



# Ventilatory response to exercise in cardiopulmonary disease: the role of chemosensitivity and dead space

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The "appropriate"  $V_E$  exercise response depends on  $V'CO_2$ , arterial  $PCO_2$ ,  $V_D/V_T$  and respiratory mechanics <http://ow.ly/M1IZ30gGN1w>

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**ABSTRACT** The lungs and heart are irrevocably linked in their oxygen ( $O_2$ ) and carbon dioxide ( $CO_2$ ) transport functions. Functional impairment of the lungs often affects heart function and *vice versa*. The steepness with which ventilation ( $V_E$ ) rises with respect to  $CO_2$  production ( $V'CO_2$ ) (*i.e.* the  $V_E/V'CO_2$  slope) is a measure of ventilatory efficiency and can be used to identify an abnormal ventilatory response to exercise. The  $V_E/V'CO_2$  slope is a prognostic marker in several chronic cardiopulmonary diseases independent of other exercise-related variables such as peak  $O_2$  uptake ( $V'O_2$ ). The  $V_E/V'CO_2$  slope is determined by two factors: 1) the arterial  $CO_2$  partial pressure ( $P_aCO_2$ ) during exercise and 2) the fraction of the tidal volume ( $V_T$ ) that goes to dead space ( $V_D$ ) (*i.e.* the physiological dead space ratio ( $V_D/V_T$ )). An altered  $P_aCO_2$  set-point and chemosensitivity are present in many cardiopulmonary diseases, which influence  $V_E/V'CO_2$  by affecting  $P_aCO_2$ . Increased ventilation-perfusion heterogeneity, causing inefficient gas exchange, also contributes to the abnormal  $V_E/V'CO_2$  observed in cardiopulmonary diseases by increasing  $V_D/V_T$ . During cardiopulmonary exercise testing, the  $P_aCO_2$  during exercise is often not measured and  $V_D/V_T$  is only estimated by taking into account the end-tidal  $CO_2$  partial pressure ( $P_{ETCO_2}$ ); however,  $P_aCO_2$  is not accurately estimated from  $P_{ETCO_2}$  in patients with cardiopulmonary disease. Measuring arterial gases ( $P_aO_2$  and  $P_aCO_2$ ) before and during exercise provides information on the real (and not "estimated")  $V_D/V_T$  coupled with a true measure of gas exchange efficiency such as the difference between alveolar and arterial  $O_2$  partial pressure and the difference between arterial and end-tidal  $CO_2$  partial pressure during exercise.

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## Introduction

*in medio stat virtus* [virtue stands in the middle] (Aristotle, in the *Nicomachean Ethics*; Horace, in the *Satires*; Ovid, in the *Metamorphoses*)

The lungs and heart are irrevocably linked in their oxygen (O<sub>2</sub>) and carbon dioxide (CO<sub>2</sub>) transport functions. Functional impairment of the lungs often affects heart function and *vice versa*. The steepness with which ventilation ( $V^E$ ) rises with respect to CO<sub>2</sub> production ( $V^{\text{CO}_2}$ ) (*i.e.* the  $V^E/V^{\text{CO}_2}$  slope) is a measure of ventilatory efficiency and can be used to identify an abnormal ventilatory response to exercise. The interest in measuring ventilatory efficiency is that  $V^E/V^{\text{CO}_2}$  is a strong prognostic marker in several chronic cardiopulmonary diseases independent from other exercise-related prognostic factors such as peak O<sub>2</sub> uptake ( $\dot{V}O_2$ ) [1]. Furthermore, excessive ventilation for a given  $V^{\text{CO}_2}$  has the consequences of higher dyspnoea perception in individuals with cardiovascular and pulmonary disease, contributes to the development of mechanical ventilatory constraint in obstructive lung diseases, and increases O<sub>2</sub> demand in the respiratory muscles. Therefore, interventions targeting the determinants of ventilatory efficiency could improve symptoms, exercise tolerance and prognosis.

The  $V^E/V^{\text{CO}_2}$  slope is fundamentally determined by two factors: 1) the direction and magnitude of change in the arterial CO<sub>2</sub> partial pressure ( $P_{\text{aCO}_2}$ ) during exercise and 2) the fraction of the tidal volume ( $V_T$ ) that goes to dead space ( $V_D$ ) (*i.e.* the  $V_D/V_T$  ratio). The term  $V_D/V_T$  refers to the physiological dead space ratio, which is comprised of the anatomical dead space (*i.e.* conducting airways proximal to terminal bronchioles where gas exchange does not occur) and alveolar dead space that results from ventilation–perfusion mismatch (*i.e.* lung regions with low perfusion relative to ventilation). If  $P_{\text{aCO}_2}$  is reduced, the  $V^E/V^{\text{CO}_2}$  slope will increase, or if  $V_D/V_T$  is high, the  $V^E/V^{\text{CO}_2}$  slope will increase. An altered  $P_{\text{aCO}_2}$  set-point and increased chemosensitivity are also present in many cardiopulmonary diseases, which will affect  $P_{\text{aCO}_2}$  and, therefore, the  $V^E/V^{\text{CO}_2}$  slope.  $P_{\text{aCO}_2}$  is often not measured during exercise testing and instead  $V_D/V_T$  is only estimated by substituting the end-tidal CO<sub>2</sub> partial pressure ( $P_{\text{ETCO}_2}$ ) for the arterial  $P_{\text{aCO}_2}$ ; however, this produces an inappropriate estimate of  $V_D/V_T$  in individuals with cardiopulmonary disease.

This objectives of this review are 1) to outline the determinants of the ventilatory response to exercise, in health and in cardiopulmonary diseases, with particular attention to the influence of chemosensitivity and the physiological dead space ( $V_D/V_T$ ), 2) to illustrate the importance of measuring arterial gases during exercise in order to understand the real (and not “estimated”)  $V_D/V_T$ , 3) to explore the contributing roles of chemosensitivity and physiological dead space on ventilatory inefficiency observed in different cardiopulmonary diseases, and 4) to describe how interventions might improve ventilatory efficiency using a mechanistic approach.

## The ventilatory response to exercise in health and cardiopulmonary diseases

The main determinants of an appropriate exercise ventilatory response ( $V^E$ ) are  $V^{\text{CO}_2}$  (the metabolic component) and  $P_{\text{aCO}_2}$  (the control “set-point”). The dead space fraction of each breath ( $V_D/V_T$ ) and the extent to which the ventilatory system is constrained or “limited” (respiratory mechanics) will have a greater influence on the ventilatory response to exercise in cardiopulmonary diseases. To understand the relationship between  $V^E$  and these determinants during exercise, we should first consider the physiological dead space. The  $V_D/V_T$  is calculated from the Enghoff modification to the Bohr equation (equation 1) [2]:

$$\frac{V_D}{V_T} = \frac{P_{\text{aCO}_2} - P_{\text{ETCO}_2}}{P_{\text{aCO}_2}} \quad (1)$$

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In this equation,  $P_{E\text{CO}_2}$  is the mixed expired breath  $P_{\text{CO}_2}$ , which is obtained from the ratio of  $V'_{\text{CO}_2}$  to  $V'_E$  in equation 2:

$$P_{E\text{CO}_2} = \frac{V'_{\text{CO}_2}}{V'_E} \times (310/273) \times 760$$

or

$$P_{E\text{CO}_2} = \frac{V'_{\text{CO}_2}}{V'_E} \times 863 \tag{2}$$

The factor 863 accounts for corrections related to the mixed expired gas using the exercise system measurements of  $V'_E$  and  $V'_{\text{CO}_2}$ , a body temperature of 310 K, and a barometric pressure of 760 mmHg. Alveolar  $\text{CO}_2$  partial pressure ( $P_{\text{ACO}_2}$ ) is related to the  $V'_{\text{CO}_2}$  measured at the mouth and inversely related to alveolar ventilation ( $V'_A$ ). As neither  $P_{\text{ACO}_2}$  nor  $V'_A$  are easily measurable during clinical testing, we estimate  $P_{\text{ACO}_2}$  from  $P_{\text{aCO}_2}$ . However, due to ventilation–perfusion inequalities in the normal lung, there is a small difference between  $P_{\text{aCO}_2}$  and  $P_{\text{ACO}_2}$ , which is further magnified in cardiac and pulmonary diseases that increase ventilation–perfusion heterogeneity.

