Ventilatory efficiency in pulmonary vascular diseases

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Shareable abstract (@ERSpublications)
Ventilatory inefficiency is a hallmark feature of PH that reflects abnormal ventilation/perfusion matching, chemosensitivity and an altered CO_2 set-point. Minute ventilation/CO_2 production is useful in the diagnosis, management and prognostication of PH. https://bit.ly/3jnNdUG

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Abstract

Cardiopulmonary exercise testing (CPET) is a frequently used tool in the differential diagnosis of dyspnoea. Ventilatory inefficiency, defined as high minute ventilation (V'_E) relative to carbon dioxide output (V'_{CO_2}), is a hallmark characteristic of pulmonary vascular diseases, which contributes to exercise intolerance and disability in these patients. The mechanisms of ventilatory inefficiency are multiple and include high physiologic dead space, abnormal chemosensitivity and an altered carbon dioxide (CO_2) set-point. A normal V'_E/V'_{CO_2} makes a pulmonary vascular disease such as pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH) unlikely. The finding of high V'_E/V'_{CO_2} without an alternative explanation should prompt further diagnostic testing to exclude PAH or CTEPH, particularly in patients with risk factors, such as prior venous thromboembolism, systemic sclerosis or a family history of PAH. In patients with established PAH or CTEPH, the V'_E/V'_{CO_2} may improve with interventions and is a prognostic marker. However, further studies are needed to clarify the added value of assessing ventilatory inefficiency in the longitudinal follow-up of patients.

Introduction

Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are pulmonary vascular diseases that cause pulmonary hypertension (PH) (table 1). Both are characterised by a pre-capillary pattern of PH during right heart catheterisation (RHC), which is defined as an elevation in mean pulmonary arterial pressure (mPAP) >20 mmHg, elevation in the pulmonary vascular resistance (PVR) ⩾3 Wood units, and a normal pulmonary artery wedge pressure (PAWP) ⩽15 mmHg [1]. In PAH, abnormal proliferation, remodelling and rarefaction of the small pulmonary arteries leads to elevation in PVR, high pulmonary arterial pressure and right ventricular dysfunction [2, 3]. CTEPH occurs in about 3% of patients after pulmonary embolism (PE) [4, 5] as a result of persistent organised thrombus in the main, lobar, and/or segmental pulmonary arteries, and there can also be a more distal small vessel disease that resembles PAH [4].

Cardiopulmonary exercise testing (CPET) is a safe and noninvasive tool that can alert the clinician to the possibility of underlying pulmonary vascular disease, elucidate the mechanism of exertional dyspnoea in patients with known PAH or CTEPH, assess disease severity and prognosis and monitor response to

TABLE 1 Clinical classification of pulmonary hypertension (PH)

1 PAH
Idiopathic PAH
Heritable PAH
Drug- and toxin-induced PAH
PAH associated with:
Connective tissue disease
HIV infection
Portal hypertension
Congenital heart disease
Schistosomiasis
PAH long-term responders to calcium channel blockers
PAH with overt features of venous/capillaries (PVOD/PCH) involvement
Persistent PH of the newborn syndrome
2 PH due to left heart disease
PH due to heart failure with preserved LVEF
PH due to heart failure with reduced LVEF
Valvular heart disease
Congenital/acquired cardiovascular conditions leading to post-capillary PH
3 PH due to lung diseases and/or hypoxia
Obstructive lung disease
Restrictive lung disease
Other lung disease with mixed restrictive/obstructive pattern
Hypoxia without lung disease
Developmental lung disorders
4 PH due to pulmonary artery obstructions
Chronic thromboembolic PH
Other pulmonary artery obstructions
5 PH with unclear and/or multifactorial mechanisms
Haematological disorders
Systemic and metabolic disorders
Others
Complex congenital heart disease

PAH: pulmonary arterial hypertension; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis; LVEF: left ventricular ejection fraction.

treatment [6–8]. Among the many valuable variables acquired during CPET, the peak oxygen consumption (V'_{O_2} peak) and the ventilatory equivalent for carbon dioxide (V'_E/V'_{CO_2}) have been the most widely studied in cardiopulmonary diseases. During exercise, patients with pulmonary vascular disease can exhibit a range of pathological responses that include impaired cardiac output, reduced aerobic capacity, inefficient ventilation (high V'_E/V'_{CO_2}), hypoxaemia, dynamic hyperinflation, dyspnoea and peripheral muscle dysfunction (figure 1). The objectives of this article are to: 1) review the mechanisms leading to an excessive ventilatory response, or high V'_E/V'_{CO_2}, in PAH and CTEPH; and 2) to review the utility of V'_E/V'_{CO_2} in the diagnosis, prognostication and assessment of treatment response in patients with pulmonary vascular diseases.

What factors determine the V'_E/V'_{CO_2}?

The ventilatory response to exercise (V'_E) is closely linked to three variables in Equation 1 and figure 2: V'_{CO_2}, the arterial partial pressure of carbon dioxide (P_{aCO_2}), and the physiologic dead space fraction (V_D/V_T).

$$V'_E = \frac{k \times V'_{CO_2}}{P_{aCO_2} \times \left(1 - \frac{V_D}{V_T}\right)} \quad (1)$$

In Equation 1, k=863 is a constant that corrects for the different conditions of reporting gas volumes (standard temperature and pressure, dry; body temperature and pressure, saturated) and transformation of fractional concentration to partial pressure, at a body temperature of 310 K, and a barometric pressure of 760 mmHg.

