Excess ventilation and exertional dyspnoea in heart failure and pulmonary hypertension

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Abstract

Increased ventilation relative to metabolic demands, indicating alveolar hyperventilation and/or increased physiological dead space (excess ventilation), is a key cause of exertional dyspnoea. Excess ventilation has assumed a prominent role in the functional assessment of patients with heart failure (HF) with reduced (HFrEF) or preserved (HFpEF) ejection fraction, pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH). We herein provide the key pieces of information to the caring physician to 1) gain unique insights into the seeds of patients' shortness of breath and 2) develop a rationale for therapeutically lessening excess ventilation to mitigate this distressing symptom. Reduced bulk oxygen transfer induced by cardiac output limitation and/or right ventricle–pulmonary arterial uncoupling increase neurochemical afferent stimulation and (largely chemo-) receptor sensitivity, leading to alveolar hyperventilation in HFrEF, PAH and small-vessel, distal CTEPH. As such, interventions geared to improve central haemodynamics and/or reduce chemosensitivity have been particularly effective in lessening their excess ventilation. In contrast, 1) high filling pressures in HFpEF and 2) impaired lung perfusion leading to ventilation/perfusion mismatch in proximal CTEPH conspire to increase physiological dead space. Accordingly, 1) decreasing pulmonary capillary pressures and 2) mechanically unclogging larger pulmonary vessels (pulmonary endarterectomy and balloon pulmonary angioplasty) have been associated with larger decrements in excess ventilation. Exercise training has a strong beneficial effect across diseases. Addressing some major unanswered questions on the link of excess ventilation with exertional dyspnoea under the modulating influence of pharmacological and nonpharmacological interventions might prove instrumental to alleviate the devastating consequences of these prevalent diseases.

Introduction

It does not seem that all movement is exercise, but only when it is vigorous … The criterion of vigorousness is a change of respiration; those movements which do not alter the respiration are not called exercise. But if anyone is compelled by any movement to breathe more or less faster, that movement becomes an exercise for him.

Galen (129–?199/216) in "On the Preservation of Health" *(De sanitate tuenda)*

The mechanisms controlling pulmonary ventilation ($\dot{V}_E$) during exercise have riveted and puzzled scientists and physicians over many centuries [1]. It has long been established that $\dot{V}_E$ increases in tandem with carbon dioxide output ($\dot{V}_{CO_2}$) at least before hyperventilation is required to compensate for lactic acidosis on "heavy" exercise (reviewed, for instance, in [2, 3]). In many cardiopulmonary diseases, however, $\dot{V}_E$ may increase out of proportion to $\dot{V}_{CO_2}$ (excess ventilation; note: we prefer the term "excess ventilation" to
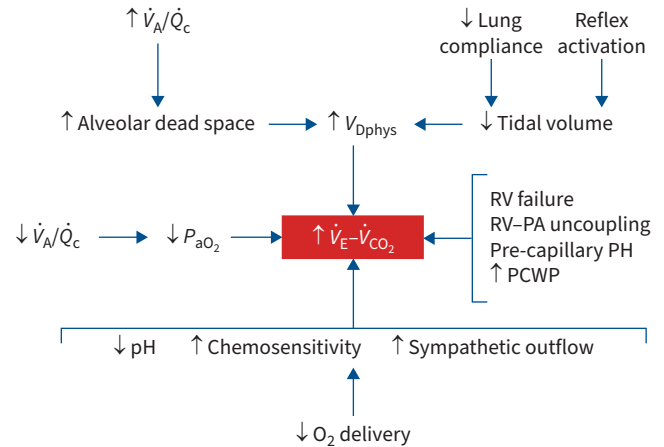
FIGURE 1 Main abnormalities in cardiopulmonary interactions that may interfere with the ventilatory control system during exercise, leading to excess exertional ventilation (increased ventilation ($\dot{V}_E$)–pulmonary CO_2 output ($\dot{V}_{CO_2}$) relationship) in patients with cardiac and/or pulmonary vascular disease. See text for elaboration. ↑: increased; ↓: decreased; $\dot{V}_A$: alveolar ventilation; $\dot{Q}_c$: capillary perfusion; V_{Dphys}: physiological dead space; P_{aO_2}: arterial O_2 partial pressure; RV: right ventricle; PA: pulmonary artery; PH: pulmonary hypertension; PCWP: pulmonary capillary wedge pressure.

refer to a high $\dot{V}_E$–$\dot{V}_{CO_2}$ rather than "ventilatory", or gas exchange, inefficiency since there is no "inefficiency" when it is associated with alveolar hyperventilation) [4] even with modest exertion, *i.e.* during daily life activities. Such heightened ventilation is readily translated into exertional dyspnoea [5], the most troublesome symptom reported by these patients [6]. Recognising the determinants and consequences of a high $\dot{V}_E$–$\dot{V}_{CO_2}$ is therefore of great clinical value to all involved in the care of patients with lung and/or heart diseases [7–9].

In the present state-of-the-art review we focus in two prevalent cardiopulmonary diseases in which excess ventilation measured during incremental cardiopulmonary exercise testing (CPET) has assumed a prominent role in the assessment of functional impairment, treatment efficacy and prognosis: heart failure (HF) [10] and pulmonary hypertension (PH) [11]. Our overarching goal is to provide the key pieces of information to the caring physician to 1) gain unique insights into the seeds of patients' shortness of breath and 2) develop a rationale for therapeutically lessening $\dot{V}_E$–$\dot{V}_{CO_2}$ to mitigate this distressing symptom (figure 1). We emphasise pharmacological and nonpharmacological interventions which shed novel light on fundamental mechanisms of disease. Since the sources of ventilatory stimulation may differ depending on the mechanisms of haemodynamic impairment and exercise limitation, we contrast HF with reduced (HFrEF) *versus* preserved (HRpEF) left ventricular ejection fraction (LVEF) and pulmonary arterial hypertension (PAH) *versus* chronic thromboembolic PH (CTEPH). We refrain from discussing the prognostic implications of excess ventilation as they have already been reviewed in detail elsewhere [10, 12, 13].

