Exertional ventilation/carbon dioxide output relationship in COPD: from physiological mechanisms to clinical applications

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The minute ventilation/carbon dioxide production relationship is relevant to a number of patient-related outcomes in COPD. Minute ventilation/carbon dioxide production, therefore, should be valued in the clinical management of these patients. https://bit.ly/3df2upH

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Abstract

There is well established evidence that the minute ventilation (V'_E)/carbon dioxide output (V'_{CO_2}) relationship is relevant to a number of patient-related outcomes in COPD. In most circumstances, an increased V'_E/V'_{CO_2} reflects an enlarged physiological dead space ("wasted" ventilation), although alveolar hyperventilation (largely due to increased chemosensitivity) may play an adjunct role, particularly in patients with coexistent cardiovascular disease. The V'_E/V'_{CO_2} nadir, in particular, has been found to be an important predictor of dyspnoea and poor exercise tolerance, even in patients with largely preserved forced expiratory volume in 1 s. As the disease progresses, a high nadir might help to unravel the cause of disproportionate breathlessness. When analysed in association with measurements of dynamic inspiratory constraints, a high V'_E/V'_{CO_2} is valuable to ascertain a role for the "lungs" in limiting dyspnoeic patients. Regardless of disease severity, cardiocirculatory (heart failure and pulmonary hypertension) and respiratory (lung fibrosis) comorbidities can further increase V'_E/V'_{CO_2}. A high V'_E/V'_{CO_2} is a predictor of poor outcome in lung resection surgery, adding value to resting lung hyperinflation in predicting all-cause and respiratory mortality across the spectrum of disease severity. Considering its potential usefulness, the V'_E/V'_{CO_2} should be valued in the clinical management of patients with COPD.

Introduction

It has been well established that changes in minute ventilation (V'_E) are tightly coupled to the rate at which metabolically produced carbon dioxide (CO_2) is released by the lungs during exercise (V'_{CO_2}, *i.e.* venous return × mixed-venous CO_2 content) [1, 2]. The submaximal ventilatory demands are particularly relevant to set the limits of exercise tolerance in patients with reduced ventilatory capacity, *e.g.* those suffering from COPD [3, 4]. In fact, relatively minor increases in the V'_E/V'_{CO_2} relationship are expected to have a large impact on the rate at which V'_E reaches a relatively-fixed "ceiling" (as roughly estimated by the maximal breathing capacity, for example (supplementary figure S1) [5].

As discussed elsewhere in this series, the V'_E required to wash out a given rate of V'_{CO_2} is inversely related to the arterial partial pressure for CO_2 (P_{aCO_2}) (since more alveolar ventilation is needed to maintain the P_{aCO_2} at a low compared to a high value), and positive related to the fraction of tidal volume (V_T) "wasted" in the dead space (V_D), *i.e.* the higher the physiological ($_{phys}$) V_D/V_T [1]. Since the P_{aCO_2} is maintained relatively constant as V'_{CO_2} increases (at least during moderate exercise) (supplementary figure S2c) [1], the

hyperbolic decrease in V_D/V_{Tphys} (supplementary figure S2a) is accompanied by a similar decrease in the V'_E/V'_{CO_2} ratio towards a minimum value ("nadir") (supplementary figure S2b) [6]. Thus, when V'_E is plotted as a function of V'_{CO_2} during an incremental cardiopulmonary exercise test, a linear relationship with a positive y-intercept emerges (supplementary figure S2d). In this context, increases in the intercept and/or in the slope can lead to a high V'_E/V'_{CO_2} nadir [7]. From a physiological standpoint, the higher the V_D/V_{Tphys} and the lower the P_{aCO_2} set-point, the higher the V'_E/V'_{CO_2} nadir [2]. The V_D/V_{Tphys} is the lowest at the V'_E/V'_{CO_2} nadir (supplementary figure S2a and b), allowing a more accurate estimation of the wasted ventilation. Moreover, the V'_E/V'_{CO_2} nadir has been found to be highly reproducible in normal subjects [8] and in patients with COPD [9].

In the present review we update and expand a previous review on the V'_E/V'_{CO_2} relationship published in 2017 in the *European Respiratory Journal* [10]. Although a high V'_E/V'_{CO_2} has been widely termed "ventilatory inefficiency" or "excess ventilation" [11–14], we avoid this terminology herein, because, as discussed below, substantial inefficiency (*i.e.* increased wasted V'_E) may coexist with a relatively preserved, or even reduced, V'_E/V'_{CO_2} in patients with COPD. After a concise overview on the structural and functional determinants of V'_E/V'_{CO_2} in COPD, we focus on its relevance to exertional dyspnoea and exercise tolerance, exploring the clinical scenarios in which the measurement may add to resting clinical assessment. Additionally, we provide evidence on how V'_E/V'_{CO_2} may allow us to better judge the functional impact of comorbidities, assess future risk and prognosis, and determine the effects of selected therapeutic interventions on patients' exercise tolerance (table 1). Finally, we outline some key gaps in knowledge that might benefit from additional research (table 2).

Structural and functional determinants of V'_E/V'_{CO_2} in COPD

Several studies have shown that an increased V_D/V_{Tphys}, partially due to emphysema [21, 23, 25, 28, 96, 97], constitutes an important correlate of a high V'_E/V'_{CO_2}. As discussed later, this is particularly true in patients who are not severely compromised from the mechanical standpoint, *i.e.* those who are able to increase V'_E in an attempt to overcome an increased alveolar V_D. There is some limited evidence that the increased V_D/V_{Tphys} is more closely related to an enlarged alveolar V_D *per se* rather than a small V_T [20]. Additionally, external (series) V_D predictably increased V'_E/V'_{CO_2} [18]. As in many chronic pulmonary diseases, increased regional [98], and, in some patients, "mean" alveolar ventilation/perfusion (V'/Q') ratio heterogeneity and diffusion limitation [99] are probably related to a high V_D/V_{Tphys} in COPD [100].

Impaired pulmonary perfusion of non-emphysematous areas [101] may also contribute to high V_D/V_{Tphys} and V'_E/V'_{CO_2} in a highly variable combination in subjects with similar forced expiratory volume in 1 s (FEV_1) [19, 97]. It is noteworthy that a low transfer factor of the lung for carbon monoxide (T_{LCO}), which is notoriously influenced by V'/Q' abnormalities [102], has been inversely related to V'_E/V'_{CO_2} in recent studies [22, 27]. Patients unable to expand gas exchange surface area (as assessed with T_{LCO} during exercise) relative to pulmonary blood flow showed a higher V'_E/V'_{CO_2} and a lower exercise capacity [24]. In addition, patients with mild COPD and high V'_E/V'_{CO_2} ($\geqslant$34) had lower T_{LCO} and pulmonary capillary blood volume response to exercise [26]. It is conceivable that the cross-relationships among V'_E/V'_{CO_2}, V_D/V_{Tphys} and T_{LCO} represent, in addition to emphysema, a complex combination of the effects of accelerated pulmonary vascular ageing in smokers [103], destruction/dysfunction of the alveolar–capillary bed [101], and, in some patients, hypoxic pulmonary vasoconstriction [104]. In any case, the pulmonary vascular abnormalities may progress to overt pulmonary hypertension in selected patients, an important cause of a high V'_E/V'_{CO_2} (see the section on Impact of COPD comorbidities on V'_E/V'_{CO_2}).