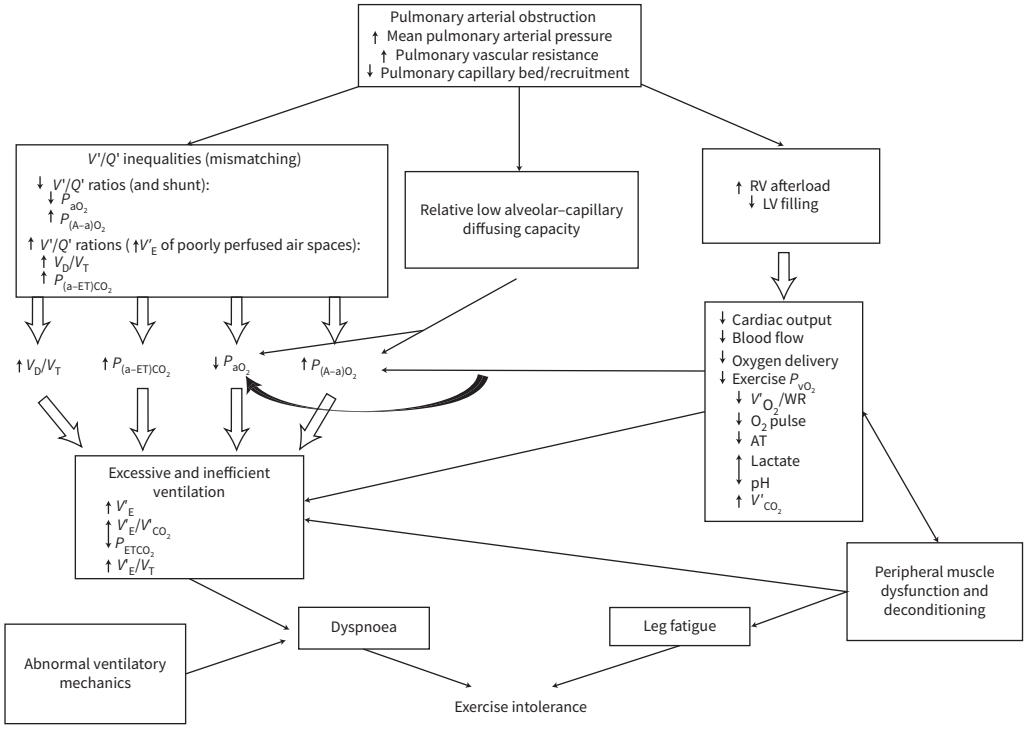

FIGURE 1 Pathophysiology and mechanisms of exercise intolerance in pulmonary hypertension. Pulmonary vascular obstruction results in high ventilation/perfusion ratios (*V′*/*Q′*), impaired cardiac output and can result in hypoxaemia due to right-to-left shunting through a patent foramen ovale. Inefficient ventilation proposes high ventilatory demand, high minute ventilation (V'_E)/carbon dioxide production (V'_{CO_2}) and dead space (V_D)/tidal volume (V_T) and low end-tidal carbon dioxide tension (P_{ETCO_2}). Cardiac limitation and peripheral muscle abnormalities result in a low anaerobic threshold (AT), early onset lactic acidosis and increased V'_{CO_2}, which provide further stimulation for excessive ventilation. Ventilatory mechanical constraints on V_T expansion also contribute to dyspnoea during exercise. LV: left ventricle; O_2 pulse: oxygen consumption (V'_{O_2}) to heart rate ratio; P_{aO_2}: arterial oxygen tension; P_{vO_2}: venous pressure of oxygen; RV: right ventricle; WR: work rate; P_{A-aO_2}: alveolar–arterial oxygen tension difference; $P_{(a-ET)CO_2}$: end-tidal partial pressure gradient of CO_2.

Rearranging Equation 1, the efficiency of ventilation (V'_E/V'_{CO_2}) can be expressed as being inversely proportional to just two factors: 1) P_{aCO_2} and 2) $(1 - V_D/V_T)$.

$$\frac{V'_E}{V'_{CO_2}} = \frac{k}{P_{aCO_2} \times \left(1 - \frac{V_D}{V_T}\right)} \quad (2)$$

During exercise, V'_E increases linearly with V'_{CO_2} due to rising metabolic demand, as extensively reviewed in WEATHERALD *et al*. [9]. There is often an inflection in the slope of V'_E/V'_{CO_2} at the respiratory compensation point (RCP) where V'_E increases disproportionately to V'_{CO_2} due to ventilatory drive stimulation from muscle afferent feedback, central command and metabolic acidosis [10]. The V_D/V_T decreases during exercise in healthy individuals as tidal volume (V_T) increases several fold and to a much greater extent than the small increase in dead space (V_D). In healthy individuals, the P_{aCO_2} remains essentially unchanged during exercise, except at very heavy intensity when hyperventilation after the RCP results in relative hypocapnia [11, 12].

Ventilatory efficiency (V'_E/V'_{CO_2}) is usually represented in three ways: 1) the slope of V'_E *versus* V'_{CO_2} from onset of exercise to the RCP inflection; 2) the ratio of V'_E/V'_{CO_2} at the anaerobic threshold (AT); and 3) the lowest value (nadir) of the V'_E/V'_{CO_2} ratio during exercise [13]. The V'_E/V'_{CO_2} nadir may be the preferred measure of ventilatory efficiency as there is less variability than V'_E/V'_{CO_2} slope and because the AT may not be evident in all individuals [13]. In healthy individuals, the V'_E/V'_{CO_2} increases with age and tends to be lower in males than females for any given age [13, 14].