The $\dot{V}_E/\dot{V}_{CO_2}$ relationship
Physiological foundations
Alveolar ventilation ($\dot{V}_A$) changes with admirable precision relative to $\dot{V}_{CO_2}$ in such a way that the arterial partial pressure for CO_2 (P_{aCO_2}) is maintained (↔) within ±3 mmHg throughout mild-to-moderate exercise (figure 2c) [14]. Such a tight control of P_{aCO_2} occurs despite a marked improvement in the efficiency of the lungs as gas exchangers: the dead space (V_D)/tidal volume (V_T) ratio (physiological dead space (V_{Dphys})) decreases (↓) hyperbolically [3] (figure 2a) because 1) V_T increases out of proportion (↑↑) to airway "anatomical" V_D and 2) the higher compliance of the alveoli over that of the airways, *i.e.* more air goes to the alveoli than the airways [15]:

$$\leftrightarrow P_{aCO_2} = \cfrac{1}{\downarrow\cfrac{\dot{V}_E}{\dot{V}_{CO_2}} \times \left(1 - \left(\cfrac{\uparrow V_D}{\uparrow\uparrow V_T}\right)\right)}$$
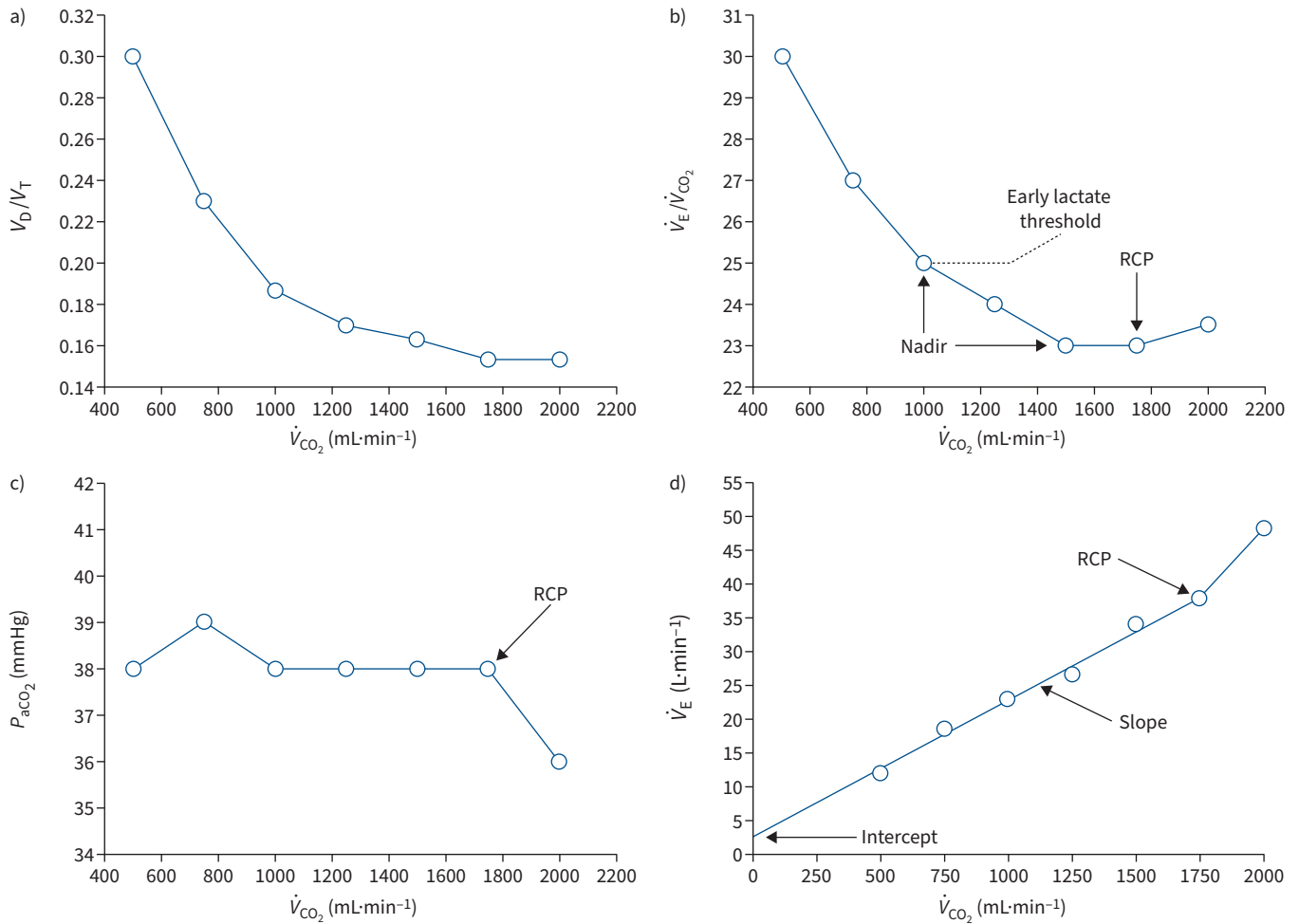
FIGURE 2 Selected ventilatory and gas exchange responses to incremental cardiopulmonary exercise testing in a young healthy male. Proportional decreases in a) dead space (V_D)/tidal volume (V_T) and b) ventilation ($\dot{V}_E$)/CO_2 output ($\dot{V}_{CO_2}$) ratios maintain c) arterial CO_2 partial pressure (P_{aCO_2}) close to resting value during mild-to-moderate exercise. d) The $\dot{V}_E/\dot{V}_{CO_2}$ response contour is established by both slope and intercept of the linear $\dot{V}_E$–$\dot{V}_{CO_2}$ relationship. Thus, the lowest (nadir) $\dot{V}_E/\dot{V}_{CO_2}$ closely approximates slope plus intercept. $\dot{V}_E$ increases out of proportion to $\dot{V}_{CO_2}$ after the respiratory compensation point (RCP) (b–d) leading to respiratory alkalosis (c) to compensate for progressive lactic acidaemia. Note the increases in nadir when the lactate threshold is reached at a low exercise intensity, i.e. before the stabilisation of $\dot{V}_E/\dot{V}_{CO_2}$. See text for further elaboration. Reproduced from [212], with permission.

