Physiological and clinical relevance of exercise ventilatory efficiency in COPD

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ABSTRACT Exercise ventilation (V'_E) relative to carbon dioxide output (V'_{CO_2}) is particularly relevant to patients limited by the respiratory system, *e.g.* those with chronic obstructive pulmonary disease (COPD). High V'_E–V'_{CO_2} (poor ventilatory efficiency) has been found to be a key physiological abnormality in symptomatic patients with largely preserved forced expiratory volume in 1 s (FEV_1). Establishing an association between high V'_E–V'_{CO_2} and exertional dyspnoea in mild COPD provides evidence that exercise intolerance is not a mere consequence of detraining. As the disease evolves, poor ventilatory efficiency might help explaining "out-of-proportion" breathlessness (to FEV_1 impairment). Regardless, disease severity, cardiocirculatory co-morbidities such as heart failure and pulmonary hypertension have been found to increase V'_E–V'_{CO_2}. In fact, a high V'_E–V'_{CO_2} has been found to be a powerful predictor of poor outcome in lung resection surgery. Moreover, a high V'_E–V'_{CO_2} has added value to resting lung hyperinflation in predicting all-cause and respiratory mortality across the spectrum of COPD severity. Documenting improved ventilatory efficiency after lung transplantation and lung volume reduction surgery provides objective evidence of treatment efficacy. Considering the usefulness of exercise ventilatory efficiency in different clinical scenarios, the V'_E–V'_{CO_2} relationship should be valued in the interpretation of cardiopulmonary exercise tests in patients with mild-to-end-stage COPD.

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To me it does not seem all movements are exercise, but only when it is vigorous. Since vigor is relative, the same movement might be exercise for one and not for another. The criterion of vigorousness is change of respiration; those movements which do not alter the respiration are not exercise.

Galen, Exercise and Massage, in *On Hygiene*, *circa* 200 AD

Introduction

Dynamic exercise, as recognised by Galen, is characteristically associated with changes in frequency and depth of breathing, *i.e.* hyperpnoea. Moreover, he cogently observed that those respiratory changes are somehow linked to exercise intensity ("movement vigorousness"). Eighteen centuries later we now know that changes in exercise pulmonary ventilation (V'_E), at least before the development of metabolic acidosis (or hypoxaemia in disease), are exquisitely commensurate to the rate at which metabolically produced carbon dioxide is released by the lungs (V'_{CO_2}, *i.e.* venous return × mixed-venous CO_2 content) [1, 2]. Thus, the response of V'_E relative to V'_{CO_2} (the V'_E–V'_{CO_2} relationship) has been named "ventilatory efficiency" [3], an implicit recognition that meeting metabolic demand to maintain arterial blood gas and pH is the overriding goal of ventilation [2]. Although increased (or even decreased) V'_E relative to V'_{CO_2} may not always inform us how efficient V'_E is relative to arterial blood gas homeostasis (see section Physiological bases), the term "ventilatory efficiency" has gained popularity to describe the exercise V'_E–V'_{CO_2} relationship [4–7].

It is rather axiomatic that the issue of exercise ventilatory efficiency is particularly relevant to patients primarily limited by ventilation, *e.g.* those with chronic obstructive pulmonary disease (COPD) [8, 9]. Surprisingly, however, its clinical importance has been mostly recognised in diseases for which mechanical–ventilatory constraints are not the dominant feature, *e.g.* heart failure [4–7, 10] and pulmonary arterial hypertension (PAH) [11, 12]. More recently, however, a substantial body of evidence has accumulated showing that abnormalities in the V'_E–V'_{CO_2} relationship during incremental cardiopulmonary exercise testing (CPET) are present across the spectrum of COPD severity. Thus, V'_E–V'_{CO_2} measurement has advanced our understanding of mechanisms of exercise intolerance and, particularly in milder COPD, exertional breathlessness. Moreover, this measurement has allowed us to better judge the functional impact of co-morbidities, to assess future risk and prognosis and to determine the complex effects of therapeutic interventions on exercise tolerance in COPD (table 1). The present manuscript will discuss these emerging findings from a clinically applied perspective with emphasis on the extant gaps in current knowledge.

Physiological bases

It is well established that the V'_E required to washout a given rate of CO_2 production is higher the lower the arterial partial pressure for CO_2 (P_{aCO_2}) (as more V'_E is needed to keep P_{aCO_2} low compared with a high value) and the larger the ventilation "wasted" in the dead space (V_D), *i.e.*

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

where V'_E/V'_{CO_2} ratio is the ventilatory equivalent for CO_2 and V_D/V_T is the physiological (anatomical plus alveolar) dead space fraction of tidal volume [2]. Of note, V_D/V_T decreases in a curvilinear manner as exercise progresses, *i.e.* more alveoli are recruited as V_T and V'_E increase (figure 1a) [67]. Thus, a major contribution to the decreasing V_D/V_T is the greater compliance of the alveoli over that of the airways, allowing greater alveoli expansion relative to the airways ([67] and reviewed in [68]). Moreover, V_T increases owing to a large increase in end-inspiratory lung volume and a small, but important, decrease in end-expiratory lung volume; thus, V_T remains positioned on the most compliant (linear) portion of the respiratory system S-shaped pressure–volume relationship (as reviewed in [69]).

In this context, if V'_E/V'_{CO_2} did not decrease in tandem with V_D/V_T the resulting alveolar hyperventilation would lower P_{aCO_2} leading to progressive respiratory alkalosis [2, 70]. Although the exact mechanisms remain controversial (see [71] and [72] for a recent debate on the topic), V'_E/V'_{CO_2} decreases in direct proportion to V_D/V_T (figure 1b). Thus, P_{aCO_2} is kept constant (↔) during mild-to-moderate exercise in healthy humans (figure 1c) [1, 2, 67, 73]:

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

TABLE 1 Overview of cardiopulmonary exercise testing-based studies on ventilatory efficiency in different clinical scenarios in chronic obstructive pulmonary disease (COPD)