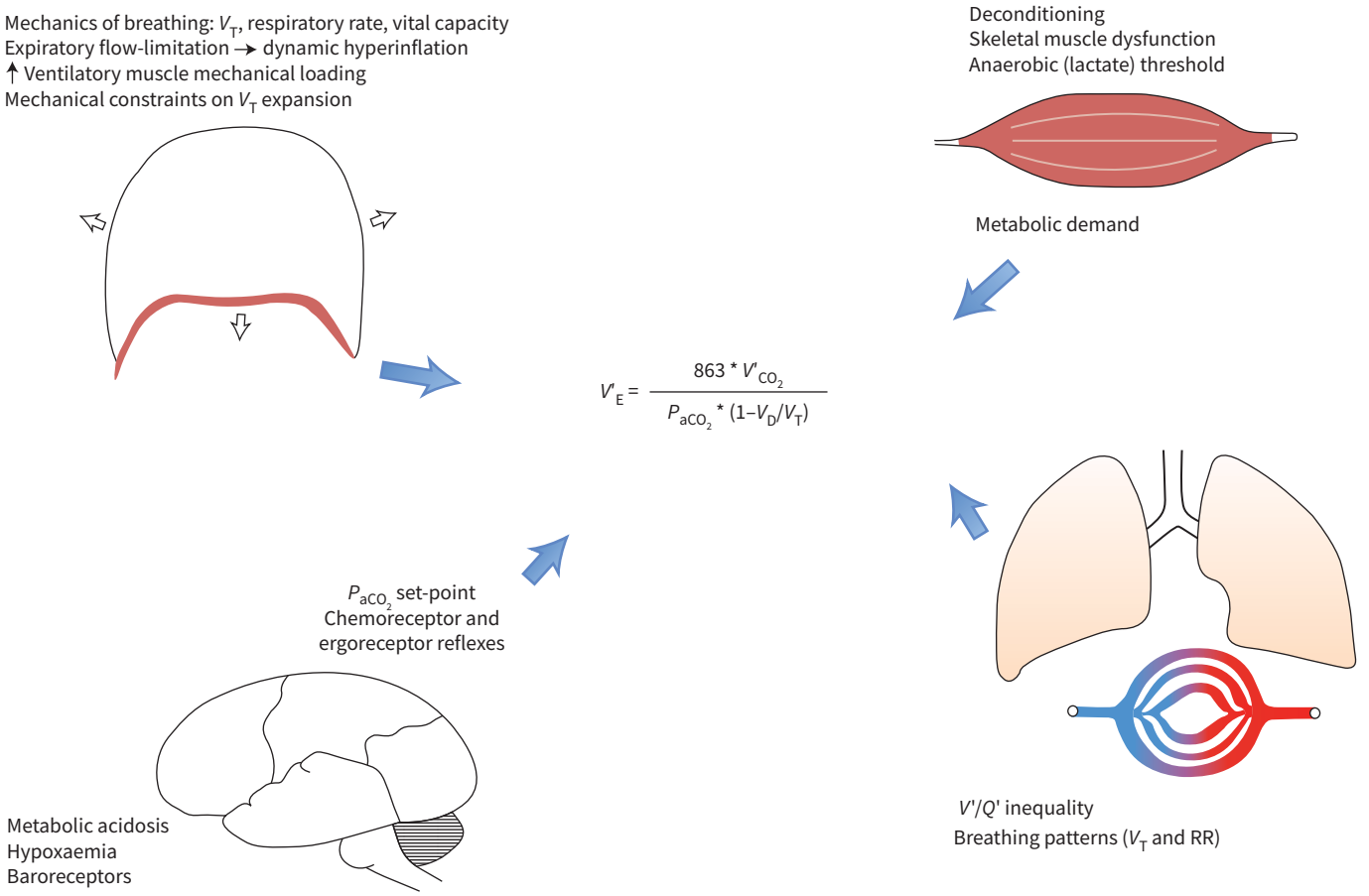

FIGURE 2 Minute ventilation (V'_E) is determined by carbon dioxide production (V'_{CO_2}), the arterial partial pressure of CO_2 (P_{aCO_2}) and the physiologic dead space to tidal volume (V_D/V_T). In addition to gas exchange impairment ventilation/perfusion (V'/Q') abnormalities and shunt, mechanical, metabolic and autonomic nervous system reflexes influence these variables to determine the ventilatory demand and ventilatory efficiency. RR: respiratory rate. Reproduced and modified from [9] with permission.

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What are the mechanisms of ventilatory inefficiency in pulmonary vascular diseases?

There are several potential mechanisms of high V'_E/V'_{CO_2} in pulmonary vascular disease [9, 15]. First, obstruction and loss of pulmonary vasculature results in heterogeneity in the matching of regional ventilation (V') and perfusion (Q'), which leads to a higher V_D/V_T [16–18]. Consequently, the efficiency of gas exchange is impaired, resulting in a higher ventilatory demand for a given V'_{CO_2} and P_{aCO_2}. While hypoxaemia is common in PAH and CTEPH and is related to the degree of ventilation-perfusion inequality in the lungs, it does not appear to be a major cause of high V'_E/V'_{CO_2} in PAH. This was shown by THEODORE and colleagues who evaluated the V'_E/V'_{CO_2} slope before and after heart–lung transplantation [19]. They demonstrated that heart–lung transplantation resulted in a marked decrease in V'_E/V'_{CO_2} slope from 57.7±6.8 to 24.7±1.6, which is not different from normal individuals. In these patients, the V'_E/V'_{CO_2} slope was not related to resting or exercise levels of the arterial partial pressure of oxygen (P_{aO_2}), P_{aCO_2} or arterial pH. In another study, TING *et al.* infused epoprostenol, a potent pulmonary arterial vasodilator, and observed acute improvements in haemodynamics and V_D/V_T with a decrease in resting V'_E/V'_{CO_2} from baseline [20]. There were no acute changes in P_{aO_2}, P_{aCO_2} or arterial pH. These studies implicated abnormal neurophysiologic and/or haemodynamic mechanisms, rather than deranged blood gases, in the pathophysiology of high V'_E/V'_{CO_2} in patients with pulmonary vascular disease.

Re-examining Equation 2, it is clear that V'_E/V'_{CO_2} will also be higher if the P_{aCO_2} is lower. Several studies have noted that many patients with PAH and CTEPH are hypocapnic at rest [21–24], which cannot be explained by high V_D/V_T. Instead, resting hypocapnia is related to abnormal chemoreflexes due to autonomic nervous system dysfunction and/or an altered P_{aCO_2} set-point [25]. Most of the available data on autonomic function is from patients with PAH, demonstrating increased sympathetic nervous system activation as measured by muscle sympathetic nerve activity (MSNA) using microneurography [26, 27]. Higher MSNA is associated with worse disease severity and clinical deterioration in PAH [28]. However, the mechanisms of sympathetic activation in PAH have not been fully elucidated. Some studies have shown that noninvasive markers of sympathetic function, such as heart rate variability and baroreflex sensitivity, are impaired in patients with PAH and are related to exercise capacity but not correlated with V'_E/V'_{CO_2} [29]. However, other indirect indicators of sympathetic function during exercise, such as chronotropic response and heart rate recovery after exercise, are correlated to V'_E/V'_{CO_2} in PAH [30]. In severe PAH and CTEPH, pressure overload leads to right ventricular (RV) dysfunction and an increase in right atrial pressure (RAP), which may directly activate the sympathetic nervous system. Elevated RAP leads to right atrial distention, which may be an important mechanism of sympathetic activation. Decreases in RAP after palliative atrial septostomy correlated with changes in MSNA [31]. This could be a potential overarching explanation for the link between autonomic dysfunction, elevated RAP and prognosis in PAH [32]. Elevated RAP is often seen in patients with severe PAH and CTEPH with RV dysfunction and volume overload. It is important to note that different mechanisms of high V'_E/V'_{CO_2} may predominate in PAH patients *versus* CTEPH patients. For example, right ventricular dysfunction may occur in PAH and CTEPH, but echocardiographic measures of RV dysfunction were only correlated with exercise capacity and V'_E/V'_{CO_2} in patients with PAH, not patients with CTEPH [33]. In CTEPH, exercise capacity and V'_E/V'_{CO_2} may be less determined by haemodynamics, RV function or autonomic hyperactivity but predominantly determined by the degree of pulmonary vascular obstruction and the V_D/V_T [34, 35].