Substituting the right side of equation 2 into equation 1, we arrive at equation 3, which explains the determinants of the ventilatory response during exercise (figure 1):

$$V'_E = \frac{863 \times V'_{\text{CO}_2}}{P_{\text{aCO}_2} \times (1 - V_{\text{D}}/V_{\text{T}})} \tag{3}$$

Rearranging equation 3, we obtain  $V'_E/V'_{\text{CO}_2}$ , which reflects the efficiency of ventilation and is represented in equation 4:

$$\frac{V'_E}{V'_{\text{CO}_2}} = \frac{863}{P_{\text{aCO}_2} \times (1 - V_{\text{D}}/V_{\text{T}})} \tag{4}$$

The slope of the relationship between  $V'_E$  and  $V'_{\text{CO}_2}$  in equation 4 is linear over a wide range and is determined by just two factors: 1)  $P_{\text{aCO}_2}$  during exercise and 2)  $V_{\text{D}}/V_{\text{T}}$ . The set-point for  $P_{\text{aCO}_2}$  and chemosensitivity influence resting  $P_{\text{aCO}_2}$  and the magnitude and direction of change during exercise. If  $P_{\text{aCO}_2}$  is driven down by a high ventilatory stimulation from sensitised peripheral chemoreceptors, baroreceptors or by ergoreceptors in skeletal muscle, the slope of the  $V'_E/V'_{\text{CO}_2}$  relationship will increase. The arterial  $\text{CO}_2$  set-point itself is influenced by factors such as metabolic acidosis, hypoxaemia, baroreceptors in the pulmonary vasculature and sympathetic nervous system hyperactivity [3–8]. If  $V_{\text{D}}/V_{\text{T}}$  is high, the  $V'_E/V'_{\text{CO}_2}$  slope will increase. There are two potential sources for a high  $V_{\text{D}}/V_{\text{T}}$  ratio: 1) a low  $V_{\text{T}}$  with respect to a normal anatomical dead space ( $V_{\text{D}}$ ) or 2) an abnormally high physiological dead space, which is considered “wasted ventilation” [9, 10]. The physiological dead space includes the anatomical dead space and alveolar dead space resulting from any of the mechanisms that impair gas exchange: alveolar ventilation–perfusion ( $V'_A/Q'$ ) inequality due to high  $V'_A/Q'$  regions (dead space) and low  $V'_A/Q'$  (shunt) regions with impaired  $\text{CO}_2$  elimination [9, 10]. During exercise in healthy individuals,  $V_{\text{D}}/V_{\text{T}}$  decreases to <20% [11], as  $V_{\text{T}}$  increases to a much greater extent than the small increase in anatomical dead space resulting from a larger end-inspiratory airway diameter [11].

The relevance of the ventilatory response to exercise in cardiopulmonary diseases lies in the fact that dyspnoea intensity rises as  $V'_E$  increases (figure 2) [12, 13]. Perhaps even more important is what an increased ventilatory response to exercise tells us about impaired gas exchange, impaired ventilatory control and altered mechanics of breathing in lung and heart diseases (figure 1). The  $V'_E/V'_{\text{CO}_2}$  slope and the value of  $V'_E/V'_{\text{CO}_2}$  at the anaerobic threshold are usually increased in cardiorespiratory diseases (*i.e.* there is inefficient ventilation). While a normal subject has to ventilate almost 20–25  $\text{L}\cdot\text{min}^{-1}$  per 1  $\text{L}\cdot\text{min}^{-1}$  of  $\text{CO}_2$  produced, patients with cardiorespiratory disease ventilate almost 30–50  $\text{L}\cdot\text{min}^{-1}$  for the same amount of  $\text{CO}_2$  produced (figure 3). In this way, the  $V'_E/V'_{\text{CO}_2}$  slope and ratio at the anaerobic threshold contain important information on how cardiopulmonary diseases affect either the lung (gas exchange and/or mechanics of breathing) or ventilatory control. Although this is not a new observation, the potential usefulness of  $V'_E/V'_{\text{CO}_2}$  as a prognostic tool to evaluate the severity, evolution, morbidity and mortality of many cardiorespiratory diseases is relatively recent. An additional advantage of using  $V'_E/V'_{\text{CO}_2}$  is that it can be obtained even with submaximal effort or when individuals do not reach their

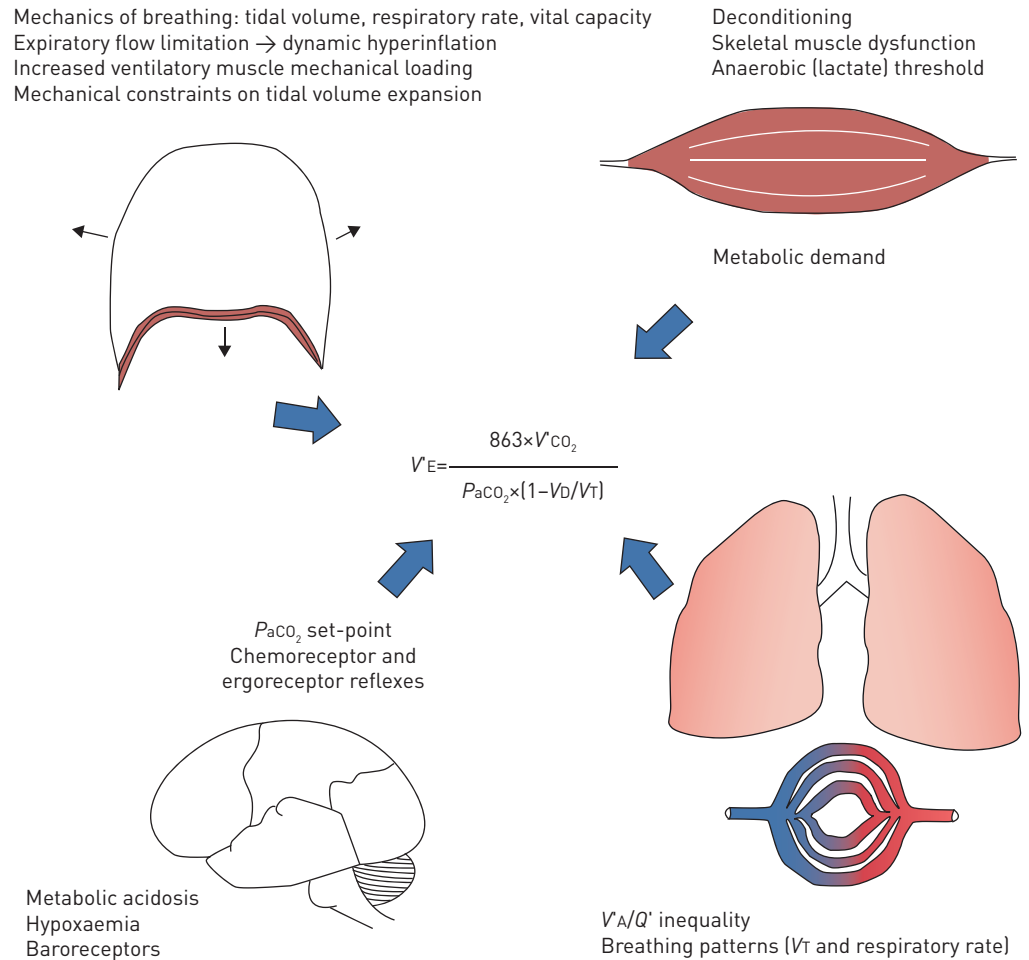


FIGURE 1 Ventilation ( $V_E$ ) is determined by carbon dioxide ( $CO_2$ ) output ( $V_{CO_2}$ ), arterial  $CO_2$  partial pressure ( $P_{aCO_2}$ ) and physiological dead space ratio ( $V_D/V_T$ , i.e. the fraction of the tidal volume ( $V_T$ ) that goes to dead space ( $V_D$ )). In addition to gas exchange impairment, ventilation–perfusion ( $V_A/Q'$ ) abnormalities and shunt, mechanical, metabolic and autonomic nervous system reflexes influence these variables to determine the ventilatory demand and ventilatory efficiency.

true peak  $VO_2$ . The prognostic significance of an elevated  $V_E/V_{CO_2}$  has been now well established in many disease states, including congestive heart failure (CHF) with reduced or preserved systolic function [1, 14–17], cystic fibrosis [18], pulmonary arterial hypertension (PAH) [19–21], chronic thromboembolic pulmonary hypertension (CTEPH) [20, 21] and idiopathic pulmonary fibrosis (IPF) [22].

Determining which mechanism (enhanced chemosensitivity, altered  $P_{aCO_2}$  set-point, mechanical constraints or high  $V_D/V_T$ ) is the predominant factor driving the increased  $V_E/V_{CO_2}$  during exercise in various cardiopulmonary diseases is challenging but can be appreciated by using arterial blood gas analysis at rest and at peak exercise during cardiopulmonary exercise testing (figure 1). In most disease states, all mechanisms contribute to variable degrees (table 1). As is often the case in medicine, *in medio stat virtus* and we could say “the answer lies somewhere in the middle”.