Clinical context	Subjects n	Disease severity	Main results
Exercise intolerance			
Palange [13]	9	FEV_1 <50%	↑V'_E–V'_{CO_2} slope in walking than cycling
O'Donnell [14]	20	FEV_1=34±3%	↓V'_E at a given V'_{CO_2} in CO_2 retainers compared with non-retainers
Nakamoto [15]	10	FEV_1=27–70%	V'_E–V'_{CO_2} slope not related to increased muscle ergoreflex activity
Ofir [16]	42	FEV_1=91±8%	↑V'_E/V'_{CO_2} nadir in mild COPD with chronic dyspnoea
Ora [17]	36	FEV_1=49±10%	↓V'_E/V'_{CO_2} nadir in obese patients with COPD
Paoletti [18]	16	FEV_1=54±18%	↓V'_E–V'_{CO_2} slope in more extensive emphysema
Guenette [19]	64	FEV_1=86±11%	No sex effect on V'_E/V'_{CO_2} nadir
Caviedes [20]	35	FEV_1=59±22%	↑V'_E/V'_{CO_2} nadir associated with lower maximal exercise capacity
Chin [21]	40	FEV_1=87±11%	↑V'_E/V'_{CO_2} with added external dead space in mild COPD
Teopompi [22]	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 [23]	32	FEV_1=93±9%	↑V'_E/V'_{CO_2} throughout incremental exercise in mild COPD
Ciavaglia [24]	12	FEV_1=60±13%	No effect of exercise modality on V'_E/V'_{CO_2} in obese patients with COPD
Barron [25]	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 heart failure
O'Donnell [26]	208	GOLD 1 and 2	↑V'_E/V'_{CO_2} throughout incremental treadmill tests in GOLD 1 and 2
Neder [27]	276	GOLD 1 to 4	↑V'_E–V'_{CO_2} slope associated with ventilation inhomogeneity in GOLD 1 and 2
Elbehairy [28]	40	FEV_1=91±10%	↑V'_E/V'_{CO_2} nadir in GOLD grade 1B with and without chronic bronchitis
Neder [29]	316	GOLD 1 to 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
Elbehairy [30]	22	FEV_1=94±10%	↑V'_E/V'_{CO_2} associated with greater V_D/V_T in symptomatic GOLD 1
Faisal [31]	48	FEV_1=63±22%	↑V'_E/V'_{CO_2} in COPD and ILD presenting with similar resting inspiratory capacity
Crisafulli [32]	51	FEV_1=55±16%	↑V'_E/V'_{CO_2} slope associated with emphysema extension on chest CT
Elbehairy [33]	20	FEV_1=101±13%	Similar V'_E/V'_{CO_2} in smokers without COPD and healthy controls
Soumagne [34]	20	FEV_1=–1.02±0.64 z-score	↑V'_E/V'_{CO_2} nadir in asymptomatic smokers with airflow obstruction
Jones [35]	19	FEV_1=82±13%	↑V'_E/V'_{CO_2} nadir associated with emphysema extension and lower transfer factor
Influence of co-morbidities			
Holverda [36]	25	NA	↑V'_E/V'_{CO_2} nadir associated with mean pulmonary artery pressure
Vonbank [37]	42	FEV_1=1.1±0.5 L	↑ Rest and peak V'_E/V'_{CO_2} in patients with associated PAH
Boerrigter [38]	47	FEV_1=55±17%	Pronounced ↑ V'_E–V'_{CO_2} slope in a sub-group (n=9) with severe PAH
Thirapataratong [39]	48	FEV_1=31±10%	No effect of β-blockers on V'_E/V'_{CO_2} nadir
Thirapataratong [40]	98	FEV_1=20±7%	No association of peak V'_E/V'_{CO_2} with PAH in severe to very severe COPD
Teopompi [41]	46	FEV_1=52±16%	↓V'_E–V'_{CO_2} slope in COPD compared with heart failure in patients with poorer exercise capacity ↑V'_E–V'_{CO_2} intercept in COPD compared with heart failure
Thirapataratong [42]	108	FEV_1=26±14%	↑V'_E/V'_{CO_2} nadir in COPD patients with coexistent coronary artery disease
Apostolo [43]	95	FEV_1=53±13%	↑V'_E–V'_{CO_2} intercept in COPD and COPD- heart failure compared with heart failure
Arbex [44]	98	FEV_1=55±17%	↑V'_E–V'_{CO_2} slope and V'_E/V'_{CO_2} nadir in COPD- heart failure compared with COPD ↓V'_E–V'_{CO_2} intercept in COPD- heart failure compared with COPD
Rocha [45]	68	FEV_1=60±18%	↑V'_E–V'_{CO_2} slope in COPD- heart failure with exercise oscillatory ventilation
Risk assessment/prognosis			
Torchio [46]	145	FEV_1=73±16%	V'_E–V'_{CO_2} slope ⩾34 predicted mortality after lung resection surgery
Brunelli [47]	225	FEV_1=81±18%	V'_E–V'_{CO_2} slope ⩾35 predicted poor outcome after lung resection surgery
Shafiek [48]	55	FEV_1=60±17%	V'_E–V'_{CO_2} slope >35 predicted poor outcome after lung resection surgery
Neder [49]	288	FEV_1=18–148%	V'_E/V'_{CO_2} nadir >34 added to resting hyperinflation to predict mortality
Alencar [50]	30	FEV_1=57±17%	V'_E/V'_{CO_2} nadir >34 and right ventricular function predicted mortality in COPD–heart failure
Effects of interventions			
Orens [51]	5	FEV_1=57±4%	Single lung transplant decreased V'_E/V'_{CO_2} peak
Somfay [52]	10	FEV_1=31±10%	Decrements in V'_E with hyperoxia correlated with decreases in V'_{CO_2}
O'Donnell [53]	11	FEV_1=31±3%	Proportional decrements V'_E and V'_{CO_2} with hyperoxia in advanced COPD
O'Donnell [54]	23	FEV_1=42±3%	Salmeterol proportionally increased V'_E and V'_{CO_2} during constant work rate exercise

Continued

TABLE 1 Continued

Clinical context	Subjects n	Disease severity	Main results
Palange [55]	12	FEV_1 <50% pred	Heliox increased V'_E/V'_{CO_2} during constant work rate exercise
O'Donnell [56]	187	FEV_1=44±13%	↑V'_E (due to higher V_T) at a given V'_{CO_2} with tiotropium compared with placebo
Porszasz [57]	24	FEV_1=36±8%	Exercise training proportionally reduced V'_E and V'_{CO_2} during constant work rate exercise
Bobbio [58]	11	FEV_1=53±20%	Lobectomy increased V'_E–V'_{CO_2} slope
Eves [59]	10	FEV_1=47±17%	Normoxic heliox increased V'_E/V'_{CO_2} more than hyperoxic heliox
Chiappa [60]	12	FEV_1=45±13%	Heliox increased V'_E/V'_{CO_2} during constant work rate exercise
Habedank [61]	8	NA	Bilateral lung transplant decreased V'_E–V'_{CO_2} slope
Gagnon [62]	8	FEV_1=67±8%	Spinal anaesthesia reduced V'_E/V'_{CO_2} during constant work rate exercise
Kim [63]	1475	FEV_1 <45%	LVRS reduced V'_E/V'_{CO_2} during unloaded exercise
Guenette [64]	15	FEV_1=86±15%	↑V'_E/V'_{CO_2} at isotime with fluticasone/salmeterol compared with placebo
Queiroga [65]	24	FEV_1=35±10%	Heliox increased V'_E/V'_{CO_2} during constant work rate exercise
Armstrong [66]	55	FEV_1=26±7%	LVRS reduced V'_E/V'_{CO_2} peak and nadir