Alveolar hyperventilation is another potential cause of a high V'_E/V'_{CO_2} in COPD [1, 2]. A chronically low P_{aCO_2} (likely due to heightened chemostimulation) [105] may shift the level at which it is centrally regulated ("set-point") downward [106], in a vicious circle. The relative contribution of a low P_{aCO_2} to a high V'_E/V'_{CO_2} remains elusive, being probably more relevant in those with cardiocirculatory comorbidities (see the section on Impact of COPD comorbidities on V'_E/V'_{CO_2}). For instance, Elbehairy *et al.* [20] found that P_{aCO_2} was inversely related to V'_E/V'_{CO_2}, though to a lesser extent than V_D/V_{Tphys}, in a group of patients with preserved FEV_1. Heightened stimulation of mechano- and metaboreceptors in the peripheral muscles ("ergoreceptors") [83] may also contribute to alveolar hyperventilation in selected patients.

It should be noted that the contribution of alveolar hyperventilation to a high V'_E/V'_{CO_2} in COPD is likely to be overestimated if one considers the end-tidal partial pressure for CO_2 (P_{ETCO_2}) rather than the P_{aCO_2} [107]. This is the case because V'/Q' abnormalities, specifically, alveolar V_D, are known to decrease P_{ETCO_2} at a given P_{aCO_2} [108] (as the former is diluted in the V_D/V_{Tphys}); an effect that increases as exercise intensifies [20]. The topic is further complicated by the fact that V_D/V_{Tphys} and P_{aCO_2} are not

TABLE 1 Overview of cardiopulmonary exercise testing-based studies on the minute ventilation (V'_E)/carbon dioxide output (V'_{CO_2}) relationship in different clinical scenarios in COPD

	Subjects n	Disease severity	Main result
Structural and functional determinants			
O'Donnell (2002) [15]	20	FEV_1 34±3%	⇓ V'_E at a given V'_{CO_2} in CO_2 retainers compared to non-retainers
Nakamoto (2007) [16]	10	FEV_1 27–70%	V'_E–V'_{CO_2} slope not related to increased muscle ergoreflex activity
Paoletti (2011) [17]	16	FEV_1 54±18%	⇓ V'_E–V'_{CO_2} slope in more extensive emphysema
Chin (2013) [18]	40	FEV_1 87±11%	⇑ $V'_E/V'_{CO_2}$with added external dead space in mild COPD
Neder (2015) [19]	276	GOLD 1–4	⇑ V'_E–V'_{CO_2} slope associated with ventilation inhomogeneity in GOLD 1 and 2
Elbehairy (2015) [20]	22	FEV_1 94±10%	⇑ V'_E/V'_{CO_2} associated with greater V_D/V_{Tphys} in symptomatic GOLD 1
Crisafulli (2016) [21]	51	FEV_1 55±16%	⇑ V'_E–V'_{CO_2} slope associated with emphysema extension on chest CT
Elbehairy (2017) [22]	62	FEV_1 65±8%	⇑ V'_E/V'_{CO_2} associated with ⇓ T_{LCO} and ⇓ V'_{O_2} peak in smokers with mild obstruction
Jones (2017) [23]	19	FEV_1 82±13%	⇑ V'_E/V'_{CO_2} linked ⇑ emphysema and ⇓ T_{LCO} to exercise intolerance in mild COPD
Behnia (2017) [24]	32	FEV_1 56±16%	⇑ V'_E/V'_{CO_2} inversely related to exercise T_{LCO}
Smith (2018) [25]	67	GOLD 1–4	⇑ V'_E/V'_{CO_2} positively related to emphysema extent
Tedjasaputra (2018) [26]	17	FEV_1 94±11%	V'_E/V'_{CO_2} nadir ⩾34 associated with ⇓ pulmonary capillary blood volume and ⇑ dyspnoea
Elbehairy (2019) [27]	300	FEV_1 61±25%	⇑ V'_E/V'_{CO_2} nadir in tandem with progressively ⇓ T_{LCO} across FEV_1 and IC tertiles
Rinaldo (2020) [28]	50	FEV_1 56±16%	⇑ V'_E/V'_{CO_2} nadir in patients with an emphysematous phenotype
Influence on physiological and sensory responses to exercise			
Palange (2000) [29]	9	FEV_1 <50%	⇑ V'_E–V'_{CO_2} slope in walking than cycling
Ofir (2008) [30]	42	FEV_1 91±8%	⇑ V'_E/V'_{CO_2} nadir in smokers with chronic dyspnoea
Ora (2009) [31]	36	FEV_1 49±10%	⇓ V'_E/V'_{CO_2} nadir in obese patients with COPD
Guenette (2011) [32]	64	FEV_1 86±11%	No sex effect on V'_E/V'_{CO_2} nadir
Caviedes (2012) [33]	35	FEV_1 59±22%	⇑ V'_E/V'_{CO_2} nadir associated with lower maximal exercise capacity
Teopompi (2014) [34]	56	FEV_1 26–80%	⇑ V'_E–V'_{CO_2} intercept related to greater dynamic hyperinflation ⇑ V'_E–V'_{CO_2} slope associated with lower maximal exercise capacity
Guenette (2014) [35]	32	FEV_1 93±9%	⇑ V'_E/V'_{CO_2} throughout incremental exercise in mild COPD
Ciavaglia (2014) [36]	12	FEV_1 60±13%	No effect of exercise modality on V'_E/V'_{CO_2} in obese patients with COPD
Barron (2014) [9]	24	FEV_1 60±13%	V'_E/V'_{CO_2} nadir showed excellent test–retest reliability (superior to V'_E–V'_{CO_2} slope) V'_E/V'_{CO_2} nadir showed better test–retest reliability in COPD than HF
O'Donnell (2014) [37]	208	GOLD 1 and 2	⇑ V'_E/V'_{CO_2} throughout incremental treadmill tests in GOLD 1 and 2
Elbehairy (2015) [38]	20	FEV_1 91±10%	⇑ V'_E/V'_{CO_2} nadir in GOLD grade 1B
Neder (2015) [39]	316	GOLD 1–4	⇑ V'_E–V'_{CO_2} intercept from GOLD 1 to 4 associated with exertional dyspnoea ⇑ V'_E–V'_{CO_2} slope in GOLD 1 and 2, but lower slopes in GOLD 3 and 4
Faisal (2016) [40]	48	FEV_1 63±22%	⇑ V'_E/V'_{CO_2} in COPD and ILD presenting with similar resting inspiratory capacity
Elbehairy (2016) [41]	20	FEV_1 101±13%	Similar V'_E–V'_{CO_2} in smokers without COPD and healthy controls
Crisafulli (2018) [42]	254	FEV_1 51±14%	V'_E–V'_{CO_2} slope >32 and inspiratory constraints associated with impaired HR recovery
Bravo (2018) [43]	16	FEV_1 42±9%	⇑ V'_E/V'_{CO_2} accelerates mechanical constraints and dyspnoea during interval exercise
Neder (2019) [44]	288	GOLD 1–4	Ventilatory inefficiency and inspiratory constraints best predicted dyspnoea severity
Kuint (2019) [45]	20	FEV_1 63±21%	Worsening gas trapping associated with lower $\Delta V'_E/V'_{CO_2}$ peak-nadir
Neder (2020) [46]	284	GOLD 1–4	Resting V'_E/V'_{CO_2} predicts V'_E/V'_{CO_2} nadir and exertional dyspnoea
Neder (2020) [5]	NA	NA	Regardless of ventilatory capacity, major ⇓ in modelled WR peak as V'_E/V'_{CO_2} ⇑
Influence of comorbidities			
Holverda (2008) [47]	25	NA	⇑ V'_E/V'_{CO_2} nadir associated with mean pulmonary artery pressure
Vonbank (2008) [48]	42	FEV_1 1.1±0.5 L	⇑ V'_E/V'_{CO_2} rest and peak in patients with associated PAH
Boerrigter (2012) [49]	47	FEV_1 55±17%	Pronounced ⇑ V'_E–V'_{CO_2} slope in a sub-group (n=9) with severe PAH
Thirapatarapong (2013) [50]	48	FEV_1 31±10%	No effect of β-blockers on V'_E/V'_{CO_2} nadir in a retrospective study