### The role of chemosensitivity in cardiopulmonary diseases

Ventilation during exercise is regulated by peripheral (carotid body) and central (medullary) chemoreceptors, peripheral muscle ergoreceptors and pulmonary vagal stretch receptors, which are complex systems with neurons that interact and converge in the central nervous system and feedback to a central command system (figure 1) [3, 23–25]. For a recent detailed overview on the topic of ventilatory control, see the review by DEMPSEY and SMITH [23]. Assessment of peripheral respiratory chemoreceptor sensitivity and the ventilatory response in humans has been performed experimentally using hypoxic, hyperoxic and hypercapnic challenge tests, and central hypercapnic chemosensitivity is assessed by the  $CO_2$  rebreathing technique [26–28]. In this section we will review the role of abnormal chemosensitivity in

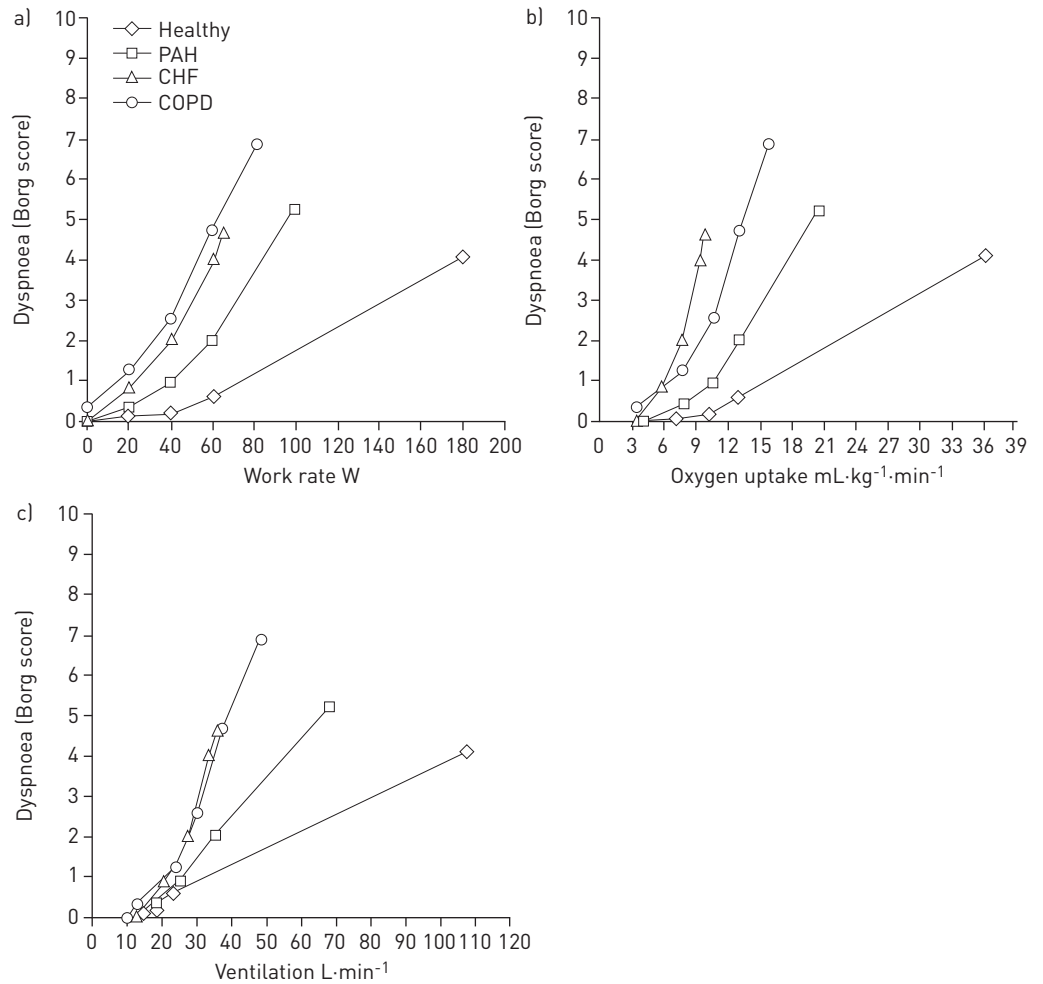


FIGURE 2 Comparison of dyspnoea ratings measured on the Borg scale during exercise in patients with cardiorespiratory diseases and healthy individuals: dyspnoea is higher at any given a) work rate, b) oxygen uptake and c) ventilation in patients with heart and lung disease compared with healthy individuals. PAH: pulmonary arterial hypertension; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease. Reproduced and modified from [13] with permission.

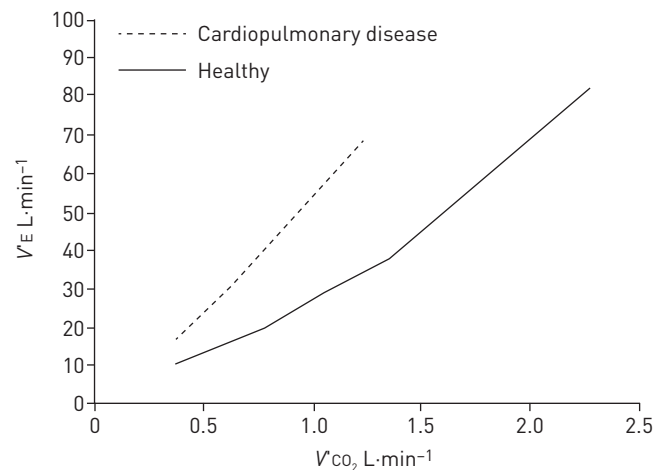


FIGURE 3 The relationship between ventilation ( $V'E$ ) and metabolic demand ( $V'CO_2$ ) in healthy individuals and patients with cardiopulmonary disease. A variety of mechanisms contribute to an increase in the  $V'E/V'CO_2$  slope in cardiopulmonary disease.

TABLE 1 Gas exchange abnormalities and mechanisms of exercise limitation and ventilatory inefficiency in cardiopulmonary diseases

	$Q_{\max}$	$V'_{E\max}$	$V_D/V_T$	$V'_E/V'_{CO_2}$ slope	$P_{aCO_2}$	Peak exercise $P_{a-ETCO_2}$	$S_{aO_2}$	Chemosensitivity	Typical pattern of exercise limitation
<b>CHF</b>	↓↓	N	↑	↑	N	↓	N	↑	Low $Q_{\max}$ , normal blood gases
<b>PAH</b>	↓↓	N	↑	↑↑	↓	↑	↓	↑	Low $Q_{\max}$ with hypoxaemia and hypocapnia
<b>COPD</b>	↓	↓↓	↑	V	V	↓	↓	V	Low maximal $V'_E$ with hypoxaemia±hypercapnia

CHF: congestive heart failure; PAH: pulmonary arterial hypertension; COPD: chronic obstructive pulmonary disease;  $Q_{\max}$ : maximal cardiac output;  $V'_{E\max}$ : maximal ventilation;  $V_D/V_T$ : physiological dead space (dead space to tidal volume ratio);  $P_{a-ETCO_2}$ : arterial–end-tidal  $P_{CO_2}$  difference at peak exercise;  $S_{aO_2}$ : arterial oxygen saturation; N: normal; ↓: decreased; ↑: increased; double arrow: primary change; V: variable (can be increased, decreased or unchanged). In CHF and PAH the primary determinant is low  $Q_{\max}$ ; in COPD the primary determinant is ventilatory limitation (low  $V'_{E\max}$ ).

the ventilatory response to exercise in patients with CHF, PAH and chronic obstructive pulmonary disease (COPD).