↑: increased; ↓: decreased; FEV_1: forced expiratory volume in one second; V'_E: ventilation; V'_{CO_2}: carbon dioxide output; PAH: pulmonary arterial hypertension; GOLD: Global Initiative for Obstructive Lung Disease; ILD: interstitial lung disease; LVRS: lung volume reduction surgery; NA: not available.

These considerations provide the physiological basis for the assertion that the V'_E/V'_{CO_2} profile provides useful information about the V_D/V_T trajectory, particularly if P_{aCO_2} is concomitantly measured [2, 67, 70, 74]. The major assumptions, however, are the absence of mechanical constraints to V'_E increase [75], *i.e.* the "output" (V'_E) can appropriately adjust to its determinants (V'_{CO_2}, V_D/V_T and P_{aCO_2}) and there is neither exercise-induced hypercapnia nor increased additional chemo-stimulation of ventilation, *e.g.* hypoxaemia [1, 2, 4, 73].

Equation 1 also helps us to understand why increases in V'_E relative to V'_{CO_2} do not necessarily imply poor ventilatory efficiency. For instance, the system is arguably not "inefficient" if a high V'_E/V'_{CO_2} is needed to keep P_{aCO_2} at a low level as determined by the respiratory controller (*e.g.* chronic respiratory alkalosis or chronic metabolic acidosis) or there is an extra source of afferent stimuli to increase ventilation (*e.g.* hypoxaemia) [10]. For the sake of simplicity, the subsequent discussion assumes that an increased slope of the V'_E–V'_{CO_2} relationship and/or an increased V'_E/V'_{CO_2} ratio equals "poor efficiency" unless otherwise specified.

Methodological considerations

In response to rapidly incremental CPET, the V'_E–V'_{CO_2} relationship has been analysed in the V'_E/V'_{CO_2} ratio *versus* V'_{CO_2} plot (figure 1b) or in the V'_E *versus* V'_{CO_2} plot (figure 1d) [4]. The lowest (nadir) V'_E/V'_{CO_2} is typically reached just before V'_E starts to increase in compensation for lactic acidosis at the respiratory compensation point (RCP) (figure 1b–d). Provided the subject can tolerate high levels of exercise (*i.e.* high V'_{CO_2}), V'_E/V'_{CO_2} virtually equals (*i.e.* "asymptotes") to the slope of the V'_E–V'_{CO_2} relationship (refer to the supplementary material for further elaboration) [76]. Thus, the V'_E/V'_{CO_2} nadir and V'_E/V'_{CO_2} at the lactate threshold are almost indistinguishable in normal subjects [74]. As the lactate threshold may not always be identified, particularly in clinical populations with low exercise capacity [77, 78], the V'_E/V'_{CO_2} nadir seems a more accurate indication of ventilatory efficiency than the V'_E/V'_{CO_2} at the lactate threshold. The V'_E/V'_{CO_2} nadir has been found to be highly reproducible in normal subjects [74] and in patients with COPD [25]. The V'_E/V'_{CO_2} nadir, however, might underestimate ventilatory efficiency if the V'_E/V'_{CO_2} descending curve is prematurely interrupted (dashed line in figure 1b), *e.g.* premature lactic acidosis or an excessively short test duration [79]. As expected, end-exercise V'_E/V'_{CO_2} is higher than the nadir as the former incorporates the hyperventilatory response to late-exercise acidosis. In other words, end-exercise V'_E/V'_{CO_2}, by definition, does not constitute an index of ventilatory efficiency in those who are able to exercise beyond the RCP. Most patients with moderate-to-severe COPD, however, either do not reach the RCP or are unable to further increase V'_E. Thus, nadir and end-exercise V'_E/V'_{CO_2} are often equivalent in most patients, with the exception of some less impaired patients with milder disease [29].

It is important to recognize that the V'_E/V'_{CO_2} response contour is intrinsically linked to how V'_E dynamically changes in relation to V'_{CO_2} taking into consideration its starting point [2, 4, 71, 72, 76]. The former is reflected by the slope of the regression line between V'_E and V'_{CO_2} and the latter by its intercept (*i.e.* V'_E when V'_{CO_2}=0) (figure 1 and figure S1). Considering that in normal subjects the V'_E intercept is often a small positive number (<3 L min^{-1} on average) [74], V'_E/V'_{CO_2} equals the slope of the V'_E–V'_{CO_2} relationship at high V'_{CO_2} values (refer to the supplementary material for further elaboration) [67, 70, 76]. It should be noted

