Exercise in Pulmonary Vascular Diseases

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Abstract

Pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension are the most common diseases of pulmonary vasculature. The physiological derangements of pulmonary hypertension result in characteristic abnormalities observed during dynamic exercise and often lead to dyspnoea and exercise intolerance. Impaired cardiac function results in reduced aerobic capacity, low anaerobic threshold and reduced value of the relationship between oxygen uptake and work rate ($\Delta V'O_2/\Delta WR$). Both high physiologic dead space and chemosensitivity contribute to elevated ratio of minute ventilation to CO_2 output ($V'_E/V'CO_2$) during exercise testing. Consequently, resting hypocapnia with low end-tidal PCO_2 throughout exercise is typically observed and is related to the severity of disease. Exertional hypoxaemia is also a variable but frequent finding during exercise, which can be related to ventilation-perfusion heterogeneity, low mixed venous O_2 content from impaired cardiac output and right-to-left shunting through a patent foramen ovale. Even in the absence of significant resting airflow obstruction, dynamic hyperinflation can occur in pulmonary vascular diseases, which contributes to exertional dyspnoea and exercise intolerance. Peripheral muscle dysfunction is another common component of exercise pathophysiology in these conditions.

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8.1 Introduction

Pulmonary hypertension is defined as a resting mean pulmonary arterial pressure (mPAP) ≥25 mmHg, which may result from primary diseases of the pulmonary vasculature, left heart disease, lung disease and systemic diseases [1]. Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are primary diseases of the pulmonary vasculature caused by obstruction, inflammation and remodelling of the pulmonary arteries and arterioles, endothelial dysfunction, vasoconstriction and thrombosis [2]. PAH may be idiopathic or caused by underlying connective tissue diseases, congenital heart disease, genetic mutations, drugs and toxins, portal hypertension or infection with human immunodeficiency virus or schistosomiasis [1]. CTEPH is a rare complication of pulmonary thromboembolism in which there is persistent obstruction of large- and medium-sized pulmonary arteries with remodelling of distal small vessels and progressive pulmonary hypertension [3, 4]. Over time, patients with pulmonary vascular diseases develop progressive increases in mPAP and pulmonary vascular resistance, which ultimately leads to right heart failure and death.

Cardiopulmonary exercise testing (CPET) is very sensitive in detecting possible impairments in a patient with early pulmonary vascular disease. Beside revealing common and non-specific symptoms like dyspnoea and exercise intolerance, CPET can highlight abnormal exercise response patterns suggestive of pulmonary vascular disease in patients with undifferentiated dyspnoea [5]. In addition to functional assessment, the CPET is helpful for the evaluation of responses to treatment and estimate prognosis [6].

This chapter will focus primarily on the dynamic exercise pathophysiology and patterns of exercise responses during CPET in patients with pulmonary hypertension and increased pulmonary vascular resistance, without significant left heart disease (Group 2 pulmonary hypertension) or a significant obstructive or restrictive ventilatory defect (Group 3 pulmonary hypertension). The features and impact of pulmonary hypertension secondary to other lung and heart diseases will not be discussed in this chapter.

8.2 Exercise Pathophysiology in PAH and CTEPH: General Hallmarks

From a pathophysiological point of view, PAH and CTEPH are characterised by obliteration and consequent obstruction of pulmonary arteries, vascular inflammation and consequent remodelling and endothelial dysfunction, which all give rise to increased pulmonary arterial resistance and elevated pulmonary arterial pressure [6]. The consequence of all this is that dead space (V_D/V_T) ventilation increases because of the reduced perfusion of well-ventilated alveoli, which is reflected "mainly" as a high ratio of minute ventilation (V'_E) to CO_2 output ($V'CO_2$) and expressed as $V'_E/V'CO_2$. During exercise, cardiac output (CO) must increase to match oxygen transport to the increasing demand by locomotor muscles [6].

Increasing pulmonary blood flow during exercise is normally guaranteed by vascular distension and recruitment to keep resistance low for the right ventricle (RV). However, in patients with pulmonary vascular disease, fixed vascular remodelling hinders normal recruitment and distension and translates into a persistently high vascular resistance, and therefore increases in CO during exercise give rise to further increases in mPAP. This progressive elevation in afterload curtails the ability of the RV to increase stroke volume, and therefore increases in CO during exercise strongly rely on heart rate (HR) [6].

High RV pressure and RV dilation lead to interventricular septal shift, which, along with reduced pulmonary venous return to the left atrium, limits left ventricular (LV) diastolic filling, systemic CO and tissue oxygen transport [6]. Arterial desaturation may also occur during exercise due to a combination of low mixed venous oxygen saturation, relative low alveolar-capillary diffusing capacity, high physiologic dead space or right-to-left shunting through a patent foramen ovale. Hypoxaemia further worsens the blunted tissue oxygen delivery, being conducive to the early onset of lactic acidosis and reduced anaerobic threshold (AT) that develop in the presence of a reduced CO [6]. Furthermore, hypoxaemia, lactic acidosis and higher VCO_2 stemming from anaerobic metabolism all contribute to an excessive increase in V'_E during exercise. These pathophysiologic mechanisms result in characteristic pattern of abnormalities observed during CPET in patients with pulmonary vascular diseases (Table 8.1) and depict the various potential contributors to dyspnoea, leg fatigue and exercise intolerance (Fig. 8.1).