In patients with CHF, there is heightened sympathetic activity and potentiated ventilatory responses when exposed to both hypercapnia [27, 29] and hypoxia [26, 30], indicating higher chemosensitivity [31]. However, while increased chemoreceptor neural output is often seen in severe CHF [30], such as in patients with Cheyne–Stokes breathing, this alone will not drive down the  $P_{aCO_2}$  unless the set-point about which  $P_{aCO_2}$  is controlled becomes depressed or unless the chemoreflexes or ergoreceptor drive are increased (figure 1) [32]. Most studies have demonstrated that CHF patients have normal blood gases at rest and that  $P_{aCO_2}$  either stays the same or declines from rest to peak exercise, similar to normal controls [8, 32–34]. Furthermore,  $P_{aCO_2}$  at peak exercise is similar between patients with milder and more severe exercise impairment in CHF, while  $V'_E/V'_{CO_2}$  increases in proportion to the severity of disease [34]. Those studies showing decreases in  $P_{aCO_2}$  at peak exercise have shown normal resting and exercise  $P_{aO_2}$ , indicating that while CHF patients may have enhanced chemoreflex responses to hypoxic challenge testing at rest, stimulation of peripheral chemoreceptors by hypoxaemia is not the main driver of high  $V'_E/V'_{CO_2}$  during exercise in CHF [32, 34–37]. If hypoxaemia does not occur during exercise in CHF patients, why are augmented peripheral chemoreflexes and elevated  $V'_E/V'_{CO_2}$  so strongly associated with mortality? First, it is likely that heightened peripheral chemosensitivity to a hypoxic challenge reflects a general state of autonomic hyperactivity in CHF, of which  $V'_E/V'_{CO_2}$  and exercise-induced periodic breathing are consequences. This hyperactive autonomic state is the likely driver of increased mortality in CHF, rather than high  $V'_E/V'_{CO_2}$  itself [36–38]. For instance, PONIKOWSKI *et al.* [36] found that, when adjusted for age, peak  $\dot{V}O_2 < 14 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  and  $V'_E/V'_{CO_2}$  slope, peripheral chemosensitivity was the most significant predictor of mortality. Second, low cardiac output and impaired  $O_2$  delivery cause increased local hydrogen ion and lactate concentrations in skeletal muscle, activating ergoreceptor reflexes that stimulate ventilation. Ergoreceptor stimulation causes a greater exercise hyperpnoea response in CHF patients than controls [39, 40], which is completely inhibited by an infusion of sodium bicarbonate and is independent of arterial lactate levels [8, 41]. A recent experimental model of heart failure demonstrated that acid-sensitive ion channels in skeletal muscle of mice with heart failure have altered composition and pH sensing properties, which may contribute to the abnormal ergoreceptor afferent stimulation in CHF; however, confirmatory studies in humans are necessary [42].

Patients with PAH have extensive proliferation, fibrosis and obstruction of the small pulmonary arteries, which leads to an increase in pulmonary arterial pressure and pulmonary vascular resistance [43, 44]. PAH patients usually exhibit ventilatory inefficiency during exercise, generally have  $V'_E/V'_{CO_2}$  slopes that are higher than CHF patients for a comparable degree of functional impairment (figure 4) and typically have lower  $P_{ETCO_2}$  [19, 37, 45]. The hyperventilatory response in PAH is partially attributed to diffuse vascular remodelling leading to increased  $V_D/V_T$  and high  $V'_A/Q'$  regions [45–49]. High physiological dead space is consistently observed in PAH patients; however, autonomic activity and chemosensitivity are also known to be increased in PAH patients [6, 37, 50, 51]. Right atrial distension contributes to sympathetic nervous system overactivity PAH through baroreceptor reflexes [52]. PAH patients are frequently hypocapnic at rest and  $P_{aCO_2}$  may further decline during exercise, suggesting that an altered  $P_{aCO_2}$  set-point and increased chemosensitivity contribute to high  $V'_E/V'_{CO_2}$  [49, 50, 53–56]. The presence of resting hypocapnia in PAH patients correlates with a lower resting cardiac output and predicts worse survival [49]. Another cause of high  $V'_E/V'_{CO_2}$  in some PAH patients is the development of a right-to-left shunt through a patent foramen ovale (PFO) during exercise, delivering hypoxaemic, acidaemic blood to

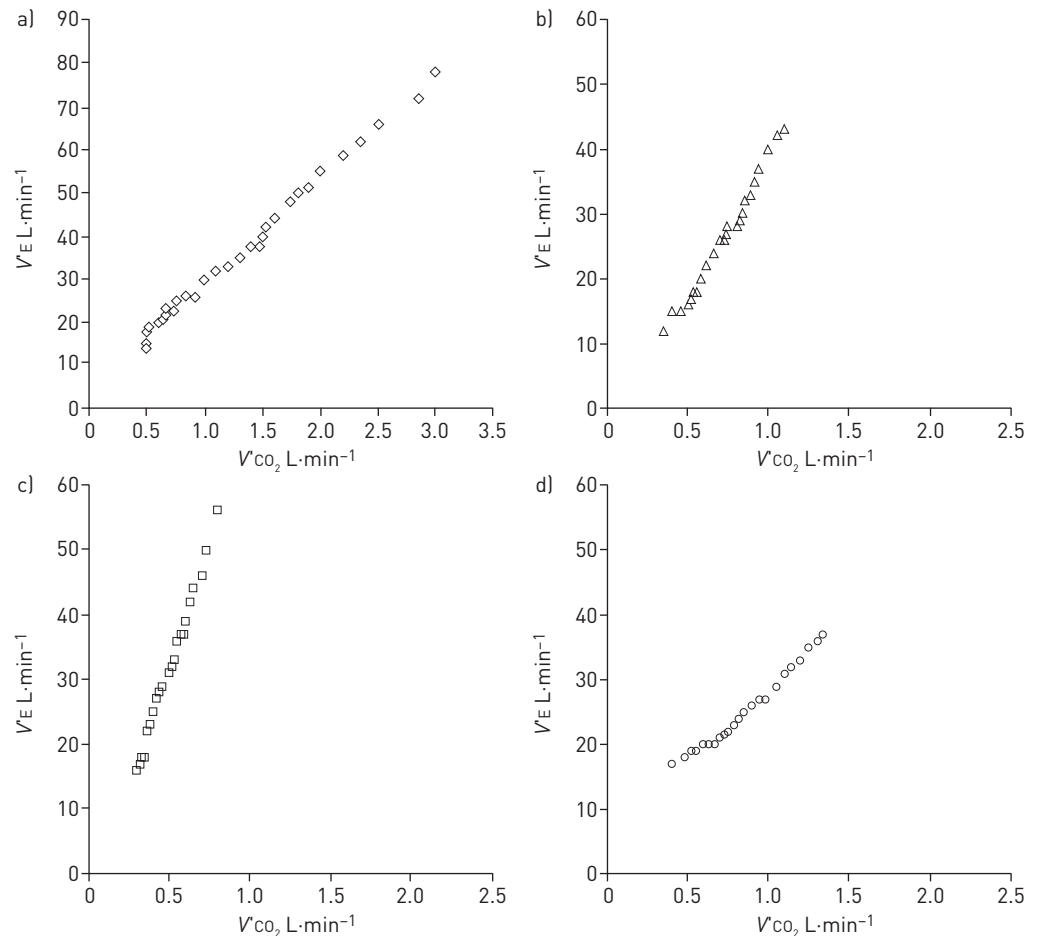


FIGURE 4 Examples of ventilatory efficiency slopes ( $V_E/V_{CO_2}$  slopes) for a) a healthy individual with a peak oxygen uptake ( $V_{O_2}$ ) of  $38 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , b) a patient with congestive heart failure (CHF) presenting with a peak  $V_{O_2}$  between  $14$  and  $18 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , c) a patient with pulmonary arterial hypertension (PAH) presenting with a peak  $V_{O_2}$  between  $14$  and  $18 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , and d) a patient with moderate to severe chronic obstructive pulmonary disease (COPD) presenting with a peak  $V_{O_2}$  of  $20 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . All patients with cardiopulmonary disease have a lower peak  $V_{O_2}$  and lower peak  $V_E$  compared with the healthy individual. For a similar degree of exercise impairment, the PAH patient has a higher  $V_E/V_{CO_2}$  slope than the CHF patient. The patient with COPD has a lower  $V_E/V_{CO_2}$  slope and higher  $V_E/V_{CO_2}$  intercept due to hyperinflation-induced mechanical constraints, which limit the increase in ventilation during exercise.

the systemic circulation, which acutely stimulates peripheral chemoreceptor-mediated hyperventilation and a drop in  $P_{ETCO_2}$  [57]. In the absence of shunting through a PFO, resting and exercise-induced hypoxaemia occur in PAH, which is related to ventilation-perfusion inequality compounded by a low mixed venous  $O_2$  partial pressure ( $P_{vO_2}$ ) from impaired cardiac output during exercise [58, 59]. However, the degree of hypoxaemia observed in most PAH patients without a PFO is not sufficient to stimulate ventilation and does not correlate with the  $V_E/V_{CO_2}$  slope [45]. The role of ergoreceptor reflexes in the exercise hyperpnoea observed in PAH is unknown. However, given the degree of impairment in cardiac output and  $O_2$  delivery in PAH patients, a similar stimulatory effect on ventilation as seen in CHF patients is likely. Both CHF and PAH are characterised by sympathetic overactivity, impairment in the respiratory control system and poor circulatory responses to exercise. The main differences are that PAH patients become hypoxaemic and hypocapnic, and they do not demonstrate exercise-induced oscillatory breathing (a pattern frequently observed in CHF as a manifestation of unstable ventilatory control) [37]. While this may be in part attributable to the effect of intrapulmonary J-receptor stimulation from high left ventricular filling pressures, a recent study found that patients with combined pre-capillary and post-capillary pulmonary hypertension had higher  $V_E/V_{CO_2}$  but lower prevalence of exercise oscillatory breathing during exercise than patients with isolated post-capillary pulmonary hypertension, despite identical pulmonary artery wedge pressure [60]. It was proposed that the presence of a pre-capillary component in pulmonary hypertension due to CHF (possibly due to arteriolar remodelling) may limit afferent neural input in the pathogenesis of oscillatory breathing or that sympathetic reflexes from right atrial distension

(similar to what has been reported in PAH) may override the chemoreflexes and “stabilise” ventilatory oscillations [52, 60].