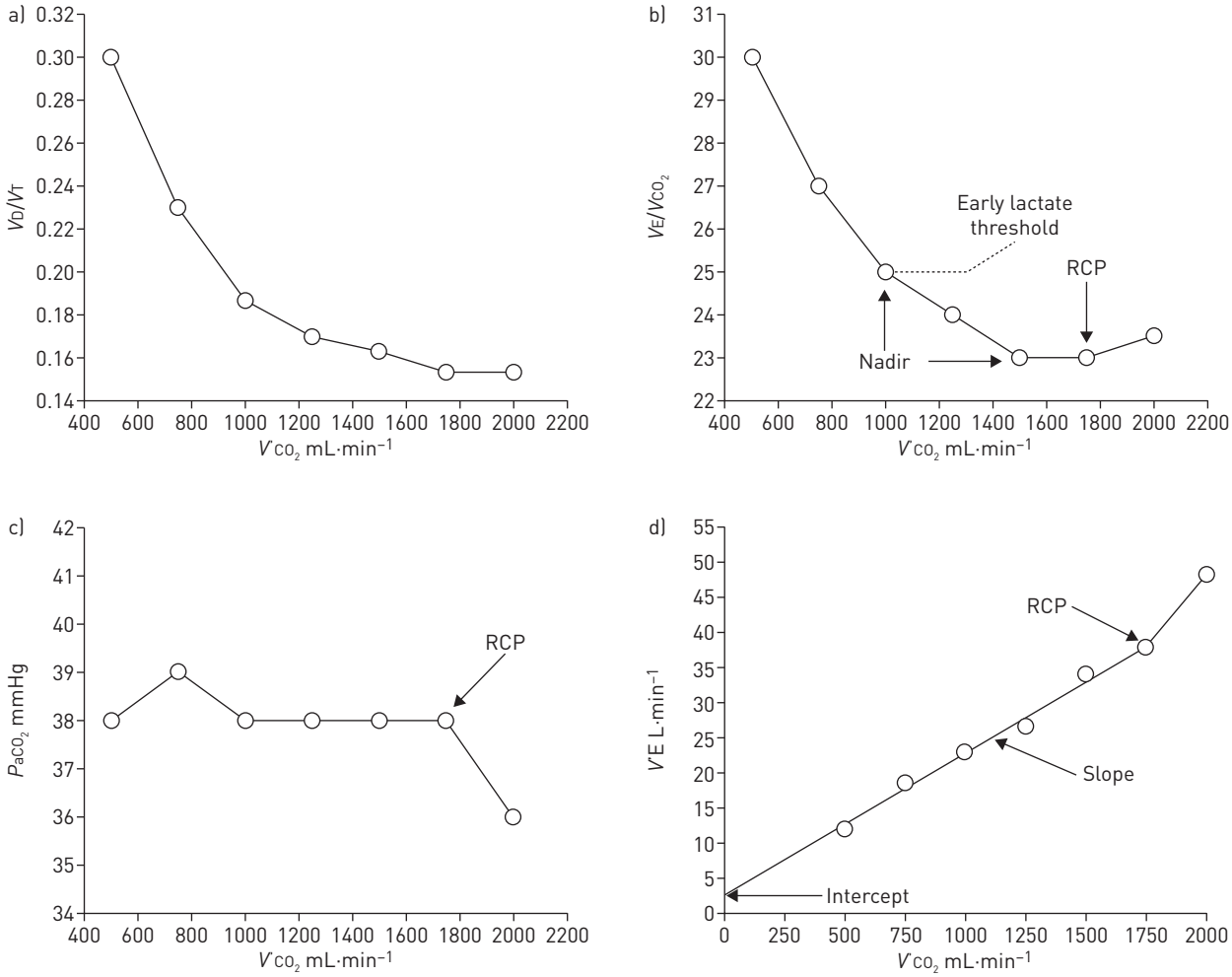


FIGURE 1 Selected ventilatory and gas exchange responses to incremental CPET in a young healthy male. Proportional decreases in dead space (V_D)/tidal volume (V_T) (a) and ventilation (V'_E)/carbon dioxide output (V'_{CO_2}) (b) ratios maintain arterial carbon dioxide partial pressure (P_{aCO_2}) close to resting value during mild-to-moderate exercise (c). The V'_E/V'_{CO_2} response contour is established by both slope and intercept of the linear V'_E–V'_{CO_2} relationship (d). Thus, the lowest (nadir) V'_E/V'_{CO_2} closely approximates slope plus intercept. V'_E–V'_{CO_2} increases out of proportion to V'_{CO_2} after the respiratory compensation point (RCP) (b–d) leading to respiratory alkalosis (c) to compensate for progressive lactacidaemia. Note the increases in nadir when the lactate threshold is reached earlier (dashed line in b).

that considering all data points (*i.e.* including those after the RCP) will necessarily increase the computed slope and reduce the computed intercept. Although this might be advantageous for prognostication in heart failure [80] and PAH [11], not only it underestimates ventilatory efficiency (equation 1) but it also does not accurately describe the underlying response profile. As mentioned, however, most patients with moderate-to-severe COPD are unable to exercise beyond the RCP. In other words, there is no upward inflection in the V'_E *versus* V'_{CO_2} response in most of these patients. Thus, in practice, drawing a single line from unloaded to peak exercise fits well the overall V'_E response in this particular sub-group of patients [29].

Some studies have examined the influence of potential modifiers on ventilatory efficiency. Ageing has been consistently associated with higher V_D/V_T and poorer ventilatory efficiency, regardless the method of expression (ratio or slope) [74, 79, 81] or level of fitness [82]. Females typically present with slightly greater V'_E–V'_{CO_2} slopes than males [79], likely a consequence of a lower V_T [83]. The fact that P_{aCO_2} does not differ between younger *versus* elderly or men *versus* women [1, 73] provides another piece of evidence that exercise V'_E increases precisely to maintain a stable alveolar ventilation/V'_{CO_2} ratio [1, 2, 4, 73]. It is also remarkable that exercise modality (walking *versus* cycling) does not seem to influence ventilatory efficiency in normal subjects [74, 81] though the V'_E–V'_{CO_2} slope was higher during treadmill walking compared with cycling in moderate-to-severe COPD [13].

Ventilatory efficiency and exercise intolerance

A substantial body of evidence has accumulated indicating that abnormalities in ventilatory efficiency across the continuum of disease severity in COPD (table 1). Poor ventilatory efficiency has been found to be a key

physiological abnormality in symptomatic patients with largely preserved forced expiratory volume in 1 s (FEV_1) (figure S4) [29, 21, 26, 28, 30, 33]. The physiological basis for these derangements seems to stem from an enlarged V_D *per se* rather than a small V_T or a low $P_{a}CO_2$ [30]. In fact, external (series) V_D predictably increased V'_E/V'_{CO_2} in these patients [21]. Additional research is warranted to investigate the structural correlates of increased V_D in mild COPD, *e.g.* microvascular disease [84], early emphysema [32, 85, 86], ventilation distribution heterogeneity [27, 86]. Regardless of the mechanism(s), high V'_E/V'_{CO_2} nadir is linked to earlier attainment of critical dynamic mechanical constraints: inspiratory reserve volume becomes critically reduced. This explains, in part, the increased exertional dyspnoea and reduced exercise capacity in mild COPD compared with age-matched healthy controls [21, 23, 26, 28, 30, 45]. This pattern of abnormalities was also seen in most patients with moderate airflow obstruction (Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 2) [29]. Collectively, these studies point to the important contribution of reduced ventilatory efficiency to dyspnea and reduced exercise capacity in smokers with only mild-to-moderate airflow obstruction [87, 88]. Interestingly, V'_E/V'_{CO_2} nadir was also increased in symptomatic [16], but not in asymptomatic [33], smokers without COPD. These findings are consistent with the notion that poor ventilatory efficiency is instrumental to explain exertional dyspnoea at the earlier stages of the disease [87].

Similarly to heart failure [89–91], V_D/V_T worsens as disease severity increases in patients with COPD [88]. Interestingly, however, while the most commonly used parameter of ventilatory efficiency in the clinical literature (the $V'_E-V'_{CO_2}$ slope) increases from mild to severe heart failure [4–7, 10], the $V'_E-V'_{CO_2}$ slope decreases and the V'_E intercept increases in severe-to-very-severe COPD compared with milder disease. Consequently, the V'_E/V'_{CO_2} nadir may remain stable (but still higher than in health) if the effects of a low

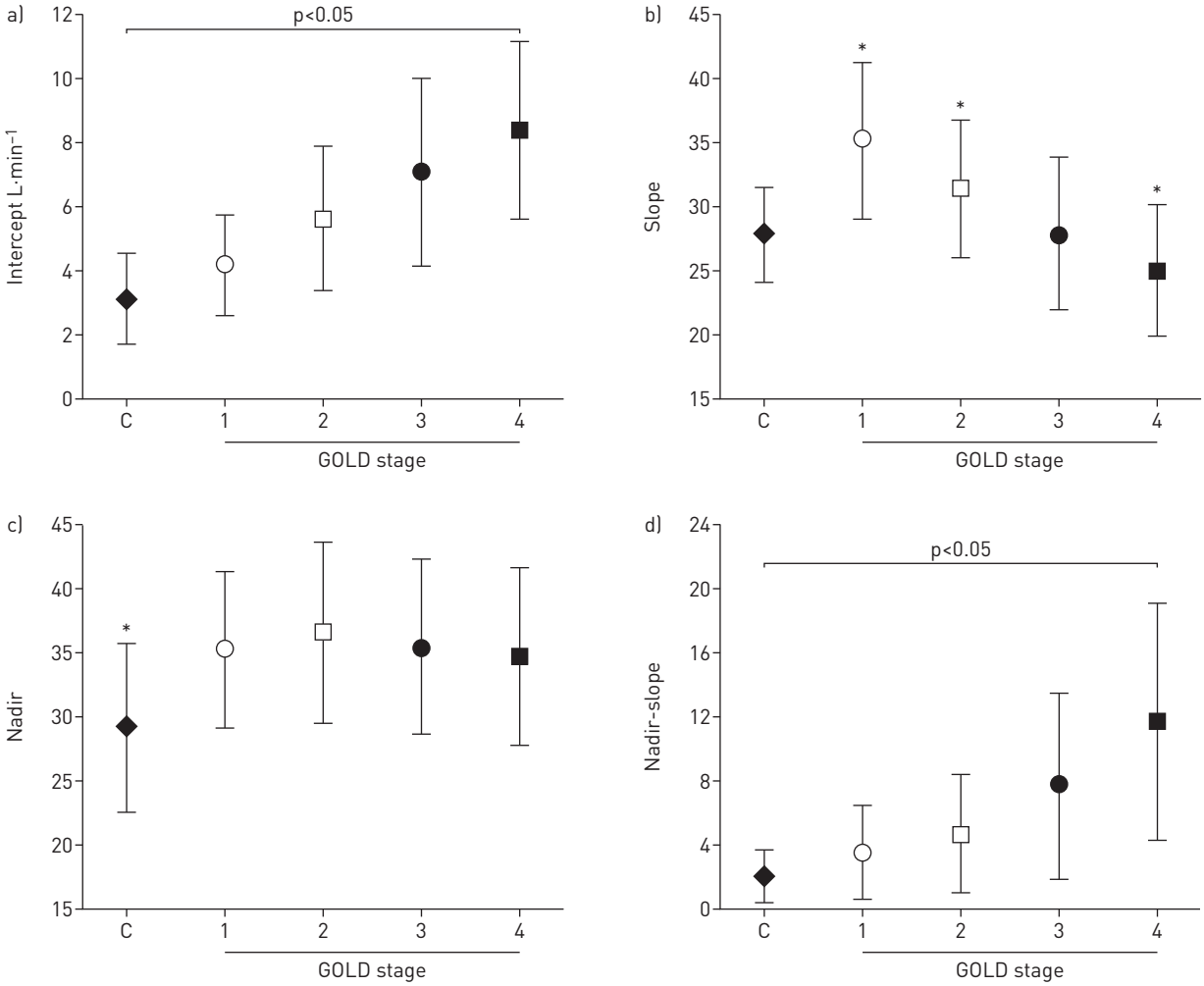


FIGURE 2 Effects of chronic obstructive pulmonary disease (COPD) severity on different parameters of ventilatory efficiency. Ventilation (V'_E)–carbon dioxide output (V'_{CO_2}) intercept increased (a) and $V'_E-V'_{CO_2}$ slope diminished (b) as the disease progressed from Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages 1 to 4. As the V'_E/V'_{CO_2} nadir depends on both slope and intercept, it remained elevated (compared with controls (C)) across disease stages (c). Increasing nadir–slope differences from GOLD stages 1 to 4 reflects the impact of a progressively higher intercept (d). Reproduced from [29] with permission from the publisher.

slope in the nadir are cancelled out by a high intercept or even diminished if the slope is markedly reduced in severe-to-very-severe COPD (figure 2 and figure S3 for representative patients) [29]. The seemingly paradoxical finding of lower $V'_E-V'_{CO_2}$ slope in advanced COPD is likely explained by worsening mechanical constraints to V'_E increase [88] and, in end-stage disease, to hypercapnia (see section Physiological bases) [14, 92]. Increases in V'_E intercept in COPD were associated with worsening dynamic hyperinflation, greater exertional dyspnoea and poorer exercise tolerance as the disease evolved [29]. Interestingly, obesity in COPD also decreased V'_E/V'_{CO_2} nadir, likely due to greater ventilatory constraints and, conceivably, a higher P_{aCO_2} set-point [17].

Little is known about the structural correlates of the $V'_E-V'_{CO_2}$ slope and the V'_E intercept in COPD. Adding external V_D in normal subjects had a more discernible effect on the V'_E intercept than the $V'_E-V'_{CO_2}$ slope both in health [68, 93, 94] and mild COPD [21]. However, in-series V_D may not perfectly mimic alveolar (in-parallel) V_D as found in patients with pulmonary diseases. Thus, the former is associated with a greater CO_2 loading in the airways (re-breathing), which might further challenge ventilatory control [71, 72]. It could be argued that as the $V'_E-V'_{CO_2}$ slope is reduced by progressive mechanical respiratory constraints in severe-to-very-severe COPD [29], a high V'_E intercept is a necessary and empirical consequence of a shallower slope independent of the V_D [92]. Nevertheless, some patients with COPD do present with shallow slopes but high intercepts and *vice versa* [29, 43]. Additional studies examining changes in $V'_E-V'_{CO_2}$ slope and V'_E intercept across the continuum of COPD severity in the context of structural abnormalities (emphysema severity, pulmonary microvascular abnormalities, small airway disease) and CO_2 chemosensitivity might shed new light on the topic (table 2).

Impact of co-morbidities on ventilatory efficiency

Poor ventilatory efficiency has been consistently reported in PAH [11, 12], heart failure [4–7, 10] and, to a lesser extent, coronary artery disease [95]. This is likely secondary to a complex interaction among increased ventilatory drive from multiple afferent sources (chemo-, baro- and ergoreception) and high V_D/V_T [96]. Impaired ventilatory efficiency persists in COPD with associated PAH [36, 37] with the highest $V'_E-V'_{CO_2}$ slope found in severe, out-of-proportion pulmonary hypertension [38]. Interestingly, the $V'_E-V'_{CO_2}$ slope did not differ in severe to very severe COPD regardless if they had coexistent PAH or not [40]. These findings support the notion that severe respiratory mechanical constraints in COPD dampen an excessive ventilatory response despite potential increases in "wasted" ventilation and other sources of afferent stimuli [29].

Joint analysis of three independent investigations [41, 43, 44] indicates that patients with COPD–heart failure overlap present with higher $V'_E-V'_{CO_2}$ slopes but lower V'_E intercepts than patients with COPD alone (figure S5). Moreover, overlap patients had greater V'_E intercepts compared with heart failure in isolation [43]. Thus,

TABLE 2 Key unanswered clinical questions on exercise ventilatory efficiency in chronic obstructive pulmonary disease (COPD)

Exercise intolerance	What are the structural determinants of increased dead space in mild disease?
	What is the physiological meaning of the $V'_E-V'_{CO_2}$ intercept?
	Is ventilatory efficiency consistently associated with specific disease phenotypes?
	How does very severe, end-stage disease impact on ventilatory efficiency?
	Is resting $V'_E-V'_{CO_2}$ clinically useful to predict exercise intolerance and dyspnea?
Influence of co-morbidities	Do emphysema extent and COPD phenotype influence ventilatory efficiency in COPD- heart failure overlap?
	Do heart failure etiology and heart failure with preserved ejection fraction influence ventilatory efficiency in overlap?
	Does oscillatory exercise ventilation impact on dyspnea and exercise intolerance in overlap?
	What is the effect of exertional hypoxia on ventilatory efficiency in hypoxemic overlap?
	Does ventilatory efficiency relate to right ventricular-pulmonary arterial coupling in COPD?
Risk assessment/prognosis	Why does ventilatory efficiency predict poor peri-operative outcome in lung resection surgery?
	What is the best parameter of ventilatory efficiency to predict poor surgical outcome across the spectrum of disease severity?
	Does poor ventilatory efficiency independently predict poor outcome in severe to very severe patients?
	How best associate ventilatory efficiency with clinical data to determine prognosis?
	Does longitudinal assessment of ventilatory efficiency improve prognosis estimation?
Effects of interventions	Do exercise training and inspiratory muscle training improve ventilatory efficiency?
	What is the most sensitive parameter to detect improvement in ventilatory efficiency?
	Do interventions aimed to improve pulmonary vascular function impact on ventilatory efficiency?
	Is there any beneficial effect on pharmacological interventions in overlap and out-of-proportion pulmonary hypertension?
	Do bronchodilators improve ventilatory efficiency in selected patients?

V'_E: ventilation; V'_{CO_2}: carbon dioxide output.

though heart failure further worsened ventilatory efficiency in COPD, lung mechanical constraints (and increased CO_2 "set-point" in more advanced COPD) blunted the overall ventilatory response compared with heart failure alone. Importantly, impaired ventilatory efficiency in COPD–heart failure overlap was associated with greater exertional dyspnoea and poorer exercise tolerance [44]. There is also recent evidence that periodic breathing, which is associated with increased V_D and poor ventilatory efficiency [96], increases dyspnoea and reduces exercise tolerance in these patients [45]. Of note, the ventilatory oscillations were associated with higher operating lung volumes; moreover, they consistently ceased when critical inspiratory constraints were reached (figure S4) [45]. This observation highlights the overriding influence of abnormal mechanics in constraining exercise ventilation in COPD, even in the presence of a heightened ventilatory drive.

It remains unclear whether emphysema extent, disease phenotype, heart failure aetiology and heart failure with preserved ejection fraction [97] influence ventilatory efficiency in individual COPD–heart failure overlap patients. For instance, coronary artery disease, even without overt heart failure, also increased ventilatory inefficiency in COPD [42]. Arterial hypoxemia leading to high hypoxic drive does not seem to contribute to poor ventilatory efficiency in overlap [44]; however, few hypoxaemic patients were enrolled in previous studies [41, 43, 44]. Although β-blockers failed to decrease the V'_E/V'_{CO_2} nadir in COPD [39], the impact of prospective pharmacological interventions on ventilatory efficiency remains unknown in COPD–heart failure overlap and in COPD patients with out-of-proportion pulmonary hypertension. Potential improvements in ventilatory efficiency might prove valuable to decrease exertional dyspnoea and improve exercise tolerance in selected patients, particularly when cardiocirculatory abnormalities predominate over mechanical constraints (table 2) [38].

Risk assessment and prognosis

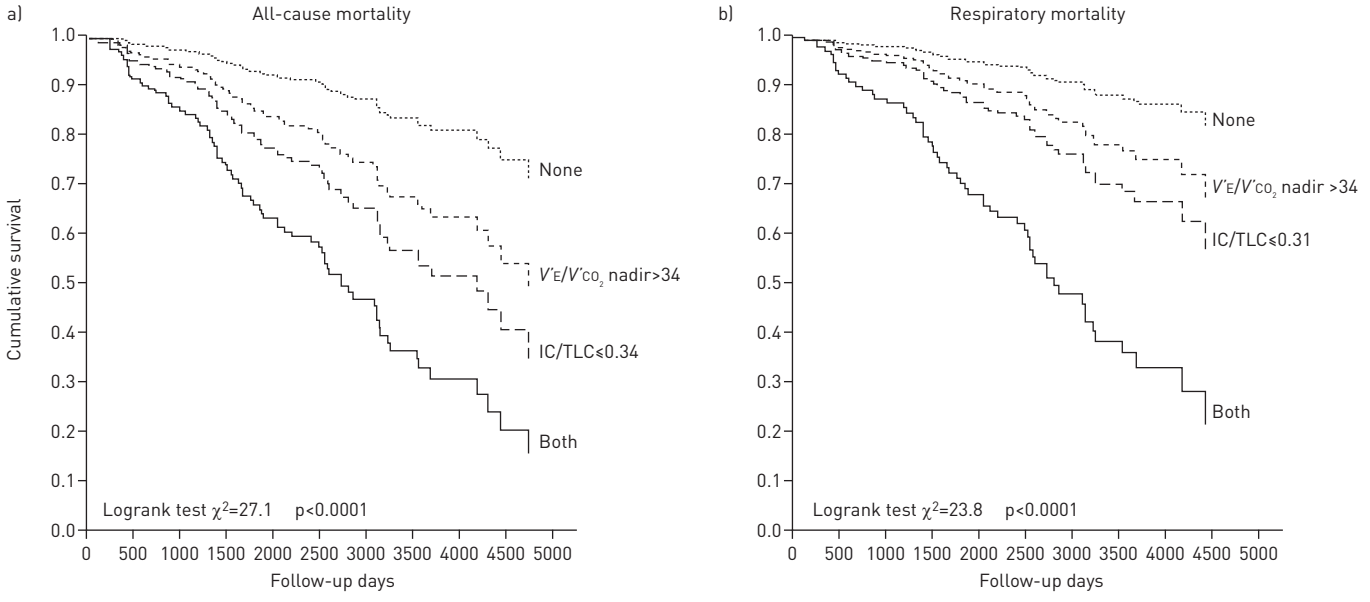
Most patients submitted to lung resection surgery due to lung cancer present with COPD [98]. Resting pulmonary function tests and, to a lesser extent, peak O_2 uptake (V'_{O_2}) [99] have been used to assess perioperative risk in these patients. There is mounting evidence that a high $V'_E-V'_{CO_2}$ slope is also a powerful predictor of poor surgical outcome for lung resection surgery [46–48], likely superior to peak V'_{O_2} [48]. In this context, a high $V'_E-V'_{CO_2}$ slope might indicate greater V_D due to more extensive emphysema and/or high pulmonary vascular pressures, poorer cardiac performance, higher sympathetic drive, worse exertional hypoxemia and greater ergorreceptor stimulation [100]. Of note, however, few patients with severe to very severe COPD (who usually present with lower $V'_E-V'_{CO_2}$ slopes) (figure 2) undergo extensive lung resection surgery and/or pre-operative CPET [46–48]. Thus, it remains to be investigated whether a low $V'_E-V'_{CO_2}$ slope predicts poor outcome in selected patients who despite severe to very severe airflow obstruction are potential candidates for resection, *e.g.* young patients with limited disease and no major co-morbidities.

Poor ventilatory efficiency (increased $V'_E-V'_{CO_2}$ slope or V'_E/V'_{CO_2} nadir) has a powerful negative association with survival in heart failure independent of peak V'_{O_2} [4–7, 10]. A recent study extended these observations to patients with COPD, regardless the presence of coexistent heart failure. Moreover, only resting lung hyperinflation added value to V'_E/V'_{CO_2} nadir as a prognosticator [49]. Interestingly, a high V'_E/V'_{CO_2} nadir predicted mortality due to respiratory and non-respiratory causes, suggesting that the above-mentioned abnormal cardiorespiratory mechanisms may also underlie increased risk of earlier mortality (figure 3) [49]. A small prospective investigation found that a high V'_E/V'_{CO_2} nadir added to impaired resting right ventricular systolic function in predicting poor outcome in COPD–heart failure overlap [50]. If these findings are confirmed in larger multicentre studies, ventilatory efficiency might become an important effort-independent prognostic parameter in patients with COPD with or without heart failure as co-morbidity (table 2).

Effects of interventions

The effects of interventions on ventilatory efficiency have been helpful to uncover the underlying mechanisms of exercise intolerance and dyspnoea in COPD while providing a physiological rationale for their main mechanism of action. For instance, interventions primarily aimed at releasing the mechanical constraints (heliox [55, 59, 60, 65], lobectomy [58], and bronchodilators [54, 56, 64]) increased V'_E at a given V'_{CO_2}. These findings fit well with the concept that an increased slope of the $V'_E-V'_{CO_2}$ relationship should not be uniformly interpreted as indicative of poor ventilatory efficiency in advanced COPD, at least from a "quantitative" perspective. Nevertheless, these interventions also reduced the operating lung volumes and exertional breathlessness; thus, it could be argued that ventilation became "qualitatively" and subjectively more efficient [88].

A different scenario emerged in response to another group of interventions which decreased V'_E at a given V'_{CO_2}. Thus, single- [51] and double-lung [61] transplantation and lung volume reduction surgery [63, 66] lessened V_D and increased V_T thereby reducing V_D/V_T with consequent benefits to ventilatory efficiency. This suggests that the marked effects of these interventions on V_D/V_T (which would lessen V'_E) relatively outweighed the consequences of lower mechanical constraints, which would otherwise increase V'_E [39, 46–49, 98–100]. Lower neural drive (*e.g.* supplemental O_2 [59], spinal anaesthesia [62]) also diminished V'_E at a given



V'E/V'CO2 nadir											
≤34	164	137	106	74	49	35	23	15	11	9	6
>34	124	108	90	72	56	39	23	11	8	6	4
IC/TLC											
>0.34	156	129	96	67	44	28	13	9	7	5	4
≤0.34	132	117	101	80	61	46	33	21	12	6	4
V'E/V'CO2 nadir and IC/TLC											
None	113	93	69	47	29	18	12	8	6	4	2
Both	81	73	64	53	40	28	19	10	4	4	2

≤34	164	137	106	74	49	35	23	15	11	9	
>34	124	108	90	72	56	39	23	11	8	6	
>0.31	174	145	128	94	53	34	25	19	15	10	
≤0.31	114	100	89	78	41	26	20	12	8	4	
None	110	94	79	48	26	16	11	9	6	4	
Both	75	68	59	53	37	25	19	7	5	4	

FIGURE 3 Value of poor ventilatory efficiency (high ventilation (V'_E)/carbon dioxide output (V'_{CO_2}) nadir) in isolation and associated with resting lung hyperinflation (low inspiratory/total lung capacity ratio (IC/TLC)) to predict all cause and respiratory mortality in patients with mild-to-severe COPD. Reproduced from [49] with permission from the publisher.