8.3 Cardiovascular Abnormalities

During cardiac systole, both the systemic and pulmonary circulations must handle the same volume of blood. The latter, however, is normally at 10% of the former's pressure. During dynamic exercise, cardiac output (CO) must increase to match oxygen delivery to demand by peripheral muscles. Even the greatly increased cardiac output of exercising healthy subjects will lead to only a modest increase in mPAP pressure, mainly because of the large capacitance of the pulmonary circulation [7], which is the consequence of the increase in left atrial pressure.

Even in early pulmonary vascular disease, when resting mPAP is not yet elevated, there is a loss of vascular distensibility [8], and mPAP rises disproportionately to CO [9, 10]. In severe PAH and CTEPH, the pulmonary vasculature cannot accommodate increased pulmonary blood flow, resulting in further and excessive increases in the right ventricular (RV) afterload during exercise [11]. Because of ventricular interdependence, severe RV pressure overload shifts the interventricular septum to the left during diastole and impairs left ventricular filling [12–16], limiting maximal CO and oxygen delivery. Thus, in patients with pulmonary vascular diseases, changes in CO during exercise are mostly mediated by increasing heart rate (HR) rather than increasing stroke volume [15, 17, 18]. The ability to increase CO during exercise is a more important determinant of peak exercise capacity than the resting CO in patients with PAH and CTEPH, as it reflects the severity of the

Table 8.1 Typical CPET abnormalities in patients with pulmonary vascular diseases

	PAH	CTEPH	PVOD
Metabolic and cardiovascular			
Peak $V'O_2$	↓	↓	↓
$V'O_2$ at AT	↓	↓	↓↓
$V'O_2$/WR	↓	↓	↓
Peak O_2 pulse	↓	↓	↓
Ventilation and mechanics			
Peak V'_E	↓	↓	↓
Breathing reserve	Normal	Normal	Normal
Dynamic hyperinflation	Possible	Possible	?
Gas exchange			
$V'_E/V'CO_2$ slope	↑	↑↑	↑↑
$V'_E/V'CO_2$ at AT	↑	↑↑	↑↑
OUE	↓	↓	?
OUES	↓	↓	?
OUEP	↓	↓↓	?
$P_{ET}CO_2$ (peak and at AT)	↓	↓↓	↓↓
SaO_2	↓	↓↓	↓↓
Peak $P_{a\text{-}ET}CO_2$	↑	↑↑	↑↑
Peak $P_{A\text{-}a}O_2$	↑	↑↑	↑↑
Peak V_D/V_T	↑	↑↑	↑↑

CPET cardiopulmonary exercise testing, *PAH* pulmonary arterial hypertension, *CTEPH* chronic thromboembolic pulmonary hypertension, *PVOD* pulmonary veno-occlusive disease, $V'O_2$ oxygen consumption, *AT* anaerobic threshold, *WR* work rate, *O_2 pulse* peak $V'O_2$-to-heart rate ratio at peak exercise, V'_E minute ventilation, $V'_E/V'CO_2$ ratio of minute ventilation to carbon dioxide production ($V'CO_2$), *OUE* oxygen uptake efficiency ($V'O_2/V'CO_2$), *OUES* oxygen uptake efficiency slope, *OUEP* oxygen uptake efficiency plateau, *$PETCO_2$* end-tidal pressure of carbon dioxide, *SaO_2* arterial oxygen saturation, *$P_{A\text{-}a}O_2$* alveolar-arterial oxygen pressure gradient at peak exercise, *$P_{a\text{-}ET}CO_2$* arterial to end-tidal carbon dioxide pressure gradient at peak exercise, V_D/V_T physiologic dead space fraction as ratio of dead space (V_D) to tidal volume (V_T) at peak exercise

underlying pulmonary vascular disease and the ability of the RV to adapt to it [19]. In patients with chronic thromboembolism but without manifest pulmonary hypertension at rest, the mPAP/CO slope during exercise is abnormally high and stroke volume increases minimally, indicating that RV stroke volume response is impaired early in the disease course [20].

These pathophysiological adaptations to the increased pulmonary arterial pressures all contribute to the cardiovascular limitation to exercise during CPET. Because of high RV afterload and low maximal CO, oxygen delivery to the skeletal muscle is impaired, manifesting as reduced aerobic capacity (low peak $V'O_2$) and early shift to anaerobic metabolism for a given $V'O_2$ (i.e., low anaerobic threshold) [21]. While maximal work rate (WR) and maximal $V'O_2$ are often reduced, the $\Delta V'O_2/\Delta WR$ relationship is also low (<8–9 $mL \cdot min^{-1}\ W^{-1}$) compared to healthy individuals or patients with left ventricular failure, reflecting impaired CO and/or abnormal peripheral muscle O_2 utilisation (Fig. 8.2) [21–25].