Continued

TABLE 1 Continued

	Subjects n	Disease severity	Main result
Thirapatarapong (2014) [51]	98	FEV_1 20±7%	No association of V'_E/V'_{CO_2} peak with PAH in severe to very severe COPD
Teopompi (2014) [52]	46	FEV_1 52±16%	⇓ V'_E–V'_{CO_2} slope in COPD compared to HF in patients with poorer exercise capacity ⇑ V'_E–V'_{CO_2} intercept in COPD compared to HF
Thirapatarapong (2014) [53]	108	FEV_1 26±14%	⇑ V'_E/V'_{CO_2} nadir in COPD patients with coexistent coronary artery disease
Apostolo (2015) [54]	95	FEV_1 53±13%	⇑ V'_E–V'_{CO_2} intercept in COPD and COPD-HF compared to HF
Arbex (2016) [55]	98	FEV_1 55±17%	⇑ V'_E–V'_{CO_2} slope and V'_E/V'_{CO_2} nadir in COPD-HF compared to COPD ⇓ V'_E–V'_{CO_2} intercept in COPD-HF compared to COPD
Rocha (2016) [56]	68	FEV_1 60±18%	⇑ V'_E–V'_{CO_2} slope in COPD-HF with exercise oscillatory ventilation
Rocha (2017) [57]	22	FEV_1 60±11%	⇑ V'_E/V'_{CO_2} more associated with hyperventilation than ⇑ $V_D/V_{T\,phys}$ in COPD-HF
Muller (2018) [58]	40	FEV_1 43±13%	V'_E/V'_{CO_2} not related to diastolic dysfunction
Cherneva (2019) [59]	104	FEV_1 1.4±0.4 L	⇑ V'_E–V'_{CO_2} slope associated with stress-induced diastolic dysfunction
Smith (2019) [60]	22	FEV_1 60±11%	⇑ V'_E–V'_{CO_2} intercept in COPD compared to HF with preserved and low ejection fraction
Goulart (2020) [61]	10	FEV_1 1.6±0.1 L	⇑ V'_E–V'_{CO_2} slope associated with disease severity in COPD-HF
Costa (2020) [62]	42	FEV_1 52±14%	⇑ V'_E/V'_{CO_2} was a key correlate of dyspnoea and exercise intolerance in CPFE
Plachi (2020) [63]	28	NA	Mechanical constraints modulate dyspnoea-V'_E differently in COPD and HF
Risk assessment/prognosis			
Torchio (2010) [64]	145	FEV_1 73±16%	⇑ V'_E–V'_{CO_2} slope predicted mortality after lung resection surgery
Brunelli (2012) [65]	70	FEV_1 81±18%	V'_E–V'_{CO_2} slope >35 predicted poor outcome after lung resection surgery
Shafiek (2016) [66]	55	FEV_1 60±17%	V'_E–V'_{CO_2} slope >35 predicted poor outcome after lung resection surgery
Neder (2016) [67]	288	FEV_1 18–148%	V'_E/V'_{CO_2} nadir >34 added to resting hyperinflation to predict mortality
Alencar (2016) [68]	30	FEV_1 57±17%	V'_E/V'_{CO_2} nadir >34 and right ventricular function predicted mortality in COPD-HF
Torchio (2017) [69]	263	GOLD 1–4	⇑ V'_E–V'_{CO_2} slope was the best predictor of death after pneumonectomy
Miyazaki (2018) [70]	974	FEV_1 78±23%	V'_E–V'_{CO_2} slope predicted 90-day and 2-year survival after lung resection for cancer
Ellenberger (2018) [71]	151	FEV_1 82±21%	V'_E/V'_{CO_2} nadir >40 predicted 4-year survival after lung resection for cancer
Crisafulli (2018) [42]	254	FEV_1 51±14%	⇑ V'_E–V'_{CO_2} slope associated with a delay in post-exercise heart rate
Effects of interventions			
Orens (1995) [72]	5	FEV_1 57±4%	Single lung Tx decreased V'_E/V'_{CO_2} peak
Somfay (2001) [73]	10	FEV_1 31±10%	Decrements in V'_E with hyperoxia correlated with decreases in V'_{CO_2}
O'Donnell (2001) [74]	11	FEV_1 31±3%	Proportional decrements V'_E and V'_{CO_2} with hyperoxia in advanced COPD
O'Donnell (2004) [75]	23	FEV_1 42±3%	Salmeterol proportionally increased V'_E and V'_{CO_2} during constant work rate exercise
Palange (2004) [76]	12	FEV_1 <50% pred	Heliox increased V'_E/V'_{CO_2} during constant work rate exercise
O'Donnell (2004) [77]	187	FEV_1 44±13%	⇑ V'_E (due to higher V_T) at a given V'_{CO_2} with tiotropium compared to placebo
Porszasz (2005) [78]	24	FEV_1 36±8%	Exercise training proportionally reduced V'_E and V'_{CO_2} during constant exercise
Bobbio (2005) [79]	11	FEV_1 53±20%	Lobectomy increased V'_E–V'_{CO_2} slope
Eves (2006) [80]	10	FEV_1 47±17%	Normoxic heliox increased V'_E/V'_{CO_2} more than hyperoxic heliox
Chiappa (2009) [81]	12	FEV_1 45±13%	Heliox increased V'_E/V'_{CO_2} during constant work rate exercise
Habedank (2011) [82]	8	NA	Bilateral lung Tx decreased V'_E–V'_{CO_2} slope
Gagnon (2012) [83]	8	FEV_1 7±8%	Spinal anesthesia reduced V'_E/V'_{CO_2} during constant work rate exercise