V'_{CO_2}. Interestingly, some investigations found proportional decrements in V'_E and V'_{CO_2} with O_2 supplementation [52, 53]. This suggests that lower chemoreceptor drive to breathe is not the only mechanism underlying reduction in V'_E during hyperoxia in COPD. Limited evidence also suggests that V'_E tends to decrease in tandem with V'_{CO_2} after exercise training in COPD [57]. This is somewhat surprising considering the potential beneficial effects on breathing pattern (high V_T leading to a low V_D/V_T) and peripheral muscle afferent stimuli [101]. Additional studies are warranted to further investigate the consequences of training on ventilatory efficiency, including the potential beneficial effects of inspiratory muscle training [102].

These considerations raise the question of why inhaled bronchodilators have not consistently changed the V'_E–V'_{CO_2} relationship in COPD [103]. However, it should be recognised that ventilatory efficiency has not been specifically investigated in bronchodilator trials. Since high-intensity, constant work rate exercise testing is more sensitive than incremental CPET for the purpose of bronchodilator evaluation [104, 105], there are only sparse data on effects of bronchodilators on V'_E–V'_{CO_2} slope and V'_E intercept during incremental tests. For instance, less mechanical constraints tending to increase V'_E [39, 46–49, 98–100] may be off-set by a lower V_D/V_T, which tends to decrease V'_E [50, 55, 59, 60]. Such complex interactions would probably vary among subjects in large clinical trials. This topic also merits more detail analysis as inter-individual changes in ventilatory efficiency may explain the reported variability on exercise tolerance and dyspnoea despite apparent beneficial effects on resting lung mechanics in recent trials (table 2) [103]. For example, in mild COPD, effective bronchodilation and lung deflation may not translate into improved dyspnoea and exercise endurance if decreased ventilatory efficiency (and consequent increased inspiratory neural drive) remain unchanged [16, 106].

Applying ventilatory efficiency to clinical management of COPD

Based on the evidence summarised in table 1, there are some specific scenarios in which the V'_E–V'_{CO_2} measurement can be useful to address clinically relevant issues in patients with COPD. Firstly, most symptomatic patients with preserved or only mildly reduced FEV1 are chronically sedentary [30]. Establishing an association between excess exercise ventilation and greater dyspnoea scores would provide evidence that patient's exercise intolerance is not a mere consequence of detraining [9, 16, 87]. This might prompt a more proactive approach to early treatment [107]. Secondly, some patients with COPD might present with

"out-of-proportion" breathlessness (to FEV_1 impairment) [9, 88]. Poor ventilatory efficiency, often driving faster rates of dynamic hyperinflation [9, 16, 87], would provide a mechanistic explanation to patients' symptoms. This might indicate room for treatment optimisation, including pharmacological (*e.g.* dual bronchodilatation) [103] and non-pharmacological (*e.g.* pulmonary rehabilitation to decrease ventilatory demands) [57, 108]. Thirdly, marked increases in V'_E/V'_{CO_2} nadir should raise concerns regarding coexisting pulmonary hypertension [36, 39] or, in the right clinical context, heart failure [43, 44]. This is particularly true in the absence of another potential explanation for increased "wasted" ventilation, such as extensive emphysema on chest computed tomography [18]. Identification of co-morbidities increasing exercise ventilation and symptom burden is also important to avoid the potential iatrogenic consequences of excessive bronchodilator inhalation in patients with coexistent cardiovascular disease [109, 110]. Thus, further cardiological assessment might be warranted in these patients. Fourthly, a high V'_E/V'_{CO_2} nadir in COPD patients with lung cancer should raise concerns regarding increased risk of peri-operative complications [46–48]. This might influence the decision in favour of a more economical resection in high-risk patients. Fifthly, identification of a high V'_E/V'_{CO_2} nadir in a severely hyperinflated patient would indicate higher risk of a life-threatening exacerbation [49]. Thus, the patient would benefit from closer follow up and optimisation of anti-exacerbation measures (*e.g.* phosphodiesterase inhibitor, action plan, macrolide prophylaxis). Finally, documenting improved ventilatory efficiency after lung transplantation [51, 61] or lung volume reduction surgery [63, 66] would provide objective evidence of efficacy of these costly treatment approaches.

Conclusions

Compared with heart failure, for which the determinants and clinical consequences of an abnormal exercise $V'_E-V'_{CO_2}$ relationship have been well established, the value of ventilatory efficiency measurement during exercise has only recently become a target for systematic scrutiny in COPD (table 1). As in heart failure, the $V'_E-V'_{CO_2}$ slope and the V'_E/V'_{CO_2} nadir are consistently increased in patients with mild to moderate COPD likely exposing unsuspected but clinically significant ventilation/perfusion abnormalities within the lungs. Conversely, while these specific efficiency parameters continue to worsen as heart failure progresses, this is not necessarily the case with advancing COPD due to increasing ventilatory constraints. Thus, a seemingly "normal" $V'_E-V'_{CO_2}$ slope does not rule out abnormal ventilatory efficiency in more advanced COPD. Higher V'_E intercept as COPD worsens, however, may result in a progressively higher V'_E/V'_{CO_2} nadir. In fact, the contribution of a high V'_E intercept to V'_E/V'_{CO_2} nadir increases as COPD evolves (as detailed in the supplementary material). Thus, the V'_E intercept might add important information to the interpretation of ventilatory (in)efficiency in patients with severe to very severe COPD.

Although much remains to be discovered, there is growing evidence that measurement of exercise ventilatory efficiency has potential clinical utility across the spectrum of disease severity in COPD. The V'_E/V'_{CO_2} nadir seems a particularly useful index of ventilatory efficiency across the continuum of disease severity, being linked to important clinical outcomes such as dyspnoea, reduced exercise capacity and even mortality (table 1). Based on recent studies, ventilatory efficiency measurements may be important for the individualised assessment of exercise intolerance in mild-to-moderate COPD, notably in individuals with disproportionate dyspnoea (table 1).

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