver oxygen per heartbeat and can be related to stroke volume or peripheral arterial extraction. Reduction in  $\text{O}_2$  pulse as the work

TABLE 2 Absolute and relative contraindications for cardiopulmonary exercise testing (adapted from ATS/ACCP statement on cardiopulmonary exercise testing) (1).

Absolute	Relative
Acute myocardial infarction (3–5 days)	Left main coronary stenosis or its equivalent
Unstable angina	Moderate stenotic valvular heart disease
Uncontrolled arrhythmias causing symptoms or hemodynamic compromise	Severe untreated arterial hypertension at rest or hemodynamic compromise (>200 mm Hg systolic, >120 mm Hg diastolic)
Syncope	Tachyarrhythmias or brady-arrhythmias
Active endocarditis	High-degree atrioventricular block
Acute myocarditis or pericarditis	Hypertrophic cardiomyopathy
Symptomatic severe aortic stenosis	Severe pulmonary hypertension
Uncontrolled heart failure	Advanced or complicated pregnancy
Acute pulmonary embolus or pulmonary infarction	Electrolyte abnormalities
Thrombosis of lower extremities	Orthopedic impairment that compromises exercise performance
Suspected dissecting aneurysm	
Uncontrolled asthma	
Pulmonary edema	
Room air desaturation at rest $\leq 85\%^*$	
Respiratory failure	
Acute non-cardiopulmonary disorder that may affect exercise performance or be aggravated by exercise (i.e., infection, renal failure, thyrotoxicosis)	
Mental impairment leading to inability to cooperate	

\*multiplication sign.



rate increases suggests an issue with oxygen delivery. The ratio of change in oxygen consumption to changes in work rate (exercise factor) is usually 10 mL/min/W in healthy individuals. If this ratio cannot be achieved, it suggests impairments in the cardiac output with exercise. The gas exchange parameters will imply the presence of PH, but ultimately cardiac catheterization will be required to make the diagnosis of PAH.

With regards to diagnosis, current ESC/ERS guidelines include CPET among the recommended evaluations for patients with unexplained exertional dyspnea with indeterminate echo findings for PH (3). In symptomatic patients with systemic sclerosis, CPET with normal peak  $V_{O_2}$  suggests against the presence of PH, reducing the need for screening RHC (33). Similarly, for patients with connective-tissue diseases, HIV, or portal



hypertension, CPET is a recommended modality to screen for PAH. Additionally, CPET as an endpoint in clinical trials has been used in many consensus working groups.

### 3.3 Cardiopulmonary exercise testing in chronic thromboembolic pulmonary disease

Patients with persistent symptoms after an acute pulmonary embolism with a “post-PE syndrome” can benefit from further characterization of their impairment (34). Patients with CTEPH and CTEPD can have similar symptoms and perfusion defects, but the difference is in the lack of resting PH in the latter. Investigators have described in CTEPD a marked reduction in peak  $V_{O_2}$ , high  $V_E/V_{CO_2}$  at anaerobic threshold, and slightly decreased  $P_{ETCO_2}$  (35). In a study combining CPET with right heart catheterization and stress echocardiography, Peak  $V_{O_2}$  was negatively correlated with mPAP and PVR, while  $V_E/V_{CO_2}$  at AT was positively correlated with mPAP and PVR (35).

Regarding patients with concerns for CTEPH, CPET is included in the recommended workup along with echocardiography and BNP/NT-proBNP (36). This is corroborated by data from Held et al. (37), who described that a score combining  $P_{(A-a)O_2}$ ,  $P_{(c-ET)CO_2}$  (capillary to end tidal carbon dioxide gradient),  $P_{ETCO_2}$  at anaerobic threshold, and  $V_E/V_{CO_2}$  slope, had a sensitivity of 83.3% and a specificity of 92.2% for the diagnosis of CTEPH, even in patients whose echocardiogram was normal. Zhu et al. (38) divided CTEPH patients by levels of severity defined by mean pulmonary artery criteria, and described the parameters associated with significant differences in oxygen uptake efficiency slope and plateau,  $V_E/V_{CO_2}$ , peak  $V_{O_2}$  and  $V_E$  at anaerobic threshold depending of the pulmonary artery pressure.

CPET is also useful to monitor response to treatment and assess disease severity in CTEPH. It has been used to monitor response in surgical patients post pulmonary thromboendarterectomy, balloon pulmonary angioplasty and inoperable patients medically managed with PDE5 inhibitors or endothelin receptor agonists (39, 40).

The differences between PAH and CTEPH have been described by some authors. Sun et al. (41) have described lower  $P_{ETCO_2}$  than in PAH when compared to CTEPH patients. Other parameters that have been compared is the response of oxygen uptake efficiency at peak and anaerobic threshold, and patient with PAH have higher values than patients with CTEPH not in proportion with hemodynamic severity (42).

## 4 Conclusion

As PAH and CTEPH diagnosis and management continue to improve the evaluation of the exercise capacity of individuals

with the use of CPET may be a key tool to understand the true source of their limitations. Abnormal responses to exercise can be better characterized with the use of CPET and allow for physiologically tailored interventions. We can help stratify the disease via this comprehensive and reproducible method.

## Author contributions

AC: Writing – review & editing, Writing – original draft. SL: Writing – review & editing, Writing – original draft, Visualization, Resources. GR: Writing – original draft, Investigation. YB: Writing – review & editing, Visualization, Resources, Data curation. FR: Writing – review & editing, Visualization, Supervision, Resources, Investigation, Funding acquisition, Conceptualization. EO: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal Analysis, Data curation, Conceptualization.

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