Two recent studies support the importance of abnormal chemoreflexes and a lower P_{aCO_2} set-point in the inefficient ventilation observed in pulmonary vascular diseases. Our group recently demonstrated that the maximal value of end-tidal partial pressure of CO_2 (P_{ETCO_2}) between the AT and RCP, an indicator of the P_{aCO_2} set-point, was significantly lower in hypocapnic patients with PAH, CTEPH, and pulmonary veno-occlusive disease [22]. In a broad group of patients with pulmonary vascular disease, maximal P_{ETCO_2} was a stronger correlate of peak V'_{O_2} (r=0.64) and V'_E/V'_{CO_2} slope (r=−0.86) than P_{aCO_2} or V_D/V_T. This suggests that an altered P_{aCO_2} set-point is an important determinant of exercise capacity and ventilatory inefficiency in pulmonary vascular disease. FARINA *et al.* used hypoxic and hypercapnic challenge testing to test the role of peripheral and central chemoreflexes in PAH (n=16) [24]. Peripheral chemoreflex responses to hypoxia and hypercapnia and the central hypercapnic chemosensitivity reflex were all increased compared with healthy individuals. The peripheral reflexes were not related to any exercise variables; however, the central hypercapnic response was correlated with the alveolar ventilation (V'_A) to V'_{CO_2} slope (r=0.65), indicating that overactive central autonomic CO_2 chemoreflexes are an important contributor to exercise hyperventilation in PAH [24].

Dynamic hyperinflation results in mechanical limitation to V_T expansion during exercise and can limit the rise in V'_E relative to V'_{CO_2} in patients with COPD [36, 37]. Interestingly, dynamic hyperinflation occurs in up to 60% of PAH and CTEPH patients in the absence of smoking or overt airflow obstruction, which increases dyspnoea for a given V'_E [23]. Although the mechanisms of dynamic hyperinflation in pulmonary

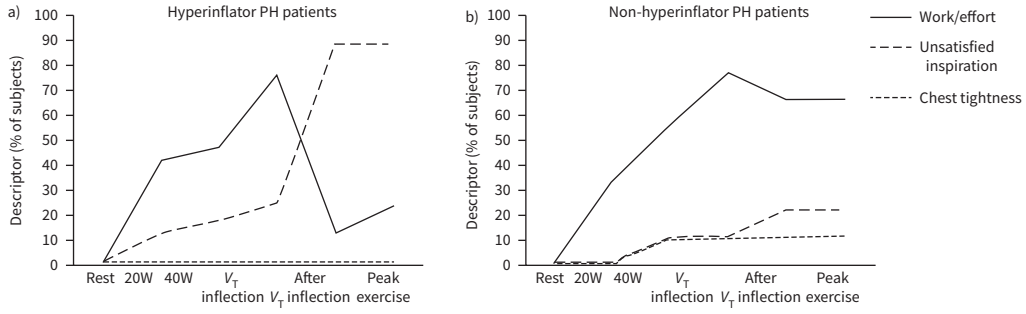

FIGURE 3 a) Selection frequency of the three descriptor phrases evaluated during symptom-limited incremental cycle exercise in patients with pulmonary hypertension (PH) who hyperinflate (hyperinflators) during exercise: increased work/effort, unsatisfied inspiration and chest tightness. Data are presented as mean at rest, at 20 W (iso-WR 1), at 40 W (iso-WR 2), at the tidal volume (V_T) inflection point, after the V_T inflection point and at peak exercise. b) Selection frequency of the three descriptor phrases evaluated during symptom-limited incremental cycle exercise in patients with PH who deflate (nonhyperinflators) during exercise: increased work/effort, unsatisfied inspiration and chest tightness. Data are presented as mean at rest, at 20 W (iso-WR 1), at 40 W (iso-WR 2), at the V_T inflection point, after the V_T inflection point and at peak exercise. Reproduced and modified from [38] with permission.

vascular disease are not exactly known, our group recently demonstrated that patients with PAH and CTEPH who develop dynamic hyperinflation during exercise have a lower V'_E/V'_{CO_2} slope than those who did not develop dynamic hyperinflation [38]. Dyspnoea perception in these hyperinflators was more related to "air hunger" and unsatisfied inspiration, likely related to the mechanical constraint on V_T (figure 3). In contrast, descriptors of "breathing a lot" and increased work/effort predominated in nonhyperinflators who had higher V'_E and higher V'_E/V'_{CO_2}. This study illustrates the complex relationships between respiratory mechanics and ventilatory inefficiency in PAH and CTEPH.

Is ventilatory inefficiency useful in the diagnosis of pulmonary hypertension?

Ventilatory inefficiency is not unique to pulmonary vascular disease but is a hallmark feature, as demonstrated in a seminal paper by Sun *et al*. [39]. Both V'_E/V'_{CO_2} slope and V'_E/V'_{CO_2} at AT correlated with disease severity as measured by New York Heart Association (NYHA) functional class, although peak V'_{O_2} was more strongly related to NYHA class and haemodynamic severity. In patients with mild PAH, V'_E/V'_{CO_2} was significantly higher than normal controls, suggesting that ventilatory inefficiency could be a useful marker of early disease [39]. As such, a normal V'_E/V'_{CO_2} makes pulmonary vascular disease unlikely and an invasive investigation, such as RHC, is not usually warranted in this situation unless other clinical data point strongly towards PH. In contrast, high V'_E/V'_{CO_2} is not specific to pulmonary vascular disease but warrants further investigation for PH when present, especially in the absence of other causes (*e.g.* parenchymal lung disease, heart failure).