The role of autonomic overactivity and peripheral chemosensitivity in the ventilatory response to exercise in COPD is less well studied, despite the high risk of cardiovascular mortality in COPD patients and the frequent presence of concurrent CHF [61, 62]. Sympathetic activity is increased in COPD and has been associated with increased mortality [63–65]. A recent study of moderate to severe COPD patients without hypoxaemia or cardiovascular disease found increased carotid chemoreceptor activity and ventilatory responses to hypoxia compared with age-matched controls, but this was not correlated with  $V^E/V^{\prime}CO_2$  [66]. However, other studies including more severe COPD patients have suggested no increased ventilatory response to hypoxia [67]. The peripheral chemoreceptor response to hypoxia is further potentiated in the setting of acute hypercapnia [68], but even in COPD patients with chronic resting hypoxaemia and hypercapnia, the ventilatory drive to hypoxia or hypercapnia remains intact [69]. This complex and contradictory relationship between increased chemoreceptor drive and the ventilatory response in COPD is related to mechanical constraints imposed by hyperinflation, at rest and/or during exercise, which prevent an increase in  $V^E$  despite intact central respiratory drive (see the later section on the role of ventilation–perfusion heterogeneity and  $V_T$  in ventilatory inefficiency for further details).

### The arterial–end-tidal $P_{CO_2}$ difference, $V_D/V_T$ and chemosensitivity

The  $V_D/V_T$  calculated from equation 1 reflects anatomical dead space and alveolar dead space, which is sensitive to  $V_T$  changes and  $V^{\prime}A/Q^{\prime}$  inequality [10, 70]. In addition to correlating with  $V_D/V_T$ , the arterial–end-tidal  $P_{CO_2}$  difference ( $P_{a-ETCO_2}$ ) reflects gas exchange inefficiency and possibly high chemosensitivity during exercise. To better understand the  $P_{a-ETCO_2}$  difference, consider how exhaled  $P_{CO_2}$  changes during expiration at rest and during exercise (figure 5). Normally, a continuous plot of expired  $P_{CO_2}$  versus time has three phases: 1) early in expiration,  $P_{CO_2}$  remains near zero as the anatomical dead space empties, then 2) there is a rapid increase in  $P_{CO_2}$  as gas from well-ventilated alveoli mixes with the remaining gas from the anatomical dead space and 3)  $P_{CO_2}$  slowly rises until end-expiration ( $P_{ETCO_2}$ ) as the remainder of the alveolar gas is exhaled. Thus,  $P_{ETCO_2}$  is the peak of the intra-breath  $P_{CO_2}$  oscillation, whereas the mean alveolar  $CO_2$  ( $P_{ACO_2}$ ) is estimated from the mid-point of the expiratory  $P_{CO_2}$  oscillation [9]. During exhalation, the magnitude of  $P_{ACO_2}$  (and therefore  $P_{ETCO_2}$ ) depends on the mixed venous  $P_{CO_2}$  ( $P_{VCO_2}$ ),  $V^{\prime}A$ , ventilation–perfusion inequality and the time for exhalation. The  $P_{ACO_2}$  is always slightly less than the  $P_{aCO_2}$  in normal lungs because of normal degrees of  $V^{\prime}A/Q^{\prime}$  inequality and shunt, a difference which is magnified in cardiopulmonary diseases with abnormal degrees of  $V^{\prime}A/Q^{\prime}$  inequality. The  $P_{aCO_2}$  is usually higher than  $P_{ETCO_2}$  as a result of the normal amounts of  $V^{\prime}A/Q^{\prime}$  inequality and fluctuations of  $P_{ACO_2}$  during expiration. This results in a small  $P_{a-ETCO_2}$  difference which is usually positive but  $<5$  mmHg in normal individuals [71–73]. In some healthy individuals, the  $P_{a-ETCO_2}$  difference may be negative at rest. This can occur with a prolonged expiratory time or larger  $V_T$ , both of which allow the expired  $CO_2$  to continue rising above  $P_{aCO_2}$  [9, 73, 74]. When a healthy individual exercises (figure 5),  $P_{ETCO_2}$  increases because there is a larger fluctuation in  $P_{ACO_2}$  during each breath as a result of larger  $V_T$ , the higher  $P_{VCO_2}$  returning to the lungs and a continuously decreasing lung volume during exhalation. As  $P_{ETCO_2}$  rises and  $P_{aCO_2}$  remains stable (or even decreases slightly) during exercise, the  $P_{a-ETCO_2}$  difference becomes negative in most normal individuals [73, 74]. Conversely, a  $P_{ETCO_2}$  that is lower than  $P_{aCO_2}$  during exercise (a positive  $P_{a-ETCO_2}$  at peak exercise) is indicative of impaired gas exchange. JONES *et al.* [73] derived two equations that explain the factors that determine the  $P_{a-ETCO_2}$  difference in normal individuals (equation 5) and how  $P_{aCO_2}$  can be predicted noninvasively from  $P_{ETCO_2}$  (equation 6):

$$P_{aCO_2} - P_{ETCO_2} = 6.7 - (0.00173 \times V_T) - (0.0011 \times V^{\prime}CO_2) - (0.11 \times P_{ETCO_2}) \quad (5)$$

$$P_{aCO_2} = 5.5 + (0.90 \times P_{ETCO_2}) - (0.0021 \times V_T) \quad (6)$$

Equation 6 has frequently been used to estimate  $P_{aCO_2}$  during exercise, and therefore  $V_D/V_T$ , from  $P_{ETCO_2}$  and  $V_T$ . While this may be reasonable for estimating  $P_{aCO_2}$  in groups of individuals without lung disease ( $r=0.915$ ), it tends to overestimate  $V_D/V_T$  [75]. In patients with cardiopulmonary diseases, equation 6 does not accurately estimate  $P_{aCO_2}$  due to multiple factors, including altered chemosensitivity, increased  $V^{\prime}A/Q^{\prime}$  inequality and the variable time it takes for  $CO_2$  emptying from lung regions with a heterogeneous extent of disease [34, 55, 72, 74, 76].

How might  $P_{a-ETCO_2}$  reflect increased chemosensitivity? When a rapid shallow breathing pattern (low  $V_T$ , high breathing rate) occurs voluntarily or as a result of high chemosensitivity, there is less expiratory time for the  $P_{ETCO_2}$  to rise (figure 5) and the  $P_{ETCO_2}$  decreases to a greater extent than the  $P_{ECO_2}$  used in calculating  $V_D/V_T$  in equation 1. In this situation  $V_D/V_T$  may still decline during exercise while  $P_{a-ETCO_2}$