Continued

TABLE 1 Continued

	Subjects n	Disease severity	Main result
Kim (2012) [84]	1475	FEV_1 <45%	LVRS reduced V'_E/V'_{CO_2} during unloaded exercise
Guenette (2013) [85]	15	FEV_1 86±15%	⇑ V'_E/V'_{CO_2} at isotime with fluticasone/salmeterol compared to placebo
Queiroga (2013) [86]	24	FEV_1 35±10%	Heliox increased V'_E/V'_{CO_2} during constant work rate exercise
Armstrong (2015) [87]	55	FEV_1 26±7%	LVRS reduced V'_E/V'_{CO_2} peak and nadir
Gloeckl (2017) [88]	10	FEV_1 38±8%	No effect of whole-body vibration training on V'_E/V'_{CO_2} in severe COPD
Langer (2018) [89]	20	FEV_1 47±19%	No effect of inspiratory muscle training on V'_E/V'_{CO_2} during constant-WR exercise
O'Donnell (2018) [90]	14	FEV_1 62±10%	No effect of dual bronchodilation on V'_E/V'_{CO_2} during constant-WR exercise
Behnia (2018) [91]	25	FEV_1 1.5±0.6 L	No effect of dietary nitrate supplementation on V'_E/V'_{CO_2} nadir
Elbehairy (2018) [92]	20	FEV_1 50±15%	No effect of acute bronchodilation on V_D/V_T and V'_E/V'_{CO_2}
Perrotta (2019) [93]	25	FEV_1 61±22%	⇓ V'_E–V'_{CO_2} slope and ⇑ peak V'_{O_2} after high-intensity exercise training
Gravier (2019) [94]	50	FEV_1 62±19%	No effect of pulmonary rehabilitation on lung cancer patients undergoing PR
Hasler (2020) [95]	20	FEV_1 64±19%	⇓ V'_E/V'_{CO_2} and ⇑ WR peak with supplemental O_2 in non-hypoxaemic patients

⇓: decreased; ⇑: increased; FEV_1: forced expiratory volume in 1 s; CO_2: carbon dioxide; GOLD: Global Initiative for Chronic Obstructive Lung Disease; V_D/V_{Tphys}: physiological dead space; CT: computed tomography; T_{LCO}: transfer factor of the lung for carbon monoxide; V'_{O_2}: oxygen uptake; IC: inspiratory capacity; HF: heart failure; ILD: interstitial lung disease; NA: not available/not applicable; WR: work rate; PAH: pulmonary arterial hypertension; CPFE: combined pulmonary fibrosis and emphysema; Tx: transplant; LVRS: lung volume reduction surgery; PR: pulmonary rehabilitation; O_2: oxygen; V_T: tidal volume; HR: heart rate.

independent variables. For instance, the extent to which the mean alveolar CO_2 tension decreases in response to hyperventilation (high overall ratio alveolar V'/Q') is underestimated by P_{aCO_2}, thereby artificially increasing V_D/V_{Tphys} as measured by the Bohr–Enghoff method [109, 110]. Moreover, larger fluctuations in end-capillary CO_2 pressure due to a high V_D/V_{Tphys} may overstimulate the peripheral and central chemoreceptors, leading to a low P_{aCO_2} [111].

It remains unclear whether the V'_E–V'_{CO_2} slope and the V'_E intercept have specific structural and physiological determinants in COPD. The addition of external V_D had a more discernible effect on the V'_E intercept than the V'_E–V'_{CO_2} slope both in health [110, 112, 113] and mild COPD [18]. However, a high intercept may merely reflect the expected effect of shallow slope (secondary to worsening mechanical constraints; figure 1), independent of the V_D [39, 114]. In individual cases, there is some disconnection between the directional changes of slope and intercept, suggesting that they may provide additive information [39, 54]. As outlined in table 2, relating V'_E–V'_{CO_2} slope and V'_E intercept to structural abnormalities (emphysema burden, microvascular abnormalities, small airways disease) and CO_2 chemosensitivity might shed new light on this topic.

Influence of V'_E/V'_{CO_2} on the physiological and sensory responses to exercise in COPD

A substantial body of evidence has been accumulated pointing out abnormalities in the V'_E/V'_{CO_2} relationship across the spectrum of COPD severity (table 1). In particular, a high V'_E/V'_{CO_2} has been consistently found in dyspnoeic patients with preserved or only mildly reduced FEV_1 (supplementary figure S3) [18, 20, 35, 37–39, 115]. A high V'_E/V'_{CO_2} nadir in flow-limited patients accelerates the rate of dynamic lung hyperinflation and earlier attainment of critical dynamic inspiratory constraints [116]. In fact, the rate of decline of the dynamic inspiratory reserve volume to its minimal value is superior to conventional "breathing reserve" at peak exercise in the assessment of exertional dyspnoea in mild to advanced COPD [44] (figure 2). Patients showing a high V'_E/V'_{CO_2} also showed a low tolerance to short bursts of high-intensity interval exercise, an exercise modality which is associated with more preserved breathing reserve [43]. Interestingly, a recent study found that even a high resting V'_E/V'_{CO_2}, if associated with a low inspiratory capacity, predicts the burden of exertional dyspnoea in patients with COPD [46]. Therefore, a high V'_E/V'_{CO_2} and the dynamic inspiratory constraints, are jointly relevant to explain increased exertional dyspnoea and poor exercise capacity in COPD compared with age-matched healthy

TABLE 2 Key unanswered questions on the mechanisms and consequences of minute ventilation (V'_E)/carbon dioxide output (V'_{CO_2}) abnormalities in COPD

Exercise intolerance	What are the structural determinants of increased V_D/V_{Tphys} in milder disease? What is the relevance of alveolar hyperventilation to increase V'_E/V'_{CO_2}? Does it change with disease severity? What is the physiological meaning (if any) of the V'_E–V'_{CO_2} intercept? Is the V'_E/V'_{CO_2} consistently associated with specific disease phenotypes? How does very severe, end-stage disease influence V'_E/V'_{CO_2}? Is resting V'_E/V'_{CO_2} useful to predict exercise intolerance and dyspnoea in patients unable to exercise?
Influence of comorbidities	Do emphysema severity and COPD phenotype influence V'_E/V'_{CO_2} in COPD-HF? Do HF aetiology and HF with preserved ejection fraction influence V'_E/V'_{CO_2} in COPD-HF? What is the effect of exertional hypoxia on V'_E/V'_{CO_2} in hypoxaemic patients with COPD-HF? Does V'_E/V'_{CO_2} relate to right ventricular–pulmonary arterial coupling in COPD? How does the severity of restriction influence V'_E/V'_{CO_2} in CPFE?
Risk assessment/ prognosis	Why does a high V'_E/V'_{CO_2} predict poor peri-operative outcome in lung resection surgery? What is the best V'_E/V'_{CO_2} parameter to predict poor surgical outcome across the spectrum of disease severity? Does V'_E/V'_{CO_2} independently predict poor outcome in severe to very severe patients? How to best associate V'_E/V'_{CO_2} with clinical data to determine prognosis? Does the longitudinal assessment of V'_E/V'_{CO_2} improve prognosis estimation?
Effects of interventions	What is the most sensitive parameter to detect improvement in V'_E/V'_{CO_2}? Can exercise training and/or inspiratory muscle training improve V'_E/V'_{CO_2} in selected patients? Do interventions aimed to improve pulmonary vascular function impact on V'_E/V'_{CO_2}? Is there any beneficial effect of specific pharmacological interventions on V'_E/V'_{CO_2} in COPD-HF and disproportionate pulmonary hypertension? Can long-term bronchodilation improve V'_E/V'_{CO_2} in selected patients?