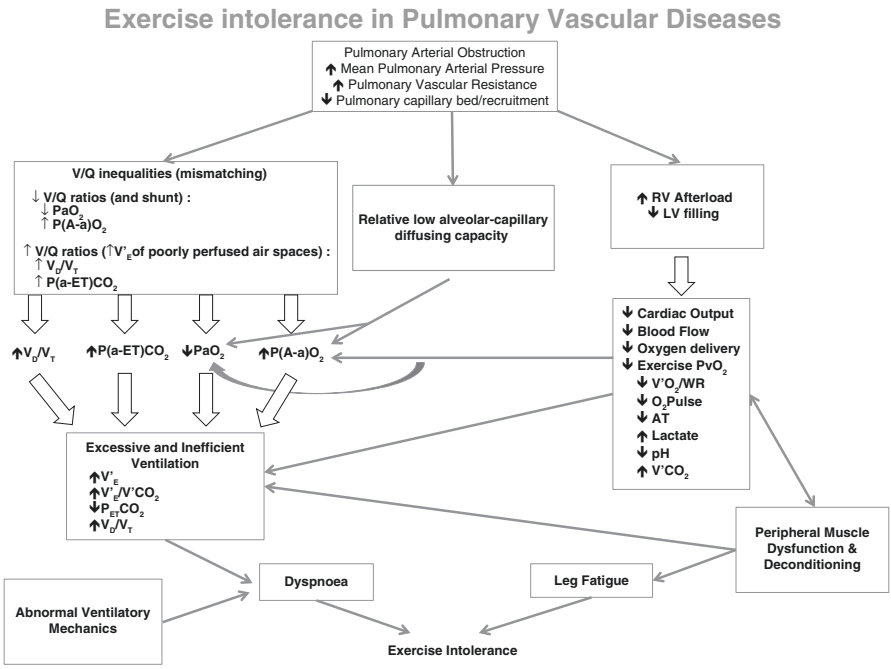

Fig. 8.1 Pathophysiology and mechanisms of exercise intolerance in pulmonary hypertension. Pulmonary vascular obstruction results in high ventilation-to-perfusion ratios and impaired cardiac output and can result in hypoxaemia due to right-to-left shunting through a patent foramen ovale. Inefficient ventilation proposes high ventilatory demand, high $V'_E/V'CO_2$ and V_D/V_T and low $P_{ET}CO_2$. Cardiac limitation and peripheral muscle abnormalities result in a low anaerobic threshold, early-onset lactic acidosis and increased $V'CO_2$, which provide further stimulation for excessive ventilation. Ventilatory mechanical constraints on tidal volume expansion also contribute to dyspnoea during exercise. *Abbreviations*: *V′/Q′* ventilation-to-perfusion ratio, *RV* right ventricle, *LV* left ventricle, V'_E minute ventilation, $V'_E/V'CO_2$ ratio of minute ventilation to carbon dioxide production, $P_{ET}CO_2$ end-tidal pressure of carbon dioxide, V_D/V_T dead space to tidal volume fraction, $V'O_2$ oxygen consumption, *WR* work rate, *O_2 pulse* $V'O_2$-to-heart rate ratio, $V'CO_2$ carbon dioxide production, PvO_2 venous partial pressure of oxygen, PaO_2 arterial partial pressure of oxygen, $PaCO_2$ arterial partial pressure of carbon dioxide. This is an original figure, no permission is required

Stroke volume is an important contributor to the increase in CO during exercise, and we have previously discussed that it is significantly impaired in pulmonary vascular disease. It is, however, very difficult to measure and a surrogate measure can be used.

Given Fick's equation where CO is equal to $V'O_2$ divided by the arteriovenous O_2 difference (CaO_2–CvO_2) and that CO = HR × stroke volume, the equation can be rearranged as $V'O_2$/HR (O_2 pulse) = stroke volume × (CaO_2–CvO_2). Thus, in the absence of arterial desaturation, a reduced O_2 pulse reflects an impaired stroke volume response during exercise. This means that cardiac output solely depends on increasing heart rate, leading to a decreased and flattened profile of

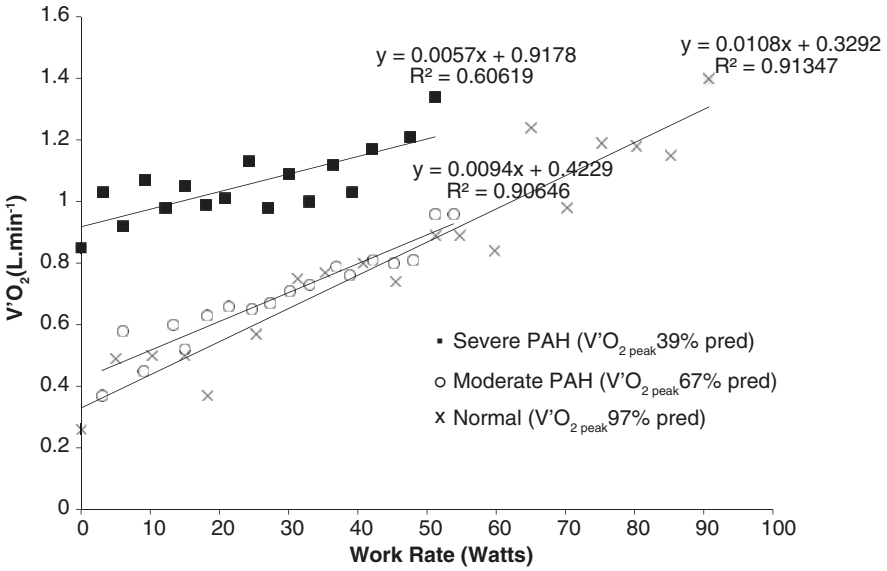

Fig. 8.2 Comparison of oxygen consumption ($V'O_2$) to work rate (WR) relationships. A normal individual with peak $V'O_2$ of 97% has a $V'O_2$/WR slope of 10.8 mL per Watt. A patient with pulmonary arterial hypertension (PAH, pulmonary vascular resistance 9.3 Wood units) and a preserved cardiac index (CI = 2.7 L·min·m^{-2}) and moderately reduced peak $V'O_2$ of 67% predicted has a borderline reduction in the $V'O_2$/WR slope of 9.4 mL per Watt. The patient with PAH and severe reduction in peak $V'O_2$ (39% predicted) demonstrates a reduced $V'O_2$/WR slope of 5.7 mL per Watt. Note that the difference in y-intercept ($V'O_2$) at WR of 0 Watts is largely related to variability in body mass between these individuals. Original figure. Data from authors' own laboratory

the O_2 pulse ($V'O_2$/HR) [21, 23]. Poor RV function and stroke volume response may lead to low systolic blood pressure (SBP) during exercise, and symptoms of pre-syncope or even syncope may occur. A peak exercise SBP < 120 mmHg during CPET should be considered an ominous sign [26]. Vagal reactivation after exercise is an important mechanism underlying HR recovery in the first 30 s–60 s after exercise and is abnormally slow in individuals with cardiac impairment [27]. Recovery of HR after exercise is delayed in PAH patients compared to controls, and slower HR recovery (<18 beat per minute decrease in the first minute post-exercise) is associated with worse resting haemodynamics, lower peak $V'O_2$ and a worse prognosis [28, 29].

Thus, the primary abnormalities of cardiovascular variables during exercise testing in patients with moderate to severe pulmonary vascular disease are (1) reduced peak $V'O_2$ and peak WR, (2) low anaerobic threshold, (3) reduced $\Delta V'O_2/\Delta WR$, (4) low and flattened O_2 pulse and (5) low maximal HR with delayed HR recovery (Fig. 8.1 and Table 8.1).

8.3.1 Ventilatory Abnormalities

For most patients with pulmonary vascular disease, exercise is not limited by encroachment upon their predicted maximal ventilatory capacity; ventilation (V'_E) at peak exercise is usually low [21, 22, 30, 31]. In the absence of concurrent asthma or chronic obstructive pulmonary disease, mechanical ventilatory constraint (dynamic hyperinflation) is not expected in pulmonary vascular diseases during CPET and, if present, is not as clinically relevant as in COPD.

Resting spirometry in patients with PAH is usually normal or may show mild restriction [32] or reduced mean expiratory flow (MEF) at 75%, 50% and 25% of vital capacity and increased residual volume-to-total lung capacity ratio (RV/TLC), suggestive of peripheral airways obstruction and gas trapping [33, 34].

Breathing patterns during exercise are more rapid and shallow in patients with PAH as opposed to normal individuals. Compared to healthy controls, up to 60% of PAH patients exhibit a reduction in inspiratory capacity during exercise, suggesting dynamic hyperinflation or impaired inspiratory muscle function [33, 35]. Even in the setting of a normal resting FEV_1/FVC, the presence of expiratory flow limitation and rapid shallow breathing patterns during exercise can promote dynamic hyperinflation in some PAH patients, which may lead to more severe dyspnoea (Figs. 8.3 and 8.4) [33].

Diaphragmatic muscle atrophy and weakness are present in patients with severe PAH or CTEPH [36–38] but did not appear to be involved in the dynamic reduction in

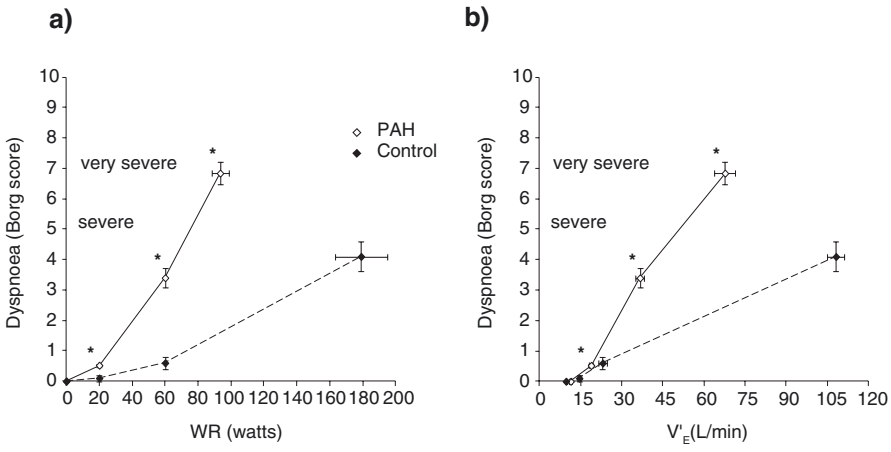

Fig. 8.3 Exertional dyspnoea intensity as measured by Borg score is displayed in response to (**a**) increasing work rate (WR) and (**b**) increasing minute ventilation (V'_E) during symptom-limited cardiopulmonary exercise testing in 25 patients with pulmonary arterial hypertension (PAH) and 10 healthy control subjects. *: $p < 0.05$, PAH vs. healthy control at rest and standardised exercise work rates (20–60 W) and peak exercise. From reference [33], with permission