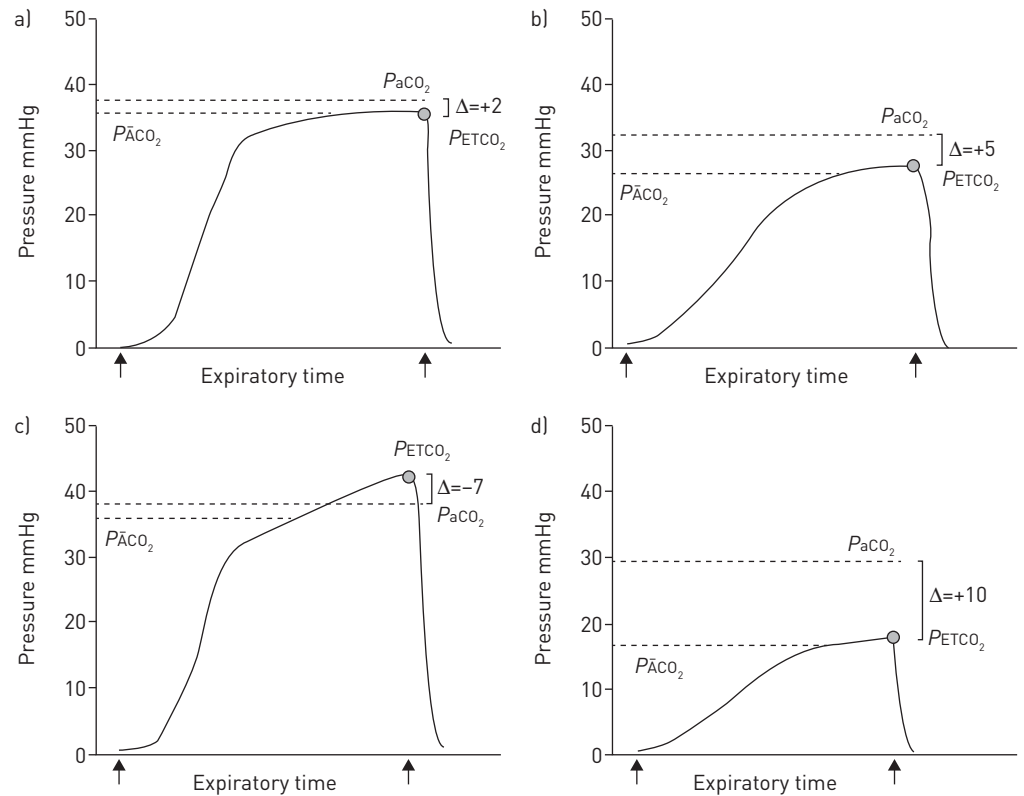


FIGURE 5 Capnography tracings at a, b) rest and c, d) during exercise for a, c) a normal individual and b, d) a patient with pulmonary arterial hypertension (PAH). The mean alveolar  $\text{CO}_2$  partial pressure ( $P\bar{A}\text{CO}_2$ ) is estimated from the mid-point of the expiratory  $P\text{CO}_2$  profile, which depends on the mixed venous  $P\text{CO}_2$  and the expiratory time. The end-tidal  $P\text{CO}_2$  ( $P_{\text{ETCO}_2}$ ; indicated by a circle) is at the end of the intra-breath  $P\text{CO}_2$  oscillation measured at the mouth. As a result of this oscillation in the  $P\text{CO}_2$ , in normal individuals at rest (a) the  $P_{\text{ETCO}_2}$  is greater than the  $P\bar{A}\text{CO}_2$  and below the arterial  $P\text{CO}_2$  ( $P_{\text{aCO}_2}$ ). The small arterial–alveolar  $\text{CO}_2$  difference results from ventilation–perfusion inequality in the normal lungs. Thus, there is an arterial–end-tidal ( $P_{\text{a-ETCO}_2}$ ) difference ( $\Delta$ ) that is positive at rest. During exercise (c), increasing tidal volume and increased mixed venous  $\text{CO}_2$  results in the  $P_{\text{ETCO}_2}$  exceeding the  $P_{\text{aCO}_2}$ , giving a negative  $P_{\text{a-ETCO}_2}$  difference. Patients with PAH have low  $P_{\text{aCO}_2}$  and  $P_{\text{ETCO}_2}$  at rest (b) reflecting ventilation–perfusion inequality, altered chemosensitivity and lower  $P_{\text{aCO}_2}$  set-point, with a  $P_{\text{a-ETCO}_2}$  difference that is positive, and further increases during exercise (d).

increases (figure 6) [55]. Therefore, a positive  $P_{\text{a-ETCO}_2}$  difference reflects both  $V'_A/Q'$  inequality and chemosensitivity, particularly when resting  $P_{\text{aCO}_2}$  is low. A  $P_{\text{a-ETCO}_2}$  difference that increases during exercise could be a more sensitive indication of enhanced chemosensitivity than the calculated  $V_D/V_T$  from equation 1, in addition to reflecting ventilation–perfusion inequality and inefficient gas exchange [74, 77, 78]. In patients with cardiopulmonary disease the  $P_{\text{a-ETCO}_2}$  frequently remains positive during exercise [34, 55, 79]. In CHF patients, a more positive  $P_{\text{a-ETCO}_2}$  difference at peak exercise was related to lower peak  $\text{VO}_2$  [34]. For patients with pulmonary vascular diseases the  $P_{\text{a-ETCO}_2}$  may increase from rest to peak exercise, often in the setting of resting hypocapnia and exertional hypoxaemia (figure 6) [55].

In mild to moderate COPD patients, respiratory drive is increased during exercise but  $V'_E$  is limited by mechanical constraints: expiratory flow limitation leads to dynamic hyperinflation, which results in breathing at high lung volumes where respiratory system compliance is reduced and the work of breathing is higher. In advanced COPD, this constraint is even more important. Although ventilatory responses to  $\text{CO}_2$  and hypoxia remain, a higher  $P_{\text{aCO}_2}$  set-point may result in resting hypercapnia (table 1) [69]. An elevated  $V'_E/V'_{\text{CO}_2}$  slope in mild COPD patients is predominantly related to high physiological dead space rather than an altered  $P_{\text{aCO}_2}$  set-point. Recent evidence suggests that abnormal peripheral muscle metaboreflexes are also involved in the excessive ventilatory response in COPD patients [80]. Mild COPD patients have a normal forced expiratory volume in 1 s ( $\text{FEV}_1$ ), but resting  $V_D/V_T$  and  $P_{\text{a-ETCO}_2}$  are higher compared with healthy individuals at rest [79]. The  $V'_E/V'_{\text{CO}_2}$  slope and nadir are also increased in mild COPD. Both  $V_D/V_T$  and  $P_{\text{a-ETCO}_2}$  decrease during exercise, but while  $V_D/V_T$  may decrease by >50% at peak exercise, it remains significantly higher compared with healthy controls, and the  $P_{\text{a-ETCO}_2}$  difference remains positive. The role of an altered  $P_{\text{aCO}_2}$  set-point accounting for the higher  $V'_E/V'_{\text{CO}_2}$  and  $P_{\text{a-ETCO}_2}$