V_D/V_{Tphys}: physiological dead space; HF: heart failure; CPFE: combined pulmonary fibrosis and emphysema.

controls [18, 20, 35, 37–39, 117, 118]. Interestingly, V'_E/V'_{CO_2} nadir was increased in dyspnoeic [30], but not in asymptomatic [41], smokers. These findings are consistent with the notion that a high V'_E/V'_{CO_2} is linked to exertional dyspnoea since the early stages of the disease [117].

There is sound evidence that V_D/V_{Tphys} worsens as heart failure [119–121] and COPD (as reviewed by O'Donnell *et al.* [118]) progress. However, it is interesting to note that while the V'_E–V'_{CO_2} slope is higher (and the V'_E intercept is lower) in patients with more severe heart failure [11–14, 122], the former decreases (and the latter increases) in severe to very severe COPD. Consequently, the V'_E/V'_{CO_2} nadir may remain stable (albeit higher compared to a healthy subject) if the effects of a low V'_E–V'_{CO_2} slope is cancelled out by a high V'_E intercept in severe to very severe COPD (figure 1) [39, 123]. In a large cross-sectional study, worsening dynamic hyperinflation, greater exertional dyspnoea and poorer exercise tolerance were associated with lower V'_E–V'_{CO_2} slope and higher V'_E intercept [39]. Thus, a lower V'_E–V'_{CO_2} slope in advanced COPD is largely explained by worsening mechanical constraints [45, 118] and, in end-stage disease, by a high P_{aCO_2} [15, 114]. Of note, obesity in COPD also decreased V'_E/V'_{CO_2} nadir, probably due to greater ventilatory constraints [31] and, conceivably, a higher P_{aCO_2} set-point in severely obese patients. Teasing out the relative contribution of severe mechanical constraints *versus* a blunted CO_2 chemosensitivity to decrease the V'_E–V'_{CO_2} slope constitutes a formidable challenge, since these abnormalities are intrinsically linked as COPD evolves [118].

Impact of COPD comorbidities on V'_E/V'_{CO_2}

Pulmonary arterial hypertension (PAH) [124, 125], systolic heart failure [11–14, 122] and, to a lesser extent, coronary artery disease [126] are well known causes of a high V'_E/V'_{CO_2}. The underlying mechanisms are multiple, probably involving heightened ventilatory drive from chemo-, baro- and ergoreceptors and a high V_D/V_{Tphys} [127]. Accordingly, patients with COPD and comorbid PAH do present with a high V'_E/V'_{CO_2} [47, 48] with the steepest V'_E–V'_{CO_2} slope found in severe, out-of-proportion

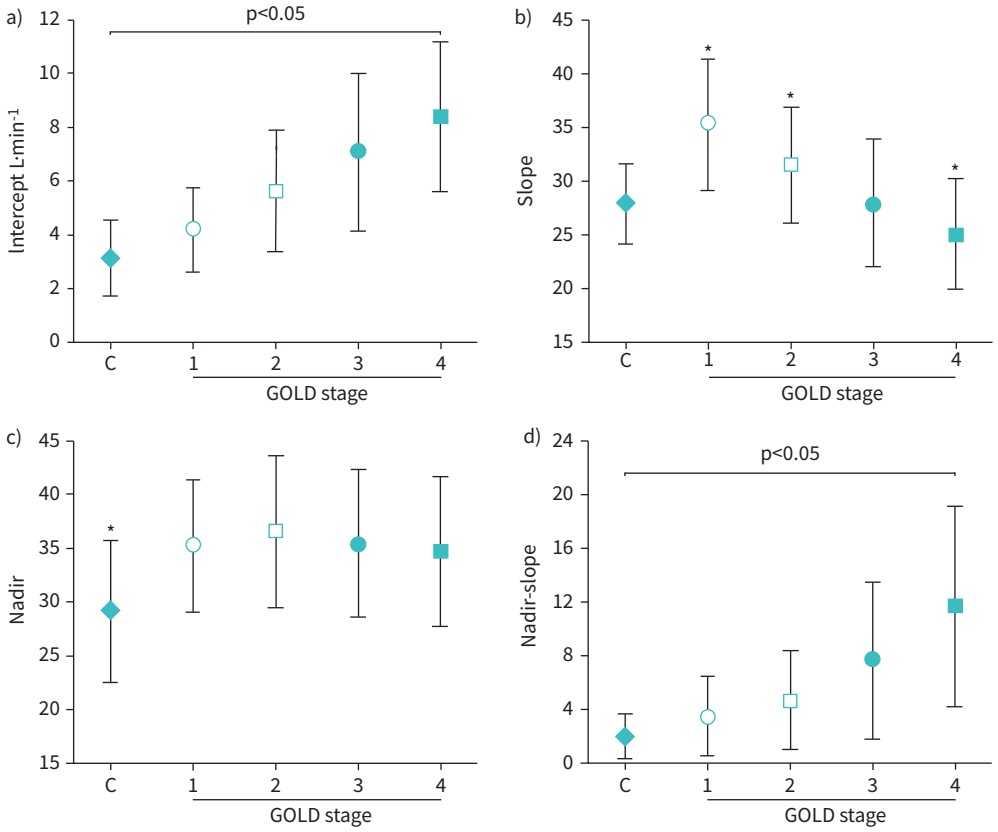

FIGURE 1 Effects of COPD severity on different parameters of the minute ventilation (V'_E)/carbon dioxide output (V'_{CO_2}) relationship. a) V'_E/V'_{CO_2} intercept increased and b) V'_E/V'_{CO_2} slope diminished as the disease progressed from Global Lung Initiative for Chronic Obstructive Lung Disease (GOLD) spirometric stages 1 to 4. c) As the V'_E/V'_{CO_2} nadir depends on both slope and intercept, it remained elevated (compared to controls (C)) across disease stages. d) Increasing nadir-slope differences from GOLD stages 1 to 4 reflects the impact of a progressively higher intercept. Data are presented as mean±SD. *: p<0.05 different from controls. Reproduced with permission [39].

pulmonary hypertension [49]. In keeping with the concept that the mechanical constraints typical of advanced COPD may blunt the ventilatory response to exertion, the V'_E–V'_{CO_2} slope did not differ in patients with severe *versus* very severe COPD who presented with coexistent PAH [51].