Thus, if $\dot{V}_E/\dot{V}_{CO_2}$ did not decrease in tandem with V_D/V_T (compare figure 2a and b), $\dot{V}_A/\dot{V}_{CO_2}$ would increase: too much fresh air relative to the rate of CO_2 transfer from capillary blood to alveoli would lead to alveolar hyperventilation, i.e. a low P_{aCO_2}. Conversely, an out-of-proportion decrease in $\dot{V}_E/\dot{V}_{CO_2}$ relative to V_D/V_T would result in a low $\dot{V}_A/\dot{V}_{CO_2}$: too little fresh air relative to the rate of CO_2 transfer flow from capillary blood to alveoli would cause alveolar hypoventilation, i.e. a high P_{aCO_2} [14, 15]. The corollary is that the lower the P_{aCO_2} and the higher the wasted ventilation in V_{Dphys}, the higher the excess ventilation (figure 2) [16]:

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

(Note: a higher wasted ventilation indicates that a larger total V_D is required to explain the observed impairment in CO_2 elimination. The V_{Dphys} as calculated by Enghoff's modification of the original Bohr's approach (the dead space fraction of the tidal volume (V_D/V_T)) includes 1) apparatus V_D, 2) anatomical V_D, 3) alveolar V_D (preserved alveolar ventilation ($\dot{V}_A$), no capillary perfusion ($\dot{Q}_c$)), 4) V_D effect (high $\dot{V}_A/\dot{Q}_c$,

usually due to normal $\dot{V}_A$ but low $\dot{Q}_c$) and 5) any contribution of shunt to increase P_{aCO_2}. In this context, 1) and 2) are "series" V_D, whereas 3) to 5) are "parallel" V_D.)

Some practicalities on $\dot{V}_E$–$\dot{V}_{CO_2}$ measurement and interpretation

The $\dot{V}_E/\dot{V}_{CO_2}$ ratio in response to incremental CPET decreases down to the estimated lactate threshold, remaining stable at its lowest value (nadir) before increasing after the respiratory compensation point (RCP) for lactic acidosis [17]. Thus, plotting $\dot{V}_E$ (y) as a function of $\dot{V}_{CO_2}$ (x) produces a linear relationship up to the RCP. It should be noted that even at an imaginary "zero" $\dot{V}_{CO_2}$, $\dot{V}_E$ is above the axis intersection (called the "intercept", usually 2–3 L·min^{-1} $\dot{V}_E$ in normal subjects) (figure 2c) [16]. It follows that the steeper the $\dot{V}_E$–$\dot{V}_{CO_2}$ slope and/or the higher the $\dot{V}_E$ intercept, the higher the $\dot{V}_E/\dot{V}_{CO_2}$ nadir [14]. Another cause of a high $\dot{V}_E/\dot{V}_{CO_2}$ nadir is an early lactate threshold as this will precociously interrupt the decreasing trajectory of $\dot{V}_E/\dot{V}_{CO_2}$, overestimating excess ventilation (figure 2b) [4]. Although the increased $\dot{V}_E$–$\dot{V}_{CO_2}$ beyond the RCP reflects the intensity of the hyperventilation required to compensate for acidosis rather than abnormalities in ventilatory control [2], drawing a single line from the start to peak exercise improves the negative prognostic value of a high $\dot{V}_E$–$\dot{V}_{CO_2}$ slope in HF [18] and PH [19]. Reference values for $\dot{V}_E/\dot{V}_{CO_2}$ nadir [20, 21] and $\dot{V}_E$–$\dot{V}_{CO_2}$ slope [22, 23] are available as well as cut-offs for clinical decision making in HF [24] and PAH [25]. As a rule of thumb, values >34–35 have been associated with negative outcomes in HF [26], chronic obstructive pulmonary disease (COPD) [27] and COPD–HF overlap [28], although the use of percentage predicted is physiologically sounder as higher values are seen in women and elderly subjects [29].

The importance of directly measuring P_{aCO_2} and V_D/V_T in dyspnoeic patients showing excess ventilation cannot be underestimated. Specifically, end-tidal partial pressure for CO_2 (P_{ETCO_2}) should not be used to estimate P_{aCO_2}, particularly in patients. For instance, resting P_{ETCO_2} is 3–4 mmHg lower than P_{aCO_2}, with their difference correlating well with wasted ventilation [30]. This is the case because less CO_2 is unloaded from capillary blood to alveoli the higher the V_{Dphys}. During exercise, P_{ETCO_2} is greater than P_{aCO_2} in health (i.e. the $P_{(a-ET)CO_2}$ difference becomes negative) due to the effects of [31]: 1) increases in pulmonary blood flow with CO_2-enriched mixed venous blood, 2) faster and more homogeneous lung emptying, and, importantly, 3) a larger V_T leading to greater sampling of alveolar gas.

Relating P_{ETCO_2} to P_{aCO_2}, therefore, can be particularly informative: whereas 1) impaired perfusion of ventilated areas leading to a high V_{Dphys} decreases P_{ETCO_2} out of proportion to P_{aCO_2} (i.e. P_{ETCO_2} fails to surpass P_{aCO_2}), 2) a narrow $P_{(a-ET)CO_2}$ coupled with a low P_{aCO_2} indicates alveolar hyperventilation [32]. Replacing P_{aCO_2} by P_{ETCO_2} to estimate V_D/V_T in scenario 1) is particularly misleading: the worse the wasted ventilation, the lower the P_{ETCO_2} relative to P_{aCO_2} and, consequently, the larger the V_D/V_T underestimation [33]. Regardless of the underlying cause(s), a lack of increase in P_{ETCO_2} [34] and/or a low peak value [35] signals more advanced PH [34, 35] and HF [36] since both 1) and 2) are markers of disease severity. High $\dot{V}_E/\dot{V}_{CO_2}$ and low P_{ETCO_2} (and P_{aCO_2}) are also seen in primary hyperventilation [37]: noncyclical surges in $\dot{V}_E/\dot{V}_{CO_2}$ and an erratic breathing pattern (dysfunctional breathing) [38] are useful to suggest, in the right clinical context, this frequent cause of unexplained dyspnoea [39].