In patients with systemic sclerosis (SSc), who are at risk of developing PAH, CPET may have a role in screening. Elevated V'_E/V'_{CO_2} in a patient with SSc suggests underlying pulmonary vascular disease and should prompt further testing. This was illustrated in a prospective study of 173 patients with SSc without known PAH who underwent CPET and RHC, in which V'_E/V'_{CO_2} was significantly higher in patients who were ultimately diagnosed with PAH (n=48) compared with those with normal haemodynamics (n=115) or post-capillary PH (n=10). The V'_E/V'_{CO_2} nadir correlated with mean pulmonary arterial pressure (rho=0.61), PVR (rho=0.58) and accurately discriminated patients who had PAH (area under the curve (AUC) 0.85, 95% CI 0.77–0.92) [40]. Using a threshold of V'_E/V'_{CO_2} nadir of 27.8 had 95.8% sensitivity and 25% specificity for detecting PAH, whereas at an "optimal" threshold of 35.5, the V'_E/V'_{CO_2} nadir had 79.2% sensitivity and 82.9% specificity. A V'_E/V'_{CO_2} nadir >45.5 effectively ruled-in PAH with a positive predictive value of 100%. Currently, many patients with SSc are screened for PAH using the DETECT algorithm which uses clinical, laboratory, and echocardiographic variables to determine the need for RHC [41]. A recent study demonstrated that V'_E/V'_{CO_2} may have additive value to the DETECT algorithm by helping to reduce the number of unnecessary invasive RHCs [42]. In 54 SSc patients who screened positive using the DETECT algorithm and underwent CPET and RHC, 17 patients (31%) had PAH which was fairly mild in severity (mean PVR 4.9±1.6 Wood units). The V'_E/V'_{CO_2} at AT had 100% sensitivity, 83% specificity, 70% positive predictive value, and 100% negative predictive value for identifying PAH, with similar performance for the V'_E/V'_{CO_2} slope (sensitivity 100%, specificity 78%, positive predictive value 63%, negative predictive value 100%) [42]. Based on these performance characteristics, a patient with a V'_E/V'_{CO_2} slope of <39 would not need RHC despite screening positive on the DETECT algorithm.

There are heritable forms of PAH, most commonly due to mutations in the *Bone Morphogenic Protein Receptor 2* (*BMPR2*) gene. Limited data and recent guidelines suggest that asymptomatic mutation carriers should be screened for PAH [43, 44]. CPET is an attractive option for screening asymptomatic carriers since ventilatory abnormalities may be present early in the development of PAH, before echocardiographic changes suggesting PH are seen or when disease features begin to manifest [45, 46]. The results of the DELPHI-2 study, which used a multimodal screening approach for asymptomatic *BMPR2* mutation carriers, suggested that a CPET-derived probability score including the V'_E/V'_{CO_2} can help detect early disease in this at-risk group [47].

The V'_E/V'_{CO_2} can be useful to distinguish between potential causes of PH. Left heart disease is the most common cause of elevated pulmonary pressure. V'_E/V'_{CO_2} is elevated in patients with heart failure and reduced ejection fraction (HFrEF) [48, 49]. However, the V'_E/V'_{CO_2} is typically much higher at rest and throughout exercise in patients with pulmonary vascular disease compared with patients with HFrEF of the same functional capacity [50–53]. A more challenging clinical scenario is differentiating PAH from heart failure with preserved ejection fraction (HFpEF) when there is PH and the left ventricular systolic function is normal on echocardiogram. Most CPET studies in HFpEF patients report mean V'_E/V'_{CO_2} slope values in the range of 35 to 40 [54–58], which is less than is typically seen in PAH [19, 34, 39, 59]. However, no studies have evaluated the utility of V'_E/V'_{CO_2} slope to discriminate between PAH and HFpEF in patients matched for a similar degree of PH or functional impairment. Approximately 22% of HFpEF patients with PH also have evidence of pulmonary vascular disease (the combined pre- and post-capillary PH phenotype), which is associated with higher mean pulmonary pressure and worse RV function than patients with HFpEF and isolated post-capillary PH [1, 60]. This likely reflects development of intrinsic pulmonary vascular disease in patients with HFpEF from global vascular remodelling in the pulmonary arteries and veins [61]. In patients with HFpEF and PH, the V'_E/V'_{CO_2} correlates with PVR, with higher V'_E/V'_{CO_2} values associated with pulmonary vascular disease and worse outcomes [62]. This is consistent with other studies showing that V'_E/V'_{CO_2} in patients with HFpEF is linked more strongly to V_D/V_T (R^2=0.50) than in patients with HFrEF (R^2=0.30) [54].

Although V'_E/V'_{CO_2} is elevated in patients with PAH and patients with CTEPH, there are important differences between these diseases and V'_E/V'_{CO_2} is often even higher in CTEPH than in PAH (figure 4). Zhai *et al*. compared CPET responses between patients with PAH (n=77) and CTEPH (n=50) who were similar in terms of functional capacity, 6-min walk distance (6MWD) impairment and haemodynamic severity [34]. In patients with CTEPH, the V'_E/V'_{CO_2} slope was significantly higher compared with patients with PAH (50.7±15.2 *versus* 44.4±15, p=0.024). V'_E/V'_{CO_2} at AT was also higher in patients with CTEPH (47.7±12.6 *versus* 42.0±8.5, p=0.008), with higher breathing frequency and V'_E at peak exercise in patients with CTEPH despite comparable peak V'_{O_2} and peak work rate (WR). The V_D/V_T at peak exercise is also higher in patients with CTEPH compared with patients with PAH [34, 63], possibly due to a relatively greater degree of pulmonary vascular obstruction. Akizuki and colleagues recently evaluated whether postural changes in ventilatory parameters could distinguish between PAH and CTEPH in a prospective cohort of 90 patients with suspected PH [64]. In the sitting position, V'_E/V'_{CO_2} was similar between PAH, CTEPH and controls, but V'_E/V'_{CO_2} decreased in controls and patients with PAH and increased in patients with CTEPH when in the supine position. As such, the positional change in V'_E/V'_{CO_2} ($\Delta V'_E/V'_{CO_2}$) was positive in CTEPH and negative in PAH and controls. A $\Delta V'_E/V'_{CO_2}$ >0.8 was able to differentiate CTEPH from PAH (AUC=0.849, sensitivity=78%, specificity=88%), which may be a useful finding to validate since positional V'_E/V'_{CO_2} is noninvasive and not dependent on patient effort during exercise.