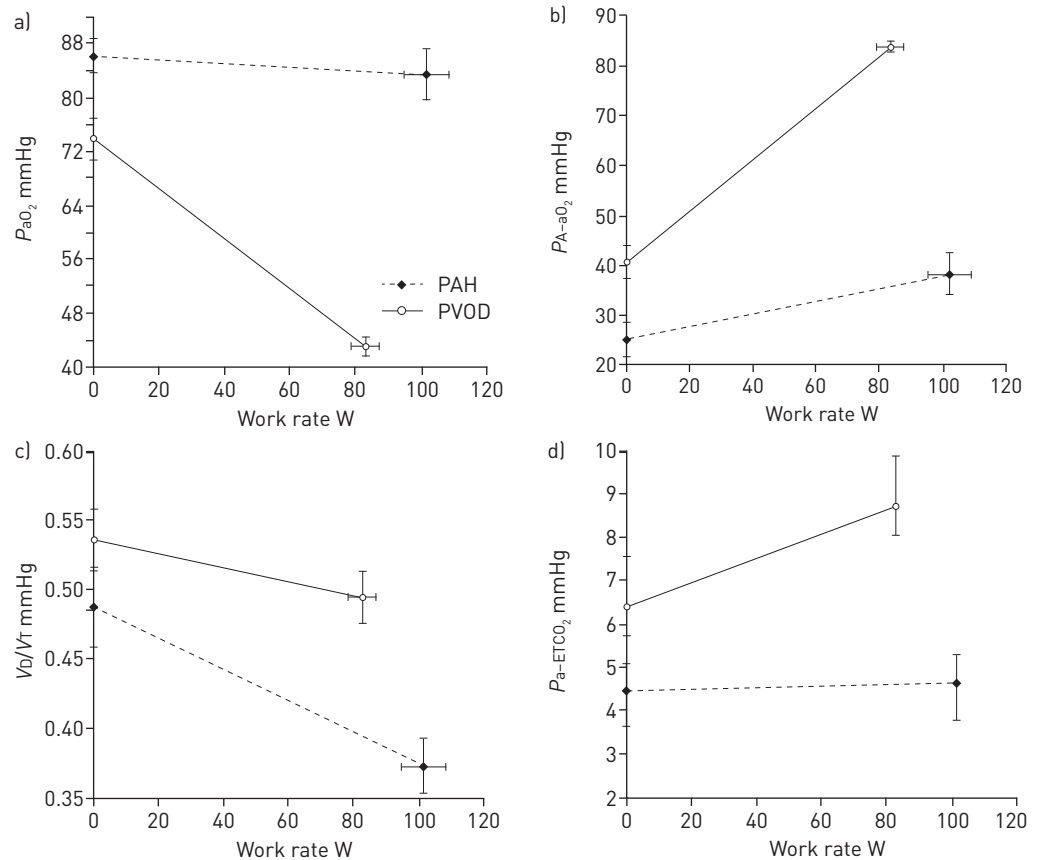


FIGURE 6 Comparison of exercise gas exchange between eight patients with pulmonary veno-occlusive disease (PVOD) and 16 patients with pulmonary arterial hypertension (PAH). a, b) Severe decreases in a) arterial  $O_2$  partial pressure ( $P_{aO_2}$ ) occurred in PVOD patients associated with widening b) alveolar-arterial  $O_2$  difference ( $P_{A-aO_2}$ ) in both groups during exercise. c) In both groups of patients with pulmonary vascular disease, dead space to tidal volume ratio ( $V_D/V_T$ ) was elevated at rest and decreased at peak exercise but remained abnormally high. d) The arterial-end-tidal  $PCO_2$  difference ( $P_{a-ETCO_2}$ ) increased in both groups at peak exercise. Information from [55].

is less likely in mild COPD. In one study, the  $P_{aCO_2}$  values at rest and peak exercise were not significantly different *versus* controls, there were no severe desaturations and  $V'_E/V'CO_2$  correlated much better with  $V_D/V_T$  than with  $P_{aCO_2}$  [77]. In a study of patients with severe COPD without hypoxaemia or hypercapnia at rest, the  $P_{a-ETCO_2}$  difference was also significantly more positive at rest and during exercise than in normal controls [74]. The  $P_{a-ETCO_2}$  correlated with  $V_D/V_T$  and negatively correlated with  $V_T$ , suggesting that the restriction to increasing  $V_T$  during exercise contributes to both  $V_D/V_T$  and the  $P_{a-ETCO_2}$  [74].

### The role of ventilation-perfusion heterogeneity and $V_T$ in ventilatory inefficiency

As discussed in the earlier section on the ventilatory response to exercise in health and cardiopulmonary diseases,  $V_D/V_T$  is sensitive to heterogeneity in  $V'_A/Q'$  but can also occur with low  $V_T$ . An important source for high  $V_D/V_T$  and an abnormally steep  $V'_E/V'CO_2$  slope in cardiopulmonary disorders is increased nonuniformity of  $V'_A/Q'$ . The degree to which low  $V'_A/Q'$  and high  $V'_A/Q'$  regions contribute differs between diseases and differs between patients with the same disease [58, 81].

What might be the source of an increased heterogeneity of pulmonary  $V'_A/Q'$  ratios in CHF and why would it provide prognostic information not provided by  $\dot{V}O_2$  peak? Lung volumes and ventilatory function in the CHF patients studied by KLEBER *et al.* [14] were relatively normal, and arterial blood  $O_2$  saturation ( $S_{aO_2}$ ) at peak exercise was normal, as is generally the case in CHF in the absence of coexisting lung disease. A recent study by KEE *et al.* [82] included patients with severe CHF (mean left ventricular ejection fraction 25.8% and mean New York Heart Association class 2.9) and without apparent lung disease, and grouped patients with high or low  $V_D/V_T$  at peak exercise. Patients with high  $V_D/V_T$  at peak exercise had higher  $V'_E/V'CO_2$ , worse exercise capacity and lower diffusion capacity for carbon monoxide. Interestingly, although peak exercise  $V_D/V_T$  correlated significantly with  $V'_E/V'CO_2$  ( $r=0.349$ ,  $p=0.001$ ), this

explained only 12% of the variability in  $V_E/V'CO_2$ , reinforcing that other mechanisms (e.g. enhanced chemosensitivity) contribute to inefficient ventilation in CHF [82]. In the absence of coexisting lung disease, ventilation increases during exercise but pulmonary perfusion may be impaired as a result of poor heart pump function, high downstream left ventricular pressure and increased pulmonary arterial pressure. Therefore, while  $V_A$  increases,  $Q'$  does not increase proportionally, resulting in a shift to a higher  $V_A/Q'$  ratio and a higher physiological dead space ( $V_D/V_T$ ) [10]. When ventilatory capacity is preserved, abnormal distribution of perfusion usually can be well compensated by raising ventilation enough to maintain a normal  $P_aCO_2$  and normal  $SAO_2$  [59].

Patients with CHF often have a reduced  $V_T$  during heavy exercise, which would also increase the  $V_D/V_T$  ratio. It had been estimated that only 33% of the increased dead space ventilation in CHF can be explained by a low  $V_T$  [83, 84]; however, other studies have found that a low  $V_T$  is the dominant reason for high exercise  $V_D/V_T$  in more severe CHF patients undergoing transplant evaluation [8, 32]. This observation of low  $V_T$  in severe CHF patients may be explained by 1) impaired ability to increase  $O_2$  delivery to the respiratory muscles in the most severe CHF patients, resulting in reduced respiratory muscle strength and lower  $V_T$  in the face of higher ventilatory demands [82], or 2) rapid shallow breathing patterns driven by enhanced peripheral chemoreflexes and ergoreflexes in patients with worse cardiac function. Coexistent lung disease may significantly alter  $V_D/V_T$  and the expected pattern of  $V_E/V'CO_2$  and gas exchange in CHF by affecting  $V_A/Q'$  heterogeneity and  $V_T$  expansion. For example, in patients with COPD and CHF overlap, the  $V_E/V'CO_2$  slope is similar to patients with CHF or COPD alone, but COPD and COPD-CHF overlap patients have a higher  $V_E/V'CO_2$  intercept than CHF patients [85]. Furthermore, among COPD patients, those with comorbid CHF had higher  $V_E/V'CO_2$  slopes, lower  $V_E/V'CO_2$  intercepts and lower  $P_{ETCO_2}$  reflecting higher ventilatory drive, and high chemosensitivity [86]. Thus, it must be cautioned that if a patient with CHF has significant coexistent lung disease, application of the  $V_E/V'CO_2$  slope to predict survival, as proposed by KLEBER *et al.* [14], becomes invalid. A recent study, however, suggested that the  $V_E/V'CO_2$  nadir may retain prognostic significance in this group with COPD and CHF overlap [87].

Similar to CHF patients, high  $V_D/V_T$  during exercise is consistently observed in patients with PAH. In contrast to CHF, resting and peak exercise blood gases are typically abnormal in PAH patients, often demonstrating hypocapnia and variable degrees of hypoxaemia [56]. In a study using the multiple inert gas elimination technique (MIGET) in four PAH patients and three CTEPH patients, DANZTKER and BOWER [54] found that  $V_A/Q'$  heterogeneity at rest was mild to moderately increased with a shift to a higher mean  $V_A/Q'$  and in most patients an additional mode of cardiac output was directed to low  $V_A/Q'$  (ratios  $<0.1$  and/or shunt) lung regions. Thus, resting hypoxaemia in this study was attributed to a combination of mild  $V_A/Q'$  heterogeneity, intrapulmonary shunt and decreased mixed venous  $O_2$  partial pressure ( $P_{vO_2}$ ) as a result of impaired cardiac output. Only one small study has assessed  $V_A/Q'$  heterogeneity using MIGET during exercise in patients with pulmonary vascular disease [58]. In this study of seven patients (five with PAH and two with CTEPH), mean  $P_{aO_2}$  decreased from  $64 \pm 6.1$  to  $56 \pm 5.4$  mmHg but there was no significant increase in the degree of  $V_A/Q'$  inequality or shunt, although the mean  $V_A/Q'$  ratio increased more than two-fold. In light of only modest increases in  $V_A/Q'$  heterogeneity and no change in inert gas dead space or  $V_D/V_T$  during exercise, the MIGET data support the idea that abnormally high  $V_E/V'CO_2$  and alveolar hyperventilation during exercise in PAH patients could be driven by inadequate cardiac output responses and autonomic dysfunction in addition to high physiological dead space [58].