Excess ventilation and exertional dyspnoea

Exertional dyspnoea in cardiopulmonary disease arises from a disparity between the neural drive to breathe from bulbo-pontine and cortical respiratory control centres and the capacity of the respiratory system to respond appropriately [40]. The patient's ability to 1) translate or 2) not translate a heightened drive into the mechanical act of breathing (V_T and $\dot{V}_E$) establishes the presence of [41]: 1) "excessive breathing" wherein V_T expansion is not mechanically constrained and the sensation of increased "work/effort" increases as a function of work rate, but is relatively proportional to $\dot{V}_E$, or 2) "impeded breathing" wherein V_T expansion is mechanically constrained and the sensation of unsatisfied inspiration increases as a function of both work rate and $\dot{V}_E$. In most circumstances, exertional dyspnoea caused by a high $\dot{V}_E$–$\dot{V}_{CO_2}$ is caused by "excessive breathing". However, in the presence of associated ventilatory impairment, a heightened $\dot{V}_E$ may hasten the development of mechanical constraints, leading to "impeded breathing" [42].

Heart failure with reduced left ventricular ejection fraction
Mechanisms of excess ventilation in HFrEF

Excess ventilation is observed in most dyspnoeic patients with moderate to severe HFrEF (LVEF <40%) [10, 12, 13]. A high $\dot{V}_E$–$\dot{V}_{CO_2}$ is commonly associated with a tachypnoeic and shallow breathing pattern, and, as the disease progresses, with cycles of waxing and waning ventilation, i.e. exertional oscillatory ventilation (EOV) [10]. There is solid evidence that V_{Dphys} does not decrease as expected in many patients showing a high $\dot{V}_E$–$\dot{V}_{CO_2}$ (figure 3) [43, 44]. Although enlarged areas of high $\dot{V}_A/\dot{Q}_c$ due to perfusion abnormalities with or without associated PH [45, 46] may increase V_D, a low V_T seems the dominant
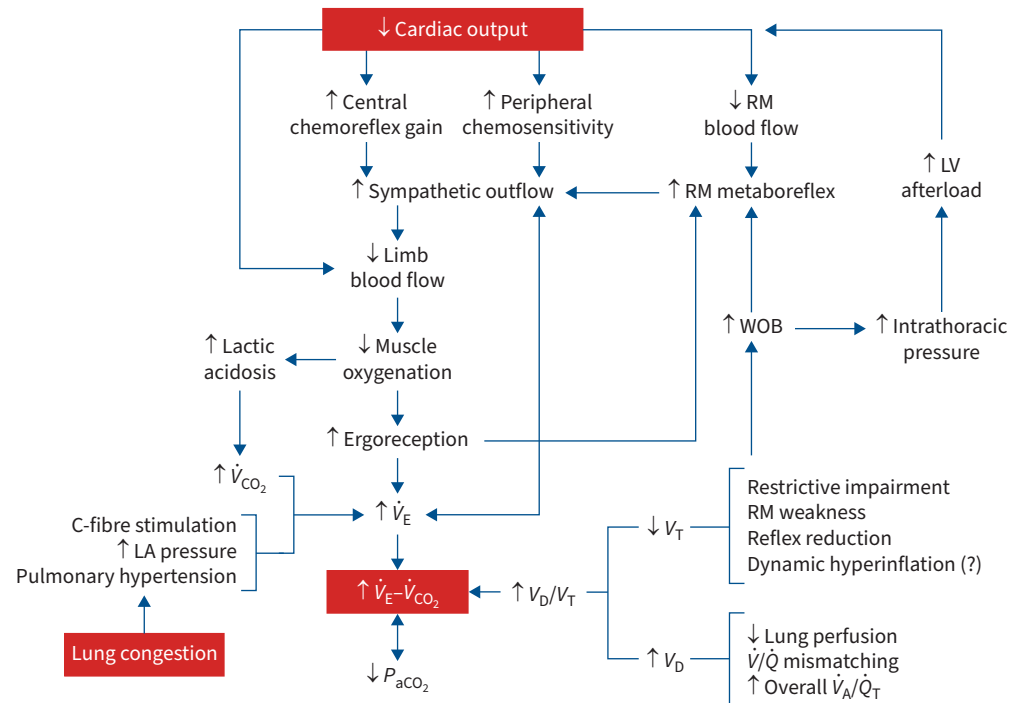
FIGURE 3 The main mechanisms linking the fundamental pathophysiological features of heart failure (HF) (low cardiac output and lung congestion) with excess exertional ventilation, i.e. high ventilation ($\dot{V}_E$)–CO_2 output ($\dot{V}_{CO_2}$) relationship. The relative importance of individual mechanisms varies according to disease phenotype, i.e. HF with reduced versus preserved ejection fraction. See text for elaboration. ↑: increased; ↓: decreased; RM: respiratory muscle; LV: left ventricle; WOB: work of breathing; LA: left atrium; V_D: dead space; V_T: tidal volume; P_{aCO_2}: arterial CO_2 partial pressure; $\dot{V}_A$: alveolar ventilation; $\dot{Q}_T$: cardiac output.

factor [47, 48] due to: 1) changes in breathing pattern induced by heightened chemostimulation [49], 2) inspiratory constraints secondary to low lung compliance [50] and 3) inspiratory muscle weakness [51].

The impact of reactive PH (i.e. beyond expected from left heart pressures) [52] on excess ventilation in HFrEF is marked: a steep $\dot{V}_E$–$\dot{V}_{CO_2}$ slope (>41), a lack of change in P_{ETCO_2} on exercise (<1.2 mmHg) (see section: Some practicalities on $\dot{V}_E$–$\dot{V}_{CO_2}$ measurement and interpretation) and EOV were highly predictive of combined pre- and post-capillary PH [53]. Although some studies reported that a high V_{Dphys} could contribute to up to 40% of the measured $\dot{V}_E$–$\dot{V}_{CO_2}$ [54, 55], the bulk of the available evidence indicates that excess ventilation is more closely related to alveolar hyperventilation secondary to (figure 3) [8]: 1) increased central command to recruit additional motor units to maintain the workload of fatiguing peripheral muscles with simultaneous increase in $\dot{V}_E$ and sympathetic nerve activity [56]; 2) heightened afferent stimuli from over-sensitised ergoreceptors [57] and excessive metabolite accumulation in the peripheral [58, 59] and respiratory muscles; 3) carotid body-mediated chemoreceptor hypersensitivity [49, 60] and heightened response of the central chemoreceptors to CO_2 [61]; 4) associated PH [53, 62, 63] and/or increased pulmonary vascular pressures/right ventricle–pulmonary artery uncoupling [64, 65], particularly when associated with mitral regurgitation and atrial fibrillation increasing backward flow and impaired pulsatile and/or resistive loading on the pulmonary circulation [66, 67]; and 5) other congestive consequences of the disease, such as increased left atrial pressure [68], J reflex due to interstitial oedema [69], right atrial strain [70] and peripheral venular distension [71].