There is mounting evidence that patients with comorbid COPD–heart failure with reduced left ventricular ejection fraction present with higher V'_E–V'_{CO_2} slope but lower V'_E intercept than patients with COPD in isolation [52, 54, 55, 60]. However, if the former patients are compared with those with heart failure alone, they show higher V'_E intercept [54, 60]. In other words, patients with COPD–heart failure typically show intermediate V'_E–V'_{CO_2} slope and V'_E intercept compared to those with each disease alone. These findings are likely explained by the increased ventilatory stimuli brought by heart failure being partially counterbalanced by the mechanical constraints (and increased P_{aCO_2} in more advanced disease) induced by COPD [128, 129]. Of note, Arbex *et al.* [55] found that exertional dyspnoea and exercise intolerance were significantly related to the overall ventilatory response to exertion in COPD–heart failure. The study by Rocha *et al.* [57] highlighted the importance of alveolar hyperventilation to increase V'_E/V'_{CO_2} and dyspnoea at a given V_D/V_{Tphys} in COPD–heart failure (supplementary figure S4). In another investigation, these authors found that COPD–heart failure patients showing impaired aerobic function (as indicated by a blunted increase in oxygen uptake (V'_{O_2}) as a function of work rate, suggesting impaired oxygen delivery) had a higher V'_E/V'_{CO_2} than their counterparts with more preserved aerobic metabolism [130]. These findings provide indirect support for a link between increased ergoreceptor activation and a high V'_E/V'_{CO_2} [83] caused (or worsened) by a cardiovascular comorbidity [115]. Periodic breathing, specifically ventilatory oscillations, induced by heart failure, a phenomenon associated with increased V_D/V_{Tphys} and V'_E/V'_{CO_2} [127], is associated with increased dyspnoea and reduced exercise tolerance in the presence of

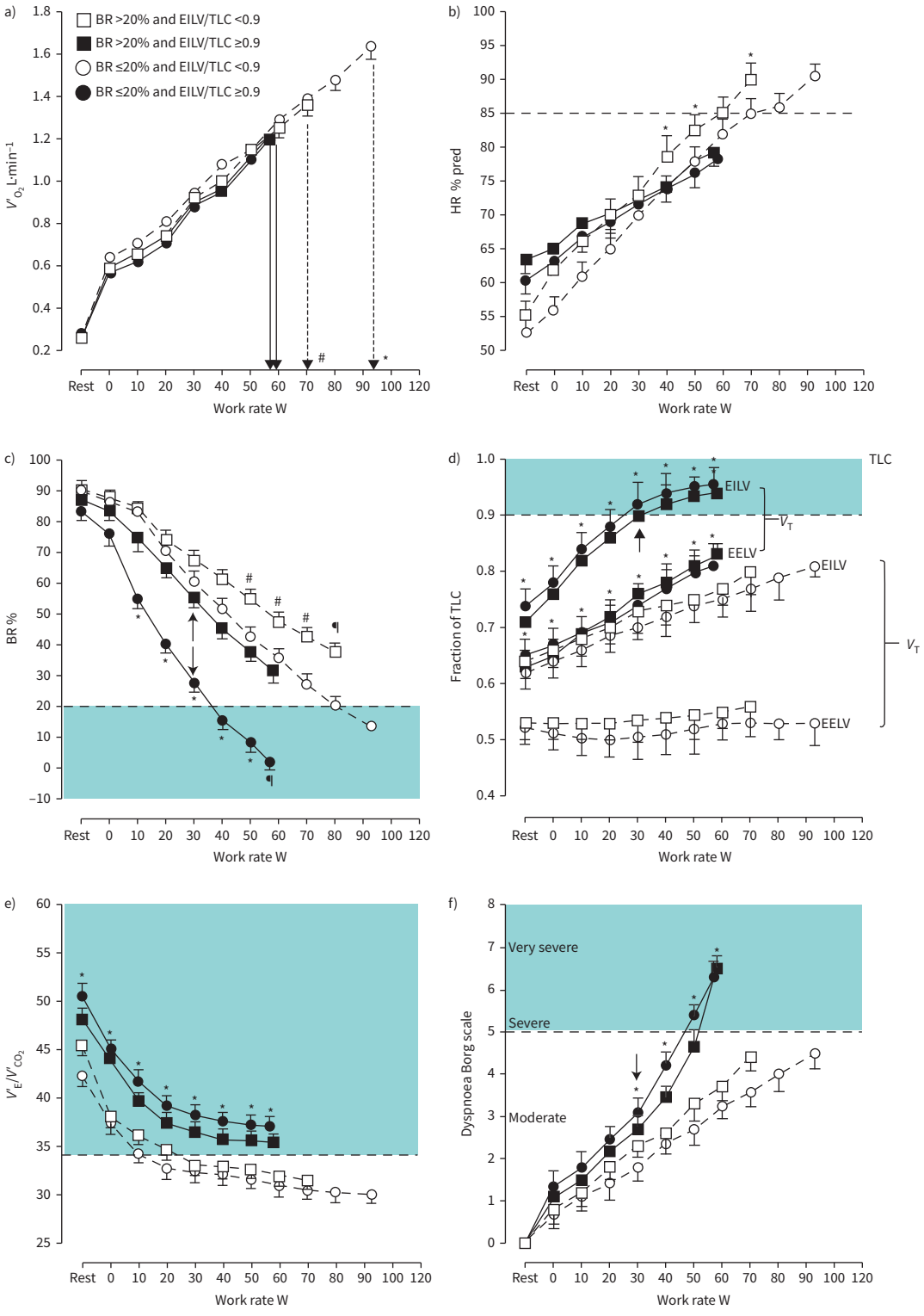

FIGURE 2 a) Metabolic, b) cardiovascular, c–e) ventilatory and f) sensory responses to symptom-limited incremental cardiopulmonary exercise testing in COPD patients presenting or not with a low breathing reserve ((BR) ⩽20% or >20%, respectively) and/or high inspiratory constraints (end-inspiratory lung volume (EILV)/total lung capacity (TLC) ⩾0.9 or <0.9, respectively). Commonly used ranges for severe physiological and sensory impairment are highlighted (shaded areas in panels c–f). The arrows in panels c), d) and f) emphasise the exercise intensity associated with a disproportionate increase in dyspnoea relative to metabolic and ventilatory demand. Note that patients who were particularly limited due to f) exertional dyspnoea (closed symbols)

presented with d) high inspiratory constraints and e) high ventilation (V'_E)/carbon dioxide output (V'_{CO_2}) ratio, regardless of c) the breathing reserve. *: p<0.05 *versus* the other groups; #: p<0.05 *versus* the remaining groups; ¶: p<0.05 *versus* BR ⩽20% or EILV/TLC <0.9 and BR >20% or EILV/TLC ⩾0.9. Data are presented as mean±SEM. V'_{O_2}: oxygen uptake; HR: heart rate; EELV: end-expiratory lung volume; V_T: tidal volume. Reproduced from [44] with permission.

underlying COPD [56]. Interestingly, the oscillatory breathing ceased at high operating lung volumes when critically high inspiratory constraints prevented further increases in V_T. As expected, this subgroup of patients with COPD–heart failure was particularly dyspnoeic, since the heightened ventilatory drive compounded the mechanical abnormalities [56].

Little is currently known on the potential modulating effects of emphysema extent, heart failure aetiology and heart failure with preserved ejection fraction [131, 60] on the V'_E/V'_{CO_2} in individual COPD–heart failure patients [128]. More subtle abnormalities in left ventricular function may increase V'_E/V'_{CO_2} in susceptible patients with COPD; in fact, coronary artery disease, even without overt heart failure, increased V'_E/V'_{CO_2} in these patients [53]. Owing to the fact that only a minority of hypoxaemic patients with COPD–heart failure have been assessed in previous studies [52, 54, 55, 60], it remains possible that a heightened hypoxic drive further increases V'_E/V'_{CO_2} in some patients. Selected interventions aimed at decreasing the ventilatory drive (such as β-blockers) have not decreased V'_E/V'_{CO_2} in patients with COPD [50], but this approach has not yet been tested in COPD–heart failure. There is conflicting evidence concerning a putative relationship between diastolic dysfunction and V'_E/V'_{CO_2} [58, 59], an issue that requires further investigation (table 2) [49].

The relevance of considering the additive effects of a high V_D/V_{Tphys} and a low P_{aCO_2} to increase V'_E/V'_{CO_2} and exertional dyspnoea has been shown by Costa *et al.* [62] in combined pulmonary fibrosis and emphysema (supplementary figure S5). Interestingly, V_D/V_{Tphys} was associated with the burden of emphysema (including admixed emphysema in areas of pulmonary fibrosis) and traction bronchiectasis, another potential source of wasted ventilation. In addition, it is conceivable that heightened peripheral chemostimulation [111] potentiated ventilatory stimulation in hypoxaemic patients, leading to a particularly deleterious combination of enlarged wasted ventilation, hypoxic stimulation and alveolar hyperventilation (supplementary figure S5).

V'_E/V'_{CO_2} for risk assessment and prognosis in COPD

Resting lung function parameters (particularly FEV_1 and T_{LCO}) have long been used to estimate the risk of peri-operative complications in patients submitted to lung resection surgery due to lung cancer [132]. Among the exercise-based measurements, more experience has been accumulated with V'_{O_2} peak [133]. More recently, some groups reported that a high V'_E–V'_{CO_2} slope may also predict a negative outcome [64–66]. For instance, Torchio *et al.* [69] reported that a high V'_E–V'_{CO_2} slope was the strongest predictor of mortality after pneumonectomies, a finding extended by Miyazaki *et al.* [70] to less extensive anatomical lung resections. Ellenberger *et al.* [71] found that a particularly high V'_E/V'_{CO_2} (>40) predicted poor survival after radical surgery for lung cancer. It remains unclear why a high V'_E/V'_{CO_2} predicts a negative surgical outcome in this context, but the reasons are probably multiple, including more severe emphysema, higher pulmonary vascular pressures, poorer cardiac performance, heightened sympathetic drive, exertional hypoxaemia and increased ergoreceptor stimulation due to severe deconditioning [134]. However, it should be recognised that the reduction in V'_E/V'_{CO_2} in severe to very severe COPD (figure 1) may decrease its predictive power in these patients, an issue that needs further investigation (table 2).

Similar to heart failure [11–14, 122], a high V'_E/V'_{CO_2} (V'_E/V'_{CO_2} nadir ⩾34) predicts poor survival in patients with COPD. Of note, lung hyperinflation added to V'_E/V'_{CO_2} to predict mortality due to respiratory and nonrespiratory causes (figure 3) [67]. Increased sympathetic stimulation, as inferred by a slow decrease in post-exercise heart rate, was observed in COPD patients with higher and worsening mechanical constraints [42], providing a potential clue for the mechanisms underlying the association between these variables and the risk of a future negative event. Furthermore, a high V'_E/V'_{CO_2} nadir compound impaired right ventricular systolic function to predict poor outcome in COPD–heart failure [68]. A high V'_E–V'_{CO_2} slope has been associated with increasing risk of hospitalisation in this specific subpopulation [61]. Pending experimental confirmation in larger studies, V'_E/V'_{CO_2} might become a relevant effort-independent prognostic parameter in patients with COPD (table 2).

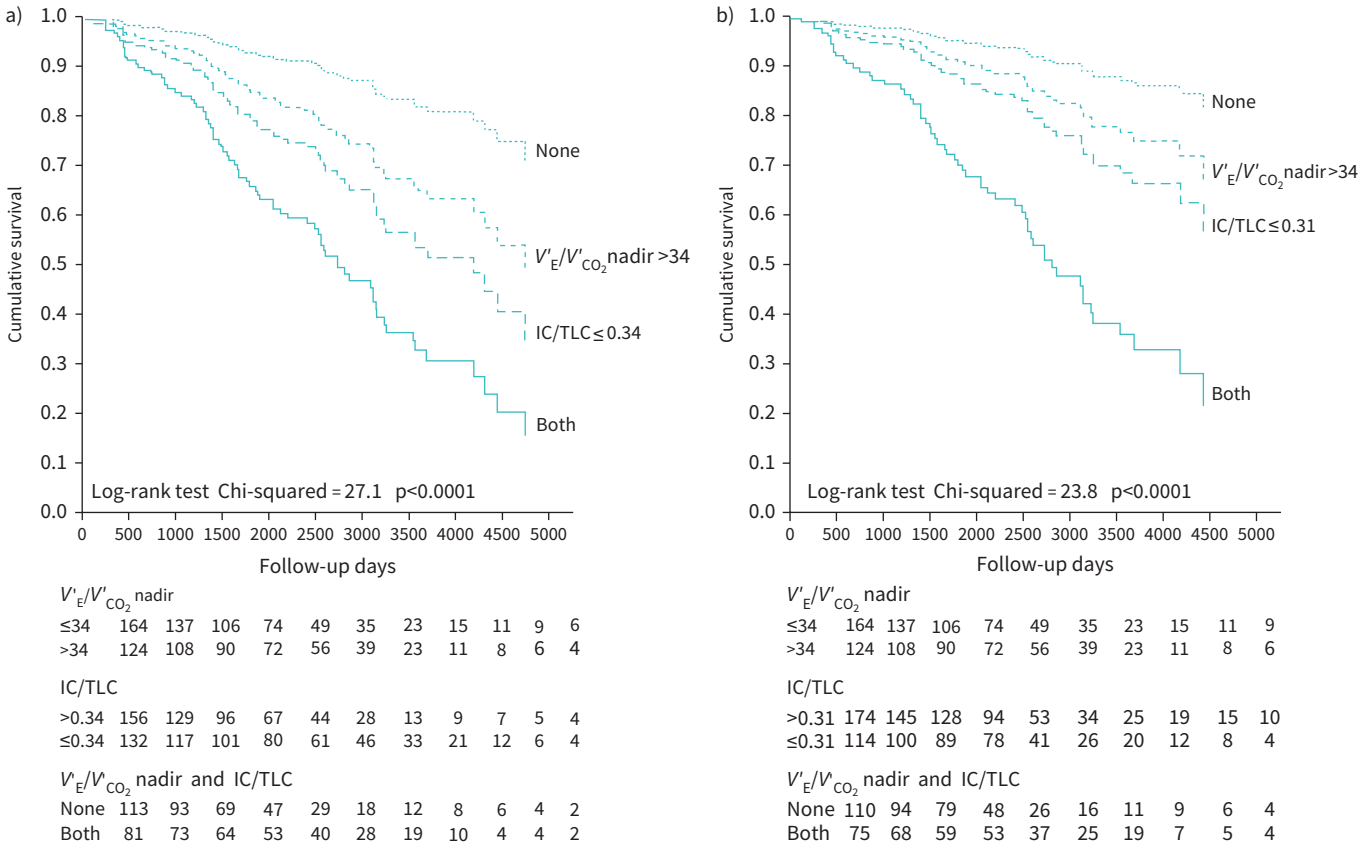

FIGURE 3 Value of high ventilation (V'_E)/carbon dioxide output (V'_{CO_2}) nadir in isolation and associated with resting lung hyperinflation (low inspiratory capacity (IC)/total lung capacity (TLC) ratio) to predict a) all-cause and b) respiratory mortality in patients with mild to severe COPD. Reproduced from [67] with permission.

Effects of interventions on V'_E/V'_{CO_2} in COPD

The effects of interventions on V'_E/V'_{CO_2} are highly variable, depending on the main mechanism of action. Thus, interventions which may lessen the mechanical constraints (heliox [76, 80, 81, 86], lobectomy [79] and bronchodilators [75, 77, 85]) typically increased V'_E at a given V'_{CO_2}. In other circumstances where the main mechanism of action was probably related to a lower V_D and/or a higher V_T (single [72] and double lung [82] transplantation and lung volume reduction surgery [84, 87]), V'_E decreased at a given V'_{CO_2}. Similarly, interventions aimed at lowering the respiratory neural drive (supplemental oxygen [82, 95], spinal anaesthesia [83]) also decreased V'_E/V'_{CO_2}. At least theoretically, exercise training may lessen V'_E/V'_{CO_2} in some patients due to high V_T leading to a low V_D/V_{Tphys} as well as delaying metabolic acidosis, thereby reducing afferent stimuli from the active peripheral muscles [135]. These mechanistic considerations raise the question of why inhaled bronchodilators have not been reported to change the V'_E/V'_{CO_2} in COPD [136]. In fact, Elbehairy *et al*. [92] found that despite appreciable lung deflation after acute bronchodilation, V_D/V_{Tphys} and V'_E/V'_{CO_2} both remained unaltered. These findings highlight the importance of wasted ventilation in regulating V'_E/V'_{CO_2} in COPD while suggesting that the higher V_T and regional alveolar ventilation after bronchodilation occurs preferentially directed in areas which were already better ventilated. Nevertheless, this topic merits more detailed analysis in longer trials (table 2).

Applying V'_E/V'_{CO_2} to clinical management of COPD

The data summarised in table 1 provide some clues on the specific scenarios in which measuring V'_E/V'_{CO_2} may have practical implications for the management of patients with COPD. Exertional dyspnoea is a ubiquitous symptom across the range of COPD severity. However, in some circumstances, it is chiefly related to unfitness, obesity, hyperventilation or comorbidities. Establishing a link between a high V'_E/V'_{CO_2} and dyspnoea in patients with only mildly to moderately reduced FEV_1 might prompt a more proactive approach to bronchodilator treatment. A similar line of reasoning applies to patients with disproportionate

dyspnoea relative to resting lung function impairment. In both circumstances, it is important to jointly analyse V'_E/V'_{CO_2} and noninvasive measurements of lung mechanics as they provide complementary information (figure 2). A high V'_E/V'_{CO_2} coupled with severely increased operating lung volumes might also suggest that the patient is poorly prepared to face the challenges brought by an acute exacerbation; thus, regardless of FEV_1, the patient might benefit from closer follow-up and optimisation of anti-exacerbation measures. Marked increases in V'_E/V'_{CO_2} might raise concerns regarding associated pulmonary vascular disease or, if appropriate, heart failure. This is particularly true when there is only a trivial burden of emphysema on high-resolution computed tomography to otherwise explain a high V'_E/V'_{CO_2}. Conversely, a lower-than-expected V'_E/V'_{CO_2} might be related to morbid obesity or another potential cause of blunted ventilatory response, including severe sleep disordered breathing, neuromuscular disease and hypercapnic respiratory failure of other aetiology. In fact, Paoletti *et al.* [17] showed that V'_E/V'_{CO_2} may decrease in more advanced emphysema as the severe mechanical constraints preclude appropriate ventilatory response to metabolic demand, despite an enlarged dead space. It follows that a low V'_E/V'_{CO_2} in patients with substantial emphysema signals for the dominance of mechanical abnormalities over the gas exchange disturbances. Therefore, in the right clinical context, this piece of information might be useful to select patients more likely to derive benefit from interventions aimed to release the mechanical constraints, *e.g.* volume reduction surgery. A high V'_E/V'_{CO_2} in COPD patients referred for resection surgery due to lung cancer should raise concerns about the increased risk of peri-operative complications. If feasible, a more limited resection might be advisable in these patients. Finally, documenting a lower V'_E/V'_{CO_2} after lung transplantation or lung volume reduction surgery might provide objective evidence attesting the efficacy of these expensive treatment approaches.

Conclusions

The relevance of abnormalities in V'_E/V'_{CO_2} during exercise has only recently become a target for systematic assessment in COPD (table 1). Whereas the V'_E–V'_{CO_2} slope and the V'_E/V'_{CO_2} nadir are frequently increased in mild to moderate COPD, increasing ventilatory constraints may lead to a "preserved" V'_E–V'_{CO_2} slope in more advanced COPD. A higher V'_E intercept may partially counterbalance the latter effect; thus, the V'_E/V'_{CO_2} nadir may still be elevated in these patients. However, in end-stage COPD, the mechanical constraints (and the associated hypercapnia) may eventually prevail, leading to a "normal" or low V'_E/V'_{CO_2} nadir. Overall, a high V'_E/V'_{CO_2} frequently exposes clinically significant V'/Q' distribution though alveolar hyperventilation may also contribute, particularly in the presence of cardiovascular comorbidities or lung fibrosis. Published evidence (table 1) indicates that the V'_E/V'_{CO_2} nadir is a particularly useful index of abnormal uncoupling between ventilation and metabolic demand in COPD, being linked to important clinical outcomes such as dyspnoea, reduced exercise capacity and even mortality. In daily practice, V'_E/V'_{CO_2} measurements are particularly useful in the individualised assessment of exercise intolerance in mild to moderate COPD, notably in individuals with disproportionate exertional dyspnoea. Providing evidence-based answers to the questions posed in table 2 may prove valuable to extend the clinical applications of V'_E/V'_{CO_2} in this patient population.

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