In mild COPD patients who have relatively normal values of FEV<sub>1</sub>, the  $V_E/V'CO_2$  slope and  $V_D/V_T$  are higher than in healthy individuals; however, this is not related to a lower  $V_T$  [79] but rather an increase in high  $V_A/Q'$  regions [81, 88]. The  $P_{aO_2}$  is maintained and may even increase during exercise in mild COPD patients, as low  $V_A/Q'$  regions can still be compensated for by an increase in total ventilation, but at the cost of higher neural respiratory drive, work of breathing and dyspnoea [79, 89]. Even in mild COPD patients with preserved  $P_{aO_2}$ , the alveolar-arterial difference ( $P_{A-aO_2}$ ),  $V_D/V_T$  and  $P_{a-ETCO_2}$  during exercise are increased compared with healthy individuals, reflecting the increased heterogeneity in  $V_A/Q'$  [90]. In severe COPD patients, in which ventilation and perfusion are poorly matched, compensatory increases in  $V_E$  are also restricted by the high resistance to airflow, dynamic hyperinflation and mechanical constraints to  $V_T$  expansion [90-92]; during exercise,  $P_aCO_2$  rises and  $SAO_2$  falls [93, 94]. The degree of  $V_A/Q'$  inequality increases modestly from Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 1 to stage 4 [92]. In contrast to PAH and CHF patients, the slope of  $V_E/V'CO_2$  decreases and the  $V_E/V'CO_2$  intercept increases with progressive severity of COPD due to the increasing importance of mechanical constraints limiting  $V_E$  and  $V_T$  [92]. However, one would not interpret the lower  $V_E/V'CO_2$  slope to mean that ventilation in severe COPD is "less inefficient". The inability to increase  $V_T$  during exercise will necessarily limit the decline of  $V_D/V_T$  during exercise. For the severe COPD patient, the  $P_{aO_2}$  decrease during exercise can be attributed to  $V_A/Q'$  heterogeneity and to the fact

that low  $V_A/Q'$  regions are being perfused by mixed venous blood with much lower  $O_2$  saturation, which cannot be compensated by increasing  $V_A$  because of severe airflow obstruction and mechanical ventilatory constraints [89]. Although the primary limitation to exercise in PAH comes from impaired cardiac function, dynamic hyperinflation develops during exercise and contributes to exertional dyspnoea in some PAH patients [7, 95].

### Interventions to improve ventilatory efficiency: a mechanistic approach

The role of increasing  $V_E$  on dyspnoea and exercise tolerance in a particular patient with cardiopulmonary disease requires consideration of several factors: whether blood gas and acid–base “requirements” are met, the cost of meeting these requirements, whether the ventilatory system is mechanically constrained, and the intensity with which the  $V_E$  response is perceived. Understanding the mechanisms that lead to high  $V_E/V_{CO_2}$  in different disease states (table 1) can help justify and guide the choice of interventions. By appropriately targeting the factors that determine an excessive ventilatory response to exercise (figure 1), an intervention may improve exertional dyspnoea, exercise capacity and, in some cases, prognosis.

For COPD patients who are typically limited by mechanical constraints on maximal ventilation and gas exchange impairment from  $V_A/Q'$  inequality, bronchodilators reduce airflow limitation (reducing or delaying the onset of dynamic hyperinflation) and improve  $V_A/Q'$  matching (which reduces  $V_D/V_T$  and improves gas exchange). Despite potentially worsening ventilation–perfusion matching, supplemental  $O_2$  improves long-term survival in hypoxaemic COPD patients [96] and also improves exercise tolerance in COPD patients by diminishing peripheral chemoreceptor drive and delaying the onset of lactic acidosis [97, 98]. As chemoreceptor stimulation increases ventilatory drive and a rapid breathing pattern,  $O_2$  may blunt the respiratory rate increase during exercise, allowing a longer expiratory time, which might prevent or delay dynamic hyperinflation. Similarly, breathing retraining exercises involving pursed-lip breathing, expiratory abdominal augmentation and relaxation techniques improve exercise performance in COPD patients predominantly by reducing the respiratory rate increase during exercise [99]. Slowing the respiratory rate thereby reduces dynamic hyperinflation-related constraints on  $V_T$ , allowing a larger  $V_T$ , which improves the  $V_D/V_T$ . Low-dose opiates also improve exercise capacity by nearly 20% in COPD patients by blunting the ventilatory reflexes to hypoxaemia and hypercapnia [100]. By limiting excessive increases in respiratory rate, opiates reduce the ventilatory demand for a given workload and reduce dynamic hyperinflation in addition to diminishing dyspnoea perception for a given  $V_E$  [100].

In contrast to COPD, CHF patients rarely desaturate during exercise, and are limited by impaired maximal cardiac output and  $O_2$  extraction, rather than ventilation [34] (table 1). Vasodilators such as sodium nitroprusside increase cardiac output and exercise capacity by improving overall  $O_2$  transport, despite increasing perfusion to low  $V_A/Q'$  regions, which may worsen  $P_{aO_2}$  [101]. As maximal ventilatory capacity is maintained in CHF, they can compensate for the high  $V_D/V_T$ , bringing the  $P_{aCO_2}$  down to normal levels at peak exercise and maintaining a normal alveolar  $O_2$  tension.  $\beta$ -Blockers improve survival in CHF with reduced systolic function [102–104], but carvedilol (which has  $\beta$ - and  $\alpha$ -blocker activity) also improves ventilatory efficiency by attenuating the influence of overactive chemoreceptor and ergoreceptor reflexes [105–110]. Diuretics reduce left ventricular filling pressure, improving the cardiac output, and also reduce  $V_D/V_T$  related to interstitial oedema.

For PAH patients, the primary factors determining the high  $V_E/V_{CO_2}$  and exercise capacity are the impaired cardiac output, high chemosensitivity and  $V_A/Q'$  inequality (table 1). Pulmonary vasodilators such as sildenafil or prostanoids improve ventilatory efficiency through several potential mechanisms [111, 112]. Prostacyclin lowers pulmonary vascular resistance and increases cardiac output, but also worsens  $V_A/Q'$  matching by increasing blood flow distribution to lower  $V_A/Q'$  regions [56]. However, by improving cardiac output and  $O_2$  delivery to the muscles, the effect of chemoreceptor and peripheral ergoreceptor stimulation might decrease. Atrial septostomy, usually reserved for severe patients refractory to other treatments, reduces sympathetic nervous system activity, improves cardiac output and possibly diminishes chemosensitivity despite worsening hypoxaemia [52]. Supplemental  $O_2$  during exercise improves ventilatory efficiency, dyspnoea, exercise capacity and endurance predominantly by diminishing chemoreflex-mediated excessive ventilation [113].

Skeletal muscle hypoperfusion and deconditioning is common in patients with cardiopulmonary diseases, and contributes to early onset lactic acidosis and higher  $V_{CO_2}$ , and thus ventilatory demand, for a given exercise load [114]. Therefore, it is not unexpected that rehabilitation programmes that involve strength and/or cardiovascular exercise training can improve exercise tolerance. Exercise training increases peripheral muscle capillarisation, which improves peripheral muscle  $O_2$  utilisation and delays the onset of metabolic acidosis, resulting in a lower ventilatory demand at any given workload [115–120]. Furthermore, it has been demonstrated that exercise training reduces exercise oscillatory ventilation and  $V_E/V_{CO_2}$  in

CHF patients [121], suggesting beneficial effects of exercise on central and peripheral autonomic chemo/ergoreflexes in cardiopulmonary diseases [80, 122]. As the presence of exercise oscillatory ventilation can exacerbate dynamic hyperinflation in CHF patients with comorbid COPD, exercise training may be a particularly important intervention in these patients [123].

### Conclusions

The efficiency of ventilation during exercise can be assessed by the  $V_E/V'CO_2$  slope or the  $V_E/V'CO_2$  value at the anaerobic threshold. An excessive ventilatory response during exercise and a high  $V_E/V'CO_2$  are consequences of high physiological dead space from ventilation–perfusion inequalities in the lung and, in many cases, from increased chemoreceptor reflexes. Autonomic hyperactivity is almost universally present but to varying degrees in cardiopulmonary disease, demonstrated by increased chemoreceptor-mediated ventilatory responses and ergoreceptor afferent activity, which all contribute to an elevated  $V_E/V'CO_2$ . The  $V_E/V'CO_2$  is therefore an integrated variable that reflects not only gas exchange impairment, but also the autonomic nervous system response to impaired cardiac function and tissue  $O_2$  delivery, explaining its prognostic importance across various diseases. Thus, while inefficiency of gas exchange and enhanced chemosensitivity may not be the primary causes of impaired exercise capacity, they can be a major source of exercise hyperpnoea and exertional dyspnoea. By assessing arterial blood gases at rest and during exercise, including the calculation of  $V_D/V_T$ ,  $PA-aO_2$  and  $Pa-ETCO_2$  differences, gas exchange impairment and the relative significance of each disturbance in a pathological ventilatory response to exercise can be better appreciated.

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