Persistent stimulation of the carotid bodies chemoreceptors increases their sensitivity to further stimuli, i.e. they respond to progressively smaller variations in CO_2 [72]. As the cardiac output deteriorates with disease progression, there is a longer circulatory time between the lungs and the chemoreceptors [73]. The resulting delay in the ventilatory response to a given variation in P_{aCO_2} predisposes to over-corrections [73]. This is further amplified by the decrease in lung volumes since the lower the CO_2 reservoir in the lungs, the greater the variation in P_{aCO_2} at a given ventilation [74]. A chronically low P_{aCO_2} may also impair the expected cerebral vasoconstriction; consequently, less H^+ accumulates close to the central chemoreceptors, further destabilising the ventilatory control system [75]. The resulting EOV is a powerful

marker of disease severity [76] and poor prognosis in HFrEF [74]. Interestingly, EOV is rarely observed in PAH compared with HFrEF with relatively similar reductions in cardiac index [77]. These data provide important supportive evidence in favour of post-capillary PH and sustained J receptor stimulation [67] causing out-of-proportion vagal reflex activation and breathing instability in HFrEF. From a practical perspective, despite a markedly steep $\dot{V}_E$–$\dot{V}_{CO_2}$ slope, the fluctuations might be missed as $\dot{V}_E$ and $\dot{V}_{CO_2}$ oscillate in phase. Thus, EOV is better appreciated (and quantified) when $\dot{V}_E$ is plotted as a function of time during incremental exercise [78].

The coexistence of respiratory diseases associated with mechanical constraints to V_T expansion, such as COPD, has a blunting effect on the rate of $\dot{V}_E$ increase, leading to shallower $\dot{V}_E$–$\dot{V}_{CO_2}$ slopes [79–81]. Interestingly, patients with coexistent HFrEF–COPD characteristically present with higher $\dot{V}_E$ intercepts than those with HFrEF alone, potentially reflecting a high resting V_{Dphys} [44]. Attainment of critically low inspiratory reserve volumes in HFrEF–COPD led to a sudden cessation of EOV but a sharp increase in dyspnoea as the heightened ventilatory drive could not be translated into higher $\dot{V}_E$ [82]. Notwithstanding the greater relevance of mechanical factors in combined cardiorespiratory disease, the highest $\dot{V}_E/\dot{V}_{CO_2}$ nadirs in HFrEF–COPD were associated with lower P_{aCO_2} rather than higher V_{Dphys} [83], confirming the central role for alveolar hyperventilation as a cause of excess ventilation in HFrEF.

Effects of selected interventions on excess ventilation in HFrEF

Seminal studies exploring the effects of interventions on excess ventilation in HFrEF found less chemoreceptor activation in response to hyperoxia [84] and low-dose opiates [85], with relatively commensurate decrements in $\dot{V}_E$–$\dot{V}_{CO_2}$ and exertional dyspnoea. In fact, carotid body denervation was associated with lower ventilation, sympatho-excitation and mortality in animals with HFrEF [86]. After a case description [87], a small (n=10) study in humans found that unilateral resection decreased sympathetic activity and ventilation [87]. Unfortunately, however, this was associated with worsening oxygenation at night. Owing to the risks associated with blunted protective responses to hypoxia (*e.g.* air flight and altitude) [88], and the deleterious consequences to comorbid respiratory disease and obstructive sleep apnoea, this approach remains largely experimental [89]. A further complicating issue is the current controversy on the optimum methodology for assessing chemoreceptor sensitivity [90]. The strong antiadrenergic effect of carvedilol (α-, β$_1$- and β$_2$-blocker) provided further evidence of the relevance of carotid bodies in promoting excess ventilation in HFrEF [91]: despite worsening pulmonary gas exchange (likely increasing V_{Dphys}) [92], carvedilol was more effective than selective β-blockers in decreasing peripheral chemoreceptor activity [93], lessening hyperventilation [94] and $\dot{V}_E$–$\dot{V}_{CO_2}$ [92]. Interestingly, long-term β-blocker treatment reduced the dyspnoea–$\dot{V}_E$ slope (less "impeded breathing") [95], suggesting lower lung congestion/higher lung compliance and/or higher inspiratory muscle strength [91, 96].

Pharmacological interventions geared towards improving pulmonary gas exchange efficiency also showed some positive effects on excess ventilation in HFrEF. For instance, the angiotensin-converting enzyme inhibitor (ACEi) enalapril [97] improved the membrane component of the diffusing capacity of the lung for carbon monoxide (D_{LCO}) [98], decreasing V_D/V_T and $\dot{V}_E$–$\dot{V}_{CO_2}$ (see section: Key unanswered questions on $\dot{V}_E$–$\dot{V}_{CO_2}$ and exertional dyspnoea; table 1) [99]. These salutary effects were ascribed to increased local concentration of prostaglandins readjusting lung vessel tone and membrane conductance [97] since they were virtually abolished by cyclooxygenase inhibition [99]. The angiotensin II receptor blocker (ARB) losartan, which lacks significant pulmonary vascular effects, did not change $\dot{V}_E$–$\dot{V}_{CO_2}$ [100, 101]. The modest/absent effect of ARBs on excess ventilation may explain recent findings showing that valsartan neprilysin inhibition was not superior to enalapril in decreasing $\dot{V}_E$–$\dot{V}_{CO_2}$ [102, 103]. Since the protection by ACEi against alveolar oedema varies according to insertion/deletion polymorphism genotypes [104], they may carry a role in explaining the variability in prevalence and severity of excess ventilation in patients with similar haemodynamic impairment (see section: Key unanswered questions on $\dot{V}_E$–$\dot{V}_{CO_2}$ and exertional dyspnoea; table 1).