The incidence of CTEPH after acute PE is approximately 3% [5]; however, routine screening for CTEPH in patients after an acute PE is currently not recommended [65]. In patients who have dyspnoea after PE, CPET and evaluation of ventilatory efficiency may help detect CTEPH. Several studies have shown that elevated V'_E/V'_{CO_2} can help detect CTEPH after acute PE. Xi and colleagues compared CPET variables between patients with established CTEPH, chronic PE without PH, recovered patients with PE and controls. A V'_E/V'_{CO_2} nadir of $\geqslant$34.35 was the best predictor of CTEPH (odds ratio 159.0, 95% CI 36.0–702.3, p<0.001) [66]. The V'_E/V'_{CO_2} was linearly related to the degree of residual pulmonary vascular obstruction on lung perfusion imaging post-acute PE. McCabe *et al.* demonstrated that CPET findings can distinguish between patients with CTEPH, chronic thromboembolic disease without PH (CTED) and sedentary controls [67]. Patients with CTEPH had a higher V'_E/V'_{CO_2} slope and higher V'_E/V'_{CO_2} at AT compared with CTED and control patients. Interestingly, in this study patients with CTEPH also had significantly higher V_D/V_T than patients with CTED despite a similar degree of pulmonary vascular obstruction between patients with CTEPH and patients with CTED. Among the best variables for differentiating from patients with CTEPH from non-CTEPH patients were the peak exercise V_D/V_T (AUC 0.88, 95% CI 0.67–0.97) and V'_E/V'_{CO_2} at AT (AUC=0.77, 95% CI 0.61–0.92) [67].

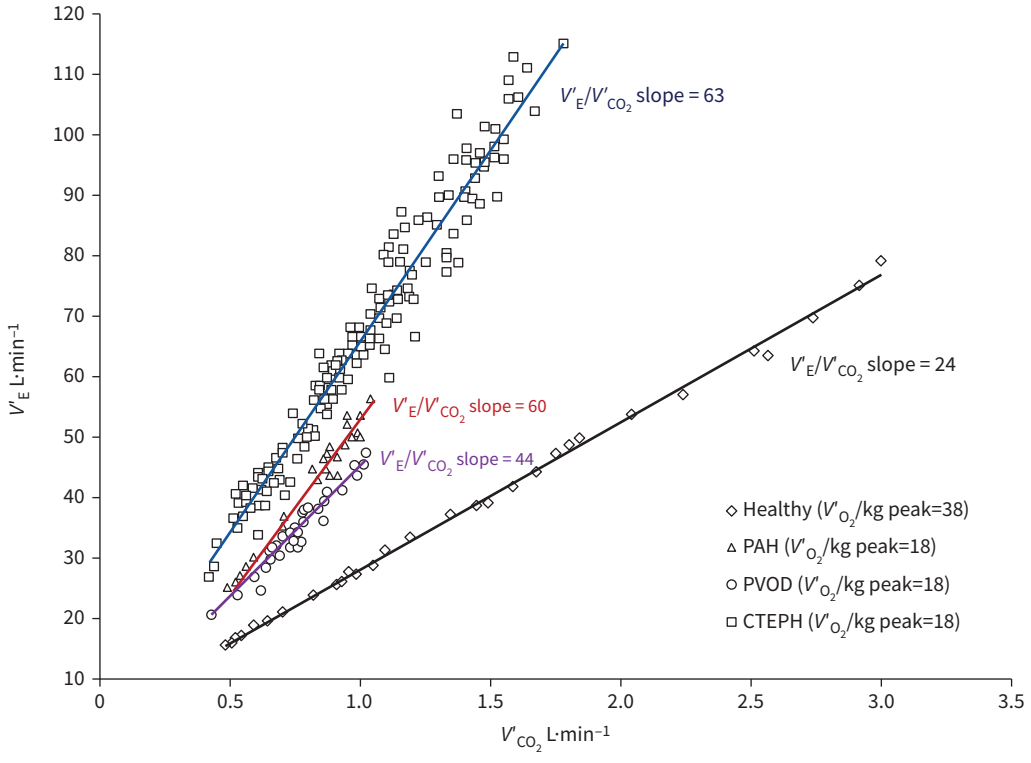

FIGURE 4 Examples of ventilatory efficiency slope (minute ventilation/carbon dioxide production (V'_E/V'_{CO_2}) slope) in a healthy subject presenting with a peak oxygen uptake (V'_{O_2}) of 38 mL·Kg^{-1}·min^{-1} (black line and rhomboid), a patient with pulmonary veno-occlusive disease (PVOD) presenting with a peak V'_{O_2} of 18 mL·Kg^{-1}·min^{-1} (violet line and circles), a patient with pulmonary arterial hypertension (PAH) presenting with a peak V'_{O_2} of 18 mL·Kg^{-1}·min^{-1} (red line and triangles) and a patient with chronic thromboembolic pulmonary hypertension (CTEPH) presenting with a peak V'_{O_2} of 18 mL·Kg^{-1}·min^{-1} (blue line and squares).

Some symptomatic patients with CTEPH will have normal estimated pulmonary arterial pressure on echocardiography or unmeasurable pressure due to insufficient tricuspid valve regurgitation. HELD and colleagues evaluated the utility of CPET to detect CTEPH and found that echocardiograms were normal or had undetectable RV systolic pressure in 31% of patients with confirmed CTEPH [68]. The V'_E/V'_{CO_2} at AT was abnormal in 12/13 (92%) of patients with CTEPH and normal echocardiography, while the V'_E/V'_{CO_2} slope was abnormal in 9/13 (69%).

Pulmonary veno-occlusive disease/pulmonary capillary haemangiomatosis (PVOD/PCH) is a rare condition characterised by a spectrum of pathologic abnormalities of the pulmonary veins and capillaries leading to pre-capillary PH [69]. It is critically important to differentiate PVOD/PCH from PAH as the former group of patients frequently develop pulmonary oedema when treated with PAH therapies, which can cause rapid deterioration and death [70, 71]. Limited data suggest that CPET may be useful to identify PVOD/PCH. Compared with stable patients with PAH with similar haemodynamic severity, patients with PVOD/PCH have lower resting and peak exercise P_{aCO_2}, higher V'_E/V'_{CO_2} slope and V'_E/V'_{CO_2} at AT, and higher peak exercise V_D/V_T [22, 72].

Is V'_E/V'_{CO_2} responsive to treatment of PAH and CTEPH?

Treatments for PAH and CTEPH have evolved over the past few decades with major advances leading to improved outcomes. In PAH, current medical therapies target the nitric oxide (NO), endothelin and prostacyclin pathways, resulting in pulmonary arterial vasodilation along with anti-proliferative effects. PAH therapies that result in acute vasodilation have inconsistent effects on V'_E/V'_{CO_2} even though haemodynamic improvements may occur immediately. Inhaled NO at 20 ppm during constant WR cycle exercise did not improve V'_E/V'_{CO_2} or most other exercise parameters in patients with PAH [73]. Short-term infusion of intravenous epoprostenol resulted in decreased V'_E/V'_{CO_2} in six of 10 patients,

which tended to parallel decreases in total PVR but not changes in mPAP or cardiac index [20]. In a small randomised trial, after 1 week of oral L-arginine (a precursor for NO synthesis) supplementation, the V'_E/V'_{CO_2} slope decreased from 43±4 to 37±3 ($p<0.05$), along with an increase in peak V'_{O_2} from 831±88 to 896±92 mL·min^{-1} ($p<0.05$) [74]. Similarly, in a mixed population of PAH and CTEPH, 3 months of oral beraprost (a prostacyclin derivative) improved V'_E/V'_{CO_2} and peak V'_{O_2} [75]. These studies suggest that high V'_E/V'_{CO_2} and treatment-related improvements are not driven by acute changes in haemodynamics or ventilation-perfusion but by intermediate- or long-term adaptations in autonomic function. Supporting this hypothesis, administration of hyperoxia to patients with PAH and CTEPH (which does not acutely affect haemodynamics or ventilation-perfusion inequality) during exercise resulted in improved exercise performance and a significant decrease in V'_E/V'_{CO_2} along with improved quadriceps and cerebral tissue oxygenation, whereas the V_D/V_T was unchanged [76].

Patients with CTEPH should be evaluated in expert surgical centres and those patients who are considered operable should undergo pulmonary endarterectomy (PEA) surgery [65, 77]. This surgical procedure removes the chronic, fibrotic material obstructing the pulmonary arteries, immediately reducing mPAP and improving pulmonary blood flow [78]. In a study of 20 patients with CTEPH who underwent PEA surgery, the greatest improvements in V'_E/V'_{CO_2} occurred within 1 month of surgery and continued to decrease by 4 months post-operatively. In contrast, the improvement in peak V'_{O_2} was more gradual as observed at 1- and 4-months of follow-up [79]. In this study, the improvements in V'_E/V'_{CO_2} post-PEA were strongly related to the decrease in PVR, whereas changes in V'_{O_2} were not related to PVR improvements. This suggests that: 1) V'_{O_2} improvements are more due to peripheral skeletal muscle adaptation from increased activity; and 2) V'_E/V'_{CO_2} may be a better and earlier noninvasive measure of surgical success.

CTED is defined as persistent obstruction of the pulmonary arteries without PH at rest. Although PH is absent at rest, patients with CTED often have abnormal haemodynamic responses to exercise and may have reduced exercise tolerance and/or experience exertional dyspnoea as a result of exercise-induced PH and ventilatory inefficiency [80, 81]. Interestingly, PEA is performed in some centres for CTED, and can significantly improve exercise haemodynamics, peak V'_{O_2}, V'_E/V'_{CO_2} and quality of life [80, 81].

Balloon pulmonary angioplasty (BPA) is a treatment option for patients with CTEPH or CTED which involves catheter-based angioplasty in the segmental and subsegmental pulmonary arteries [82]. BPA can be considered for patients with CTEPH or CTED who are not operable or who have residual disease after PEA. Several studies have demonstrated that BPA improves haemodynamics and improves ventilatory efficiency [83–87] especially when performed in the lower lung zones, presumably due to relatively larger improvements in V'_A/Q' matching when lower lobe obstruction is present [85]. Interestingly, exercise rehabilitation after BPA further improves V'_{O_2} but has no effect on V'_E/V'_{CO_2} [88]. This reinforces the concept that V'_{O_2} improvements after interventions for CTEPH and CTED include cardiopulmonary and peripheral adaptation, whereas improvements in ventilatory efficiency are primarily driven by improved pulmonary blood flow (reduced PVR and improved V'_A/Q' matching).

What is the prognostic utility of ventilatory efficiency in PAH and CTEPH?

Risk assessment is an essential component of routine care in PAH and CTEPH. A multifaceted approach is recommended by the European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines including assessment of clinical symptoms, functional capacity, RV function and exercise capacity [65]. Ideally, a risk assessment tool should be noninvasive, independently associated with an outcome of interest, sensitive to change from treatment effects, widely available and reproducible. In the 2015 ESC/ERS guidelines, CPET is included as on option to assess prognosis, with V'_{O_2} and V'_E/V'_{CO_2} slope present in the risk assessment table tool as an alternative to 6MWD. When available, CPET is recommended for younger, more fit patients since the threshold on a 6MWD >440 m may be more easily achieved compared with older patients [65]. But how strong is the data to support the use of V'_E/V'_{CO_2} as a tool in risk assessment?

V'_E/V'_{CO_2} has been assessed as a prognostic variable on its own and in conjunction with other standard tools used for risk assessment. Both V'_E/V'_{CO_2} slope and V'_E/V'_{CO_2} at AT have been associated with survival. Schwaiblmair *et al*. demonstrated in a mixed PAH (n=85) and CTEPH (n=31) population that V'_E/V'_{CO_2} was much higher in nonsurvivors than survivors over a 24-month period [89]. A V'_E/V'_{CO_2} at AT >55 was associated with a 7.8-fold relative risk of death at 2 years while a V'_E/V'_{CO_2} slope ⩾60 had a relative risk of 5.75. In this study, V'_{O_2} was not associated with outcomes. Because of the smaller number of patients with CTEPH included this study, groups were not split by aetiology to assess the prognostic value of V'_E/V'_{CO_2} independently in each disease [89]. Wensel *et al*. also showed V'_E/V'_{CO_2} slope was

associated with survival in 70 patients with PAH using univariate analysis [59]. However, peak V'_{O_2} was the only CPET variable independently associated with outcomes in multivariable analysis. OUDIZ *et al*. also reported a hazard ratio of 1.48 for each unit increase in the V'_E/V'_{CO_2} at AT, with a mean value of 54.2 in the nonsurvivor group. Also demonstrated in this study is the prognostic significance of detecting an exercise-induced shunt through a patent foramen ovale during CPET testing, for which an abrupt increase in V'_E/V'_{CO_2} was used as a diagnostic criteria [90].

V'_E/V'_{CO_2} has also been assessed in PAH associated with other conditions. DEBOECK *et al*. reported on patients with idiopathic PAH and patients with PAH associated with other conditions. They found that in idiopathic PAH, V'_E/V'_{CO_2} at AT cut-offs of 54 and 59 were predictive of survival and time to clinical worsening respectively, while in patients with PAH associated with other conditions, no variables were predictive [91]. This may be due to the heterogeneity of underlying diseases in their "associated-PAH group", as it included patients with connective tissue disease, hepatic cirrhosis, human immunodeficiency virus or schistosomiasis. A retrospective study looked at patients with systemic sclerosis, with or without a diagnosis of PAH, and showed a V'_E/V'_{CO_2} slope cut-off of 35 predictive of survival in multivariate analysis. Due to limited numbers, however, they were unable to separately analyse the PAH patients [92]. V'_E/V'_{CO_2} slope was also shown to be predictive of mortality in adult congenital heart disease patients, with the highest slopes being in the Eisenmenger population (71.2±24.6) and the idiopathic pulmonary arterial hypertension population (51.6±15) [93].

FERREIRA *et al*. demonstrated improved prognostic value of V'_E/V'_{CO_2} slope when taken at maximal exercise (V'_E/V'_{CO_2}peak), although the utility of this approach is limited by the patients' ability to reach a maximal effort [94]. Despite this, CPET variables can still be useful even in cases with submaximal effort. Since V'_E/V'_{CO_2} slope calculation does not require that a patient achieves peak effort, the V'_E/V'_{CO_2} slope and its prognostic utility are more flexible than peak values. Indeed, in one study the V'_E/V'_{CO_2} was the only independent correlate of the REVEAL (Registry to Evaluate Early and Long-term PAH Disease Management) registry risk score in multivariate analysis, with a V'_E/V'_{CO_2} slope cut-off of 40.6 discriminating patients having a high-risk REVEAL score (⩾10) with a sensitivity of 92% and specificity of 67% [95]. It remains unclear whether CPET variables, including V'_E/V'_{CO_2}, add prognostic value beyond the REVEAL risk score. Although V'_E/V'_{CO_2} at baseline was predictive of survival and PAH-targeted treatments seemed to improve V'_E/V'_{CO_2}, treatment-related changes in V'_E/V'_{CO_2} slope were not predictive of survival in one study [96].

A key message in recent guidelines and prognostic studies is that risk assessment should be multidimensional and serial over time. Although several of the studies discussed above show that high V'_E/V'_{CO_2} is a marker of poor prognosis, a pivotal question is whether V'_E/V'_{CO_2} adds value to other widely used methods such as echocardiography or invasive haemodynamics. BADAGLIACCA *et al*. prospectively studied the degree of additive benefit of CPET and echocardiography for prognostication in addition to demographic, clinical, haemodynamic and functional class details [97]. The only variables that improved prediction of clinical worsening were peak O_2 pulse and RV fractional area change. Others have also demonstrated that while V'_E/V'_{CO_2} slope as well as V'_E/V'_{CO_2} peak were associated with survival, once multivariate regression was performed, only ΔO_2 pulse added prognostic value [98]. Haemodynamic variables such as PVR and those that reflect RV function (cardiac output, stroke volume, RAP) are also important predictors of prognosis in PAH [32, 99–101]. WENSEL *et al*. evaluated the prognostic value of combining CPET-derived values with haemodynamic data from RHC [102]. They assessed several CPET variables, including V'_E/V'_{CO_2}, and found that only peak V'_{O_2}, PVR and heart rate change during exercise were independently associated with survival. Similarly, another study by BADAGLIACCA *et al*. found that the only CPET parameter independently associated with future clinical worsening was peak V'_{O_2}, while V'_E/V'_{CO_2} did not give additional prognostic information [103].

In summary, there is good evidence that CPET variables, including V'_E/V'_{CO_2}, can be used to measure disease severity and are predictive of survival and time to clinical worsening. However, the utility of V'_E/V'_{CO_2} beyond standard multidimensional prognostication tools requires further investigation.

Conclusion

CPET is a useful tool in the differential diagnosis of dyspnoea. Ventilatory inefficiency during CPET is a hallmark characteristic of PAH and CTEPH which contributes to exercise intolerance and disability in these patients. The mechanisms of ventilatory inefficiency are multiple and include high physiologic dead space, abnormal chemosensitivity and an altered P_{aCO_2} set-point. While normal V'_E/V'_{CO_2} makes pulmonary vascular disease unlikely, the finding of high V'_E/V'_{CO_2} without an alternative explanation should prompt further diagnostic testing to exclude PAH and CTEPH, particularly in patients with risk factors such as prior venous thromboembolism, systemic sclerosis or a family history. In patients with established PAH or CTEPH, the

V'_E/V'_{CO_2} may improve with treatments and is a prognostic marker. Further studies are needed to clarify the added value of assessing ventilatory inefficiency in the longitudinal follow-up of patients.

Previous articles in this series: No. 1: Laveneziana P, Di Paolo M, Palange P. The clinical value of cardiopulmonary exercise testing in the modern era. *Eur Respir Rev* 2021; 30: 200187. **No. 2:** Agnostoni P, Sciomer S, Palermo P, *et al*. Minute ventilation/carbon dioxide production in chronic heart failure. *Eur Respir Rev* 2021; 30: 200141. **No. 3:** Watson M, Ionescu MF, Sylvester K, *et al*. Minute ventilation/carbon dioxide production in patients with dysfunctional breathing. *Eur Respir Rev* 2021; 30: 200182. **No. 4:** Ward SA. Ventilation/carbon dioxide output relationships during exercise in health. *Eur Respir Rev* 2021; 30: 200160. **No. 5:** Collins SÉ, Phillips DB, Brotto AR, *et al.* Ventilatory efficiency in athletes, asthma and obesity. *Eur Respir Rev* 2021; 30: 200206. **No. 6:** Schaeffer MR, Guenette JA, Jensen D. Impact of ageing and pregnancy on the minute ventilation/carbon dioxide production response to exercise. *Eur Respir Rev* 2021; 30: 200225.

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