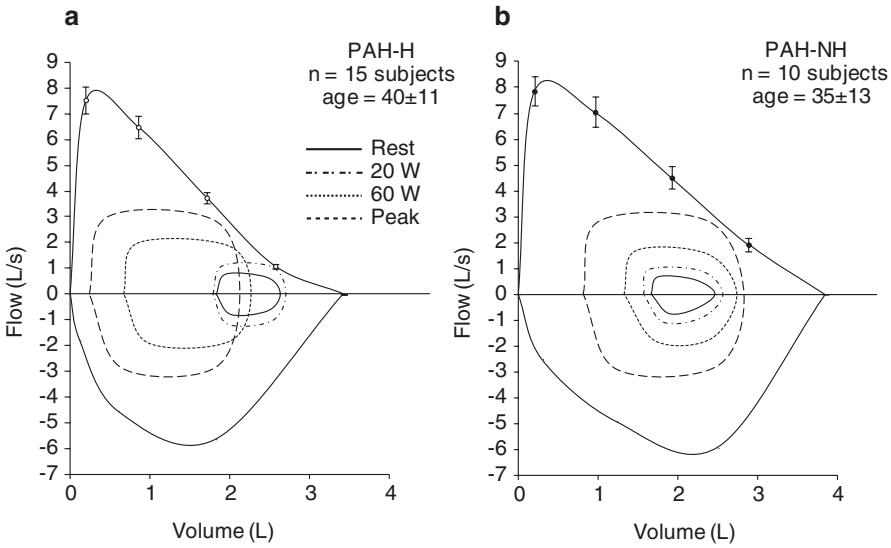

Fig. 8.4 Maximal and tidal flow-volume loops (average data) are shown at rest and during incremental cycle exercise in patients with pulmonary arterial hypertension (PAH) (**a**) with hyperinflation (PAH-H; n = 15, age 40 ± 11 years) and (**b**) without hyperinflation (PAH-NH; n = 10, age 35 ± 13 years). Tidal flow-volume loops are provided at rest, early in exercise (at 20 W), late in exercise (at 60 W) and at peak exercise. Note a significant decrease in dynamic inspiratory capacity during exercise in PAH-H compared with PAH-NH. From reference [33], with permission

IC when oesophageal manometry was performed during CPET [39]. Whether interventions such as supplemental oxygen or bronchodilators reduce or delay the onset of dynamic hyperinflation in this disease remains to be determined in these patients.

The efficiency of ventilation can be illustrated with the relationship between V'_E and carbon dioxide output ($V'CO_2$): less ventilation will be required to eliminate CO_2 in a more efficient system. It is usually reported as the $V'_E/V'CO_2$ slope or the lowest (or "nadir") value of $V'_E/V'CO_2$ during exercise. The $V'_E/V'CO_2$ slope is determined by the arterial PCO_2 ($PaCO_2$) and the physiologic dead space (V_D/V_T) according to Eq. (1):

$$V_E^{'} / V'CO_2 = \frac{863}{PaCO_2\left(1 - V_D / V_T\right)} \tag{1}$$

The V_D/V_T is calculated from the Enghoff modification to the Bohr equation in Eq. (2):

$$V_D / V_T = \frac{PaCO_2 - P_{\bar{E}}CO_2}{PaCO_2} \tag{2}$$

where $P_{\bar{E}}CO_2$ is the mixed expired breath PCO_2.

Ventilatory inefficiency (i.e. high $V'_E/V'CO_2$) and gas exchange abnormalities are hallmark features of pulmonary vascular diseases (Fig. 8.5a). In normal individuals <60 years old, the 95% confidence interval upper limit for $V'_E/V'CO_2$ slope is 33 and the $V'_E/V'CO_2$ nadir is 34 [40]. In PAH patients, $V'_E/V'CO_2$ slope and nadir are usually significantly increased compared to normal

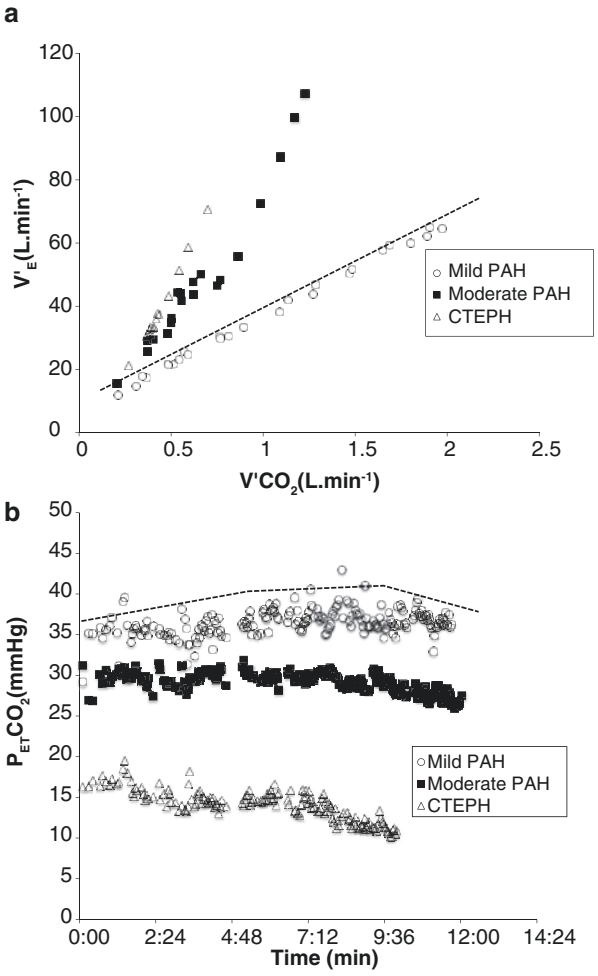

Fig. 8.5 (**a**) Ventilation (V'_E) plotted against CO_2 output ($V'CO_2$) for patients with mild (circles) pulmonary arterial hypertension (PAH), moderate PAH (solid squares) and chronic thromboembolic pulmonary hypertension (CTEPH, triangles). The dashed line represents the upper limit of normal. Note that in the patient with mild PAH, the $V'_E/V'CO_2$ slope is only mildly abnormal ($V'_E/V'CO_2$ slope = 30), whereas the patient with moderate PAH and severe CTEPH has significantly elevated $V'_E/V'CO_2$ slopes of 84–115, respectively. (**b**) End-tidal PCO_2 ($P_{ET}CO_2$) plotted against time for the same patients in (**a**). Note that the patient with mild PAH (circles) exhibits a slight increase in $P_{ET}CO_2$ during early exercise, similar to the predicted normal response (dashed line). The patient with moderate PAH exhibits a flat $P_{ET}CO_2$ during early exercise with a terminal decline coinciding with hyperventilation after the anaerobic threshold. The patient with severe CTEPH demonstrates a progressive decrease in $P_{ET}CO_2$ characteristic of severe pulmonary vascular disease. Original Fig. (**a** and **b**). Data from authors' own laboratory

individuals and are even higher than in patients with left ventricular failure, despite a similar degree of exercise impairment [23, 30, 41–43]. In patients with chronic thromboembolism without pulmonary hypertension, the $V'_E/V'CO_2$ slope, $V'_E/V'CO_2$ at anaerobic threshold and V_D/V_T are higher than in controls, indicating that ventilatory inefficiency can result from vascular obstruction and ventilation-perfusion (V'/Q') inequality, even before overt pulmonary hypertension and impaired RV function develop [44, 45]. Compared to PAH, CTEPH patients have even greater $V'_E/V'CO_2$ slope and nadir values and higher V_D/V_T at peak exercise [46, 47].

In PAH, the severity of increase in $V'_E/V'CO_2$ is related to the degree of elevation in mPAP [42, 48] and is a major determinant of peak VO_2 and New York Heart Association functional class [21]. Some authors have suggested that a combination of findings of low peak VO_2 and low anaerobic threshold, with preserved breathing reserve and $V'_E/V'CO_2$ at the anaerobic threshold >34, has 88% specificity and 85% accuracy for pulmonary vascular limitation to exercise [49].

High $V'_E/V'CO_2$ reflects wasted ventilation and is usually attributed to high V_D/V_T from ventilation-perfusion inequality, but it can also be related to high chemosensitivity from sympathetic nervous system hyperactivity or a low $PaCO_2$ set-point [50–53]. Although resting and peak exercise V_D/V_T are elevated in pulmonary vascular diseases, resting hypocapnia and exercise hyperventilation are common observations that correlate with disease severity, supporting the important contributions of chemoreceptor and sympathetic neural input and the $PaCO_2$ set-point to ventilatory inefficiency [31, 41, 46–48, 50, 52, 54–56]. The V_D/V_T calculated from Eq. (2) is sensitive to high levels of ventilation and to rapid-shallow breathing patterns; therefore high V_D/V_T may also reflect increased chemosensitivity [50–53].

Sympathetic nervous system activity is increased in patients with pulmonary hypertension and is a factor of decreased exercise capacity and worse prognosis [51, 57, 58]. The enhanced chemoreceptor output stimulates hyperventilation, which can be driven by hypoxaemia, low cardiac output and neural afferents from metabolic ergoreceptors in the peripheral muscles [50, 59–61]. Local accumulation of H^+ in skeletal muscles contributes to ergoreceptor-mediated stimulation of ventilation in patients with impaired cardiac function [62]. Right ventricular or right atrial distension may also mediate hyperventilation through sympathetic neural reflexes [56, 63]. This explains why the $V'_E/V'CO_2$, an integrated variable reflecting not only gas exchange, but cardiovascular and autonomic nervous system dysfunction, is associated with clinical outcomes in PAH and CTEPH [64, 65].

8.3.2 Gas Exchange Abnormalities

As a consequence of alveolar hyperventilation, the end-tidal PCO_2 ($P_{ET}CO_2$) measured at the mouth during CPET is frequently decreased in patients with PAH or CTEPH and does not exhibit a normal pattern of gradual increase between rest and

the anaerobic threshold, as it remains constant or decreases further (Fig. 8.5b) [22, 47, 48, 66]. A $P_{ET}CO_2$ of <40 mmHg at the anaerobic threshold may suggest underlying pulmonary vascular disease, whereas $P_{ET}CO_2 < 20$ mmHg is unusual in other diseases and raises strong suspicion of pulmonary vascular disease in a patient with dyspnoea of unknown aetiology [48, 67, 68]. Patients with CTEPH or pulmonary veno-occlusive disease (PVOD), another rare pulmonary vascular disease, tend to have even lower resting and peak exercise $P_{ET}CO_2$ values than patients with idiopathic PAH (Table 8.1) [47, 66, 68].

Arterial oxygen desaturation and wide alveolar-arterial O_2 ($P_{A\text{-}a}O_2$) gradient are common (Fig. 8.6) but not universally observed in patients with pulmonary vascular diseases [31, 47, 55, 60, 68]. In contrast, significant arterial desaturation and hypoxaemia ($PaO_2 < 60$ mmHg) are much more frequent, while also being rarely observed in patients with heart failure. Therefore, desaturation may suggest the presence of underlying pulmonary vascular disease when present in an undifferentiated dyspnoeic patient [69–71]. The widened $P_{A\text{-}a}O_2$ and arterial desaturation are primarily

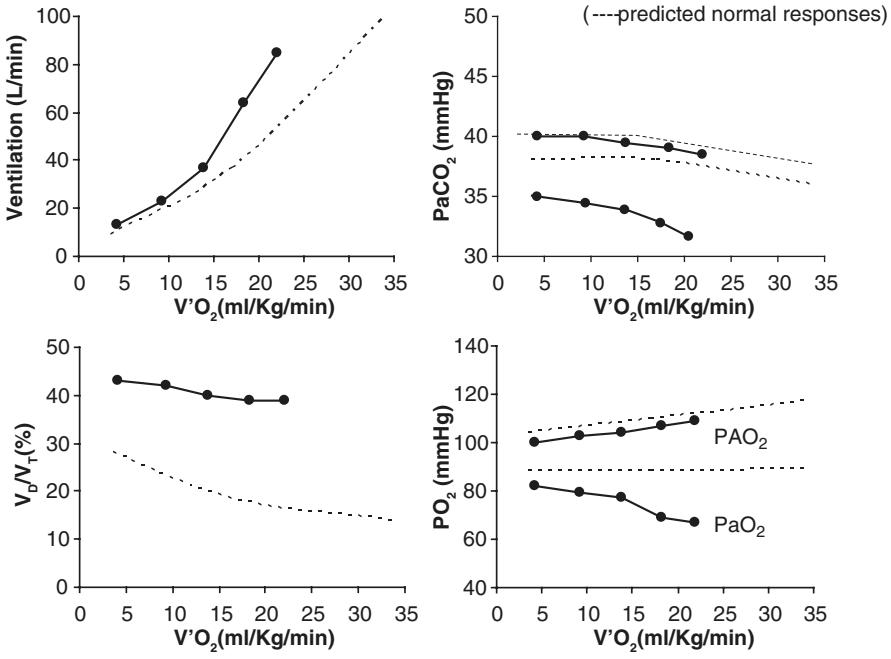

Fig. 8.6 Gas exchange abnormalities for a patient with pulmonary arterial hypertension (PAH). Dashed lines represent predicted normal responses. Note the excessive ventilation for a given $V'O_2$ (upper left panel) with high physiologic dead space (V_D/V_T) at rest and throughout exercise (lower left panel). The arterial CO_2 pressure ($PaCO_2$) is low at rest and decreases early during exercise to a greater extent than in a normal individual (upper right panel). The arterial oxygen pressure (PaO_2) decreases abnormally during exercise despite a normal increase in alveolar oxygen pressure (PAO_2), resulting in a wide and increasing alveolar-arterial O_2 difference at peak exercise (lower right panel). Original figure. Data from authors' own laboratory

related to low mixed venous PO_2 returning to the pulmonary circulation as a consequence of impaired cardiac function and oxygen delivery to peripheral muscles, which is exacerbated by ventilation-perfusion inequality in the lung [72, 73]. A pattern of exercise-induced hypoxaemia preceded by a sudden and sustained decrease in $P_{ET}CO_2$ and increase in end-tidal PO_2 ($P_{ET}O_2$) and the $V'_E/V'CO_2$ in patients with pulmonary vascular disease suggests the development of a right-to-left shunt through a patent foramen ovale (PFO) [60, 74]. This occurs when right atrial pressure rises high enough during exercise to open the PFO, shunting hypoxaemic and acidaemic blood to the systemic circulation, which acutely stimulates peripheral chemoreceptors and hyperventilation.

Normally, $P_{ET}CO_2$ increases during exercise in healthy individuals as a result of larger tidal volume and higher PCO_2 in venous blood returning to the lungs (Fig. 8.5b). Since $P_{ET}CO_2$ rises and $PaCO_2$ remains stable (or even decreases slightly) during exercise, the difference between $PaCO_2$ and $P_{ET}CO_2$ ($P_{(a\text{-}ET)}CO_2$) is slightly positive at rest and becomes negative in most normal individuals [75, 76]. In patients with pulmonary vascular disease, the excessive and inefficient V'_E driven by chemoreceptor stimulation often leads to very low $P_{ET}CO_2$ near peak exercise. Meanwhile, because of high physiologic dead space, ventilation-perfusion inequalities and rapid shallow breathing patterns, the arterial PCO_2 does not change markedly, leading to a positive $P_{(a\text{-}ET)}CO_2$ at rest and exercise [47, 55, 66, 68]. Therefore, a positive value for $P_{(a\text{-}ET)}CO_2$ from arterial blood gases performed at peak exercise reflects impaired gas exchange and/or augmented chemoreflexes.

8.3.3 Peripheral Muscle Function and Exercise in Pulmonary Hypertension

Deconditioning and peripheral muscle abnormalities are important contributors to exercise intolerance. In congestive heart failure, which shares similar limitations in cardiac output reserve as PAH and CTEPH, oxygen transport and diffusion at the level of the skeletal muscle are abnormal [77]. However, tissue oxygen saturation, oxygen extraction and muscle microcirculatory function may be impaired to an even greater degree in PAH compared with left heart failure [78, 79]. The peripheral muscle in PAH patients is structurally and functionally abnormal, with a lower relative proportion of type I fibres and reduced quadriceps, forearm and respiratory muscle strength compared to controls, which may be an important determinant of low peak VO_2 [25, 80]. Respiratory muscle strength has also been shown to be about 40% lower in CTEPH patients [37]. The mechanism of generalised skeletal muscle dysfunction in PAH may be a result of microcirculation rarefaction and an imbalance in angiogenic factors [24]. Improvements in exercise capacity with exercise training in individuals with heart failure or peripheral vascular disease [81] have been linked to improvements in skeletal muscle microcirculatory density, capillary-to-fibre ratio and mitochondrial volume [82], which may be mechanisms by which training can improve exercise capacity in stable patients with PAH [83, 84].

8.3.4 Prognostic Utility of Cardiopulmonary Exercise Testing

Several studies have shown that CPET variables independently predict prognosis in PAH and CTEPH patients. PAH patients with a peak $V'O_2$ less than 11 mL·min^{-1}·kg^{-1} or a $V'_E/V'CO_2$ slope ≥ 45 are considered at high risk with an estimated 1-year mortality of >10% according to the European Society of Cardiology/European Respiratory Society guidelines [1]. Therefore, potential treatment targets for PAH patients have been established at obtaining peak $V'O_2$ > 15 mL·min^{-1}·kg^{-1} or > 65% predicted and a $V'_E/V'CO_2$ slope of <36 [1, 85].

Peak $V'O_2$ and $V'_E/V'CO_2$ have been associated with survival in several studies comprising PAH and CTEPH patients [26, 64, 65, 86]. Wensel and colleagues demonstrated that peak $V'O_2$ provides additional prognostic value to resting haemodynamics in patients with PAH [87]. Those with a low $V'O_2$ (<46.3% predicted) and pulmonary vascular resistance (PVR) > 16 Wood units had a particularly dire prognosis, while patients with peak $V'O_2$ ≥ 46.3% predicted and a PVR < 11.6 Wood units had >90% 5-year survival.

Echocardiographic assessment of RV function in conjunction with CPET may provide incremental prognostic utility. Badagliacca and colleagues found that resting RV fractional area change on echocardiogram, in combination with the O_2 pulse from CPET (which reflect RV function and stroke volume), was an independent predictor of outcome in patients with idiopathic PAH [88]. Patients with RV fractional area change >26.5% and a peak O_2 pulse >8.0 mL·beat^{-1} had excellent long-term survival, while PAH patients with RV fractional area change <36.5% and a peak O_2 pulse <8.0 mL·beat^{-1} had significantly worse survival.

8.3.5 Cardiopulmonary Exercise Testing after Interventions

Very few randomised controlled trials of PAH therapy have included CPET variables as efficacy endpoints [89, 90].

By reducing RV afterload and improving cardiac output and oxygen delivery, PAH therapies such as calcium channel blockers, sildenafil and epoprostenol improve peak $V'O_2$ and ventilatory efficiency [91–93]. Patients who improve peak $V'O_2$, maximal heart rate and O_2 pulse after treatment have better survival, likely due to improvements in cardiac output and stroke volume [86, 94].

In CTEPH, pulmonary endarterectomy is the treatment of choice and involves the surgical removal of obstructing thromboembolic material from the pulmonary arteries. Endarterectomy leads to marked improvements in RV afterload, cardiac function and regained ability to increase stroke volume during exercise, which translates to better exercise capacity and better survival [95–100]. There is also improvement in $V'_E/V'CO_2$ soon after endarterectomy, as a likely result of immediate improvement in cardiac output and a decrease in chemosensitivity, while peak $V'O_2$ continues to improve months after surgery, likely due to rehabilitation and improved peripheral muscle conditioning [101].

Medical therapies approved for PAH are used in inoperable CTEPH patients, which improve exercise capacity and may improve gas exchange and $V'_E/V'CO_2$

[102]. Balloon pulmonary angioplasty (BPA) is another treatment option for inoperable CTEPH patients, which involves dilation of distal obstructing lesions, improving perfusion and lowering mPAP [103, 104]. Right ventricular function and stroke volume improve after BPA, leading to better exercise variables in terms of peak $V'O_2$, $\Delta V'O_2/\Delta WR$, O_2 pulse and $V'_E/V'CO_2$ [105–108]. Oxygen is also a useful intervention to improve exercise performance in patients with pulmonary vascular disease who desaturate during exercise. Supplemental oxygen during exercise increases maximal WR and endurance time and reduces $V'_E/V'CO_2$ by limiting inappropriate chemoreflex-mediated stimulation of V'_E [109].

8.4 Conclusion

Diseases of lung vasculature result from various pathological processes that converge on reducing exercise capacity and lead to early mortality. Understanding the pathophysiological substrates of these outcomes is of upmost importance in order to better orient therapeutic research. But because of the wide range of pathology involved, a one size fits all approach is suboptimal.

Exercise intolerance and dyspnoea in patients with pulmonary vascular disease are multifaceted; the key CPET-related profile responses are a reduced peak $V'O_2$ with impairment of cardiovascular function translating into a reduction in $V'O_2$/WR, low O_2 pulse, and AT, and impaired ventilatory efficiency with altered gas exchange and chemosensitivity. The presence of high $V'_E/V'CO_2$ with a low $P_{ET}CO_2$ in a patient with unexplained dyspnoea should prompt consideration of pulmonary vascular disease in the differential diagnosis and further diagnostic investigations. Abnormal respiratory mechanics and locomotor muscle dysfunction also contribute to dyspnoea, leg fatigue and exercise pathophysiology in many patients. CPET is a useful tool in assessing the degree of functional impairment and disease severity, predicting prognosis and evaluating interventional efficacy.

Key Points

- Cardiopulmonary exercise testing (CPET) in patients with pulmonary vascular diseases may reveal common and non-specific symptoms like dyspnoea and exercise intolerance.
- Dynamic exercise during CPET may provide a greater stress to the right ventricle and pulmonary circulation than static resistive exercises and could thus be more sensitive in detecting an abnormal response in a patient with early pulmonary vascular disease.
- CPET can also help evaluate the severity of disease, gauge responses to treatment and estimate prognosis in patients with known pulmonary vascular disease.
- Even in the absence of significant resting airflow obstruction, dynamic hyperinflation can occur in pulmonary vascular diseases, which contributes to exertional dyspnoea and exercise intolerance.

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