The beneficial effects of exercise training in $\dot{V}_E$–$\dot{V}_{CO_2}$ and breathing stability in HFrEF are likely multiple and interconnected: 1) improved respiratory muscle strength and endurance [105], particularly when potentiated by inspiratory muscle training [106, 107]; 2) decreased peripheral chemoreceptor sensitivity [108] and, potentially, the beneficial consequences of less hyperventilation (higher P_{aCO_2}) on the former [37]; 3) improved neurovascular control [109] and bulk muscle blood flow and distribution [110] leading to less activation of ergoreceptors [59]; and 4) enhancing muscle "quality" as intramuscular fat, likely disturbing blood flow distribution [111], strongly predicted the lessening effects of muscle afferent blockade on $\dot{V}_E$–$\dot{V}_{CO_2}$ [112].

Of note, the relevance of disturbed peripheral haemodynamics to mitigate excess ventilation has also been highlighted by the positive effects of sildenafil [113] and respiratory muscle unloading [114] which

increased muscle blood flow reducing O_2 extraction at a given O_2 uptake [115]. Part of the beneficial effects of sildenafil on excess ventilation (including EOV) [116] and dyspnoea, however, might be related by lower PH on exertion [117]. Despite all the advances in our understanding of the major clinical relevance of excess ventilation in HFrEF, its actual role in guiding pharmacological treatment in individual patients remains elusive (see section: Key unanswered questions on $\dot{V}_E$–$\dot{V}_{CO_2}$ and exertional dyspnoea; table 1) [91].

Heart failure with preserved left ventricular ejection fraction
Mechanisms of excess ventilation in HFpEF
HFpEF (LVEF ⩾50%) is characterised by mild systolic dysfunction but pronounced limitations in systolic reserve capacity during the stress of exercise. Increased left ventricular filling pressure secondary to diastolic dysfunction may cause secondary ("group 2") PH which adds to effects of chronotropic incompetence, left atrial dysfunction, arterial stiffening, autonomic imbalance, and endothelial and skeletal muscle dysfunction, to cause severe exercise intolerance [118]. Despite ample variability, $\dot{V}_E$–$\dot{V}_{CO_2}$ is typically not as elevated or frequent as in HFrEF [118]; nevertheless, the clinical implications of an increased $\dot{V}_E$–$\dot{V}_{CO_2}$ *vis-à-vis* morbidity (dyspnoea) and mortality are similar [119]. In fact, a large recent study (n=1347) found that all-cause mortality and HF hospitalisation were increased across the spectrum of HF, including those with mid-range HF, *i.e.* LVEF ⩾40–<50% [120]. Exercise-induced mitral regurgitation was commonly seen in all HF subtypes, being associated with right ventricle–pulmonary circulation uncoupling. Interestingly, these abnormalities were unexpectedly prevalent in HFpEF: concomitant increases in heart rate and peripheral O_2 extraction may signal adaptive mechanisms to backward flow redistribution [66]. For most patients with HFpEF, a high V_{Dphys} seems to overcome alveolar hyperventilation as the primary aetiological mechanism for excess exertional ventilation secondary to (figure 3) [55, 121, 122]: 1) impaired right ventricle–pulmonary arterial coupling [66] and right ventricular contractile dysfunction altering pulmonary blood flow [55], a stiff pulmonary circulation [123], and impaired gas conductance [124] jointly leading to increased areas of high $\dot{V}_A/\dot{Q}_c$ and alveolar V_D [125, 126]; and 2) a fast and superficial breathing pattern [127], likely secondary to excessive J receptor stimulation (vagally mediated reflexes) [69] associated with high pulmonary capillary wedge pressure (PCWP) [127], left atrial distention/pulmonary venous hypertension [68], reduced lung compliance due to congestion [128] and occasionally inspiratory muscle weakness [51].

The few studies that measured P_{aCO_2} during exercise in patients with HFpEF found values slightly lower than expected but still within the eucapnic range [55, 126]. The sympathetic outflow is characteristically increased in HFpEF from the earlier stages of the disease and the central chemoreflex is enhanced [129]; moreover, acute activation of central chemoreceptors leads to further increases of cardiac sympathetic outflow and impairment in cardiac function in animal models [130]. These data coupled with the known importance of skeletal muscle abnormalities at the limits of exercise tolerance in HFpEF [131] suggest that a role for increased neurochemical input to increase $\dot{V}_E$–$\dot{V}_{CO_2}$ may have been overlooked (see section: Key unanswered questions on $\dot{V}_E$–$\dot{V}_{CO_2}$ and exertional dyspnoea; table 1).

Effects of selected interventions on excess ventilation in HFpEF
The increased relevance of a high V_{Dphys} in explaining excess ventilation and higher diastolic pulmonary arterial pressure (PAP) for a given PCWP (suggesting a stiffer pulmonary circulation) in HFpEF than HFrEF might represent a higher frequency of pulmonary vascular disease in the former. Combined pre- and post-capillary PH characteristically leads to higher $\dot{V}_E/\dot{V}_{CO_2}$ compared with post-capillary PH in HFpEF [132]. Newer strategies focused on improving right ventricle function: adding to impaired aerobic capacity unveils a specific HFpEF phenotype characterised by a greater burden of right-sided heart disease and combined pre- and post-capillary PH [133]. Unfortunately, however, the vasodilators praliciguat [134] and sildenafil [135] failed to decrease the $\dot{V}_E$–$\dot{V}_{CO_2}$ slope in these patients. It remains to be tested whether subsets of patients would benefit from these medications. Intrinsic pulmonary vasculopathy and micro-vessel remodelling, for example, is more frequently found in the obese/metabolic syndrome phenotype of HFpEF [136].

Joining echocardiographic measures of right ventricle–pulmonary circulation uncoupling (*e.g.* low tricuspid annular plane systolic excursion/pulmonary artery systolic pressure ratio) [137] with excess ventilation and other clinical data (*e.g.* atrial fibrillation, high brain natriuretic peptide and severity of diastolic dysfunction) might prove useful to phenotype HFrEF patients more prone to respond to interventions aimed at improving right-side haemodynamics in HFpEF (see section: Key unanswered questions on $\dot{V}_E$–$\dot{V}_{CO_2}$ and exertional dyspnoea; table 1) [138]. A small study found lower $\dot{V}_E$–$\dot{V}_{CO_2}$ and dyspnoea with exertional O_2 supplementation in a nonhypoxaemic group of patients with HFpEF and associated PH [139]; whether this was secondary to lower pulmonary vascular pressures and/or decreased peripheral

chemosensitivity remains unclear. The mechanisms akin to those previously described for HFpEF likely explain the beneficial effects of exercise training in decreasing $\dot{V}_E–\dot{V}_{CO_2}$ in HFpEF [140], perhaps with an even greater relative contribution of "peripheral" mechanisms, *i.e.* improved microvascular and/or skeletal muscle function [141, 142].

Pulmonary arterial hypertension
Mechanisms of excess ventilation in PAH
Similar to HF, the hyperpnoeic response to exercise is characteristically exacerbated in patients with PAH [143, 144]. Recent data indicate that a high $\dot{V}_E–\dot{V}_{CO_2}$ can be found even in the early stages of the disease, *i.e.* patients showing mean PAP between 20 and 25 mmHg (see section: Key unanswered questions on $\dot{V}_E–\dot{V}_{CO_2}$ and exertional dyspnoea; table 1) [145]. The critical relevance of a high $\dot{V}_E–\dot{V}_{CO_2}$ in explaining exertional dyspnoea in PAH can be appreciated by the findings of DEBOECK et al. [146]. These authors reported higher dyspnoea scores in PAH compared with HFrEF at a given work rate; however, these differences disappeared after the higher $\dot{V}_E–\dot{V}_{CO_2}$ in PAH was taken into consideration. There is robust evidence supporting increased chemosensitivity and sympathetic overactivation as relevant contributors (figure 4) [147, 148]. For instance, higher than expected ventilation in response to hypoxic and hypercapnic breathing indicates heightened peripheral and central chemosensitivity [149, 150], and microneurographic recordings signal sympathetic hyperactivity with an increase in bursts akin to that observed in HFrEF [151]. Cerebrovascular reactivity to CO_2 might be impaired [152] in tandem with increases in central chemoreceptor sensitivity and $\dot{V}_E–\dot{V}_{CO_2}$ [153]. Hypocapnia may occur at rest and worsens during exercise [35], indicating that patients ventilate in excess to what is required to overcome an enlarged V_D [149, 154]. In fact, higher $\dot{V}_E–\dot{V}_{CO_2}$ slopes (and lower $\dot{V}_E$ intercepts) are usually found in patients with PH compared with those with HFrEF and HFpEF, showing more impaired cardiac output [146]; moreover, patients with either type of HF and secondary PH ("group 2") show steeper $\dot{V}_E–\dot{V}_{CO_2}$ slopes than those with isolated increases in post-capillary pressures [66]. Additional sources of ventilatory stimuli may arise from: 1) reflexes related to increased filling pressures of the right chambers [155]; 2) baroreflex dysfunction, particularly during blood pressure fluctuations [156]; 3) decreased pulmonary vascular distensibility leading to right ventricle–pulmonary arterial uncoupling [66]; 4) increased pulmonary artery shear stress and/or dilatation [157]; 5) skeletal muscle dysfunction [158]/disease [159] (including inspiratory muscles) and/or deconditioning leading to metaboreflex overactivation [160, 161] and increased central command in the setting of weak muscles [162]; and 6) low cardiac output due to right ventricle failure [163] and muscle capillary rarefaction [164] impairing muscle oxygenation [165].
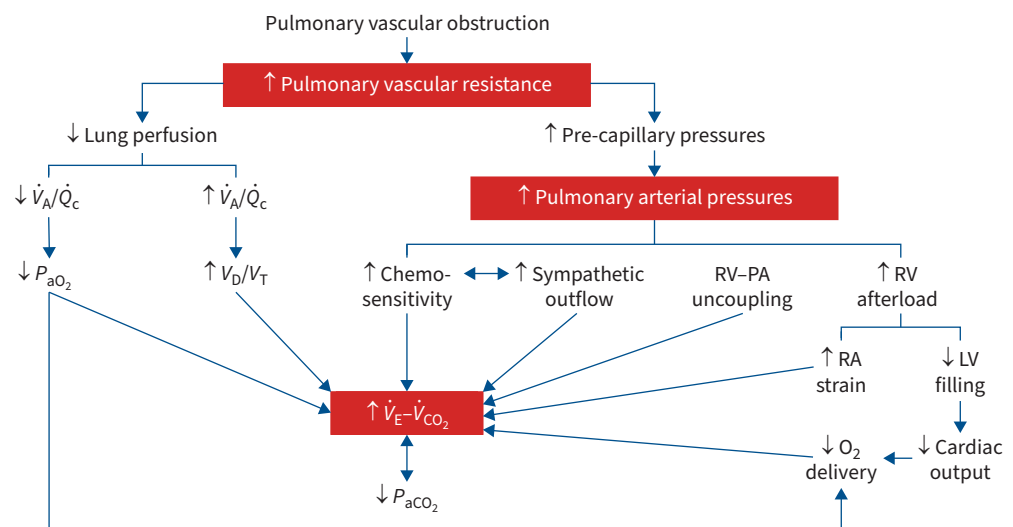
FIGURE 4 The main mechanisms linking the fundamental pathophysiological features of pulmonary hypertension (increased pulmonary vascular resistance and pulmonary arterial pressures) with excess exertional ventilation, *i.e.* high ventilation ($\dot{V}_E$)–pulmonary CO_2 output ($\dot{V}_{CO_2}$) relationship. The relative importance of individual mechanisms varies in pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. See text for elaboration. ↑: increased; ↓: decreased; $\dot{V}_A$: alveolar ventilation; $\dot{Q}_c$: capillary perfusion; P_{aCO_2}: arterial CO_2 partial pressure; V_D: dead space volume; V_T: tidal volume; RV: right ventricle; PA: pulmonary artery; LV: left ventricle; RA: right atrium.

Increased V_D/V_T related to extensive vascular remodelling and obliteration has been traditionally thought to decrease $\dot{Q}_c$ relative to $\dot{V}_A$ [166], contributing to a high $\dot{V}_E-\dot{V}_{CO_2}$ in patients with PAH [167]. An upward displacement of $\dot{V}_E/\dot{V}_{CO_2}$ as a function of P_{aCO_2} [7, 168] is also consistent with increased "wasted" ventilation [11]. Studies using the multiple inert gas exchange technique reported that V_D/V_T is consistently increased, being associated with a shift in mean $\dot{V}_A/\dot{Q}_c$ to higher-than-normal values [169]. It should be noted, however, that hyperventilation may increase the overall $\dot{V}/\dot{Q}$ relationship inequalities, which predictably increases V_D/V_T calculated by the Enghoff–Bohr equation [170]. Thus, the relative contribution of a high V_D/V_T to increasing $\dot{V}_E-\dot{V}_{CO_2}$ might be overestimated in individual patients [7].

Inspiratory capacity may decrease during exercise, indicating dynamic hyperinflation [171] and/or exercise-induced inspiratory muscle weakness [160]: preserved inspiratory muscle function regardless of changes in dynamic inspiratory capacity does suggest the former [172]. Of note, those who showed decreasing inspiratory capacity during exercise had a lower $\dot{V}_E-\dot{V}_{CO_2}$ slope, developed a plateau in V_T and described their respiratory sensations as "unsatisfied inspiration" [173], all findings previously reported in respiratory patients who reach critical inspiratory constraints [174]. Progression of diaphragm dysfunction follows haemodynamic worsening as PH progresses; interestingly, when the severity of right ventricle failure was considered, inspiratory muscle weakness did not independently contribute to exercise intolerance [175].

Effects of interventions on excess ventilation in PAH

The pulmonary arteries and the right atrium are richly innervated with sympathetic fibres. In fact, two interventional studies in severe PAH (pulmonary artery denervation [176] and atrial septostomy [177]) were associated with lower sympathetic outflow and better exercise tolerance. Given the close interconnection between chemoreceptor sensitivity, sympatho-excitation and ventilation, there is renewed interest in exploring the potential beneficial effects of adrenergic modulation [178] to lessen excess ventilation in the early stages of PAH, *i.e.* before the heightened adrenergic activity is required to compensate for a low cardiac output. In this specific context, selected β_1 stimulation may promote beneficial effects on HF gene expression and right ventricle remodelling, ultimately lessening excess ventilation (see section: Key unanswered questions on $\dot{V}_E-\dot{V}_{CO_2}$ and exertional dyspnoea; table 1) [179]. Interestingly, O_2 supplementation during exercise significantly reduced $\dot{V}_E-\dot{V}_{CO_2}$ and increased P_{aCO_2} while V_D/V_T remained unchanged, suggesting a reduction in ventilatory drive despite only modest hypoxaemia [180]. Whether this is an expression of lessened carotid body chemoreception [150] remains unclear.

In keeping with the notion that improving central haemodynamics is instrumental to mitigate excess ventilation in PAH, pulmonary vasodilators variably lessened excess ventilation, including the phosphodiesterase inhibitor sildenafil [181] and the prostacyclin analogues iloprost [182] and beraprost [183]. In fact, greater decrements in $\dot{V}_E-\dot{V}_{CO_2}$ were found in the subset of patients showing greater haemodynamic improvement in response to calcium channel blockers [184]. Moreover, failure to normalise central haemodynamics, arterial O_2 partial pressure (P_{aO_2}) and $\dot{V}_E-\dot{V}_{CO_2}$ after "treatment optimisation" with combination therapy largely explained residual exertional dyspnoea in PAH [185]. Although altered lung mechanics might not be critical to peak exercise capacity [146], their sensory consequences may have a relevant contributory role in the decision of patients to stop exercising (figure 4) [186]. Whether enhanced lung emptying with inhaled bronchodilators and/or improved inspiratory muscle strength may decrease exertional dyspnoea in these patients remains to be demonstrated (see section: Key unanswered questions on $\dot{V}_E-\dot{V}_{CO_2}$ and exertional dyspnoea; table 1).

Chronic thromboembolic pulmonary hypertension

Mechanisms of excess ventilation in CTEPH

It is somewhat axiomatic that the obstruction of larger pulmonary vessels by venous thrombi tends to increase V_D/V_T and $\dot{V}_E-\dot{V}_{CO_2}$ to a more significant extent in CTEPH patients than PAH [187]. In fact, depicting $\dot{V}_E/\dot{V}_{CO_2}$ (y) against P_{aCO_2} (x) [7, 168] showed CTEPH patients lying above (higher V_{Dphys}) and to the right (higher P_{aCO_2}) relative to those with PAH [188]. The classical explanation for increased V_{Dphys} and $\dot{V}_E-\dot{V}_{CO_2}$ in CTEPH is based on the consequences of reduced capillary blood volume, *i.e.* "true" alveolar V_D (ventilated but nonperfused gas exchange units) and increased heterogeneity of $\dot{V}_A/\dot{Q}_c$ relationships (underperfused or overperfused pulmonary zones) [188]. Variable hypoxaemia, further increasing $\dot{V}_E-\dot{V}_{CO_2}$, is ascribed to enlarged areas of low $\dot{V}_A/\dot{Q}_c$ and, in particular, a lowered mixed venous O_2 pressure [189] (figure 4). It is noteworthy that patients with chronic thromboembolic disease without resting PH also show high V_{Dphys} and $\dot{V}_E-\dot{V}_{CO_2}$, albeit to a lesser extent than patients with overt CTEPH [190]. Similar to PAH, some patients with CTEPH may present with dynamic decreases in inspiratory capacity which may constrain the limits for V_T expansion [191]. Although it remains unclear whether this represents true dynamic hyperinflation or a time-dependent decrease in inspiratory muscle strength, a low V_T may contribute to a high V_D/V_T in these patients. A role for impaired lung mechanics cannot be ruled out: CTEPH patients with inspiratory muscle weakness did show a lower V_T and higher dyspnoea/$\dot{V}_E$

relationship [191]. As discussed in the following, the distinct effect of some interventions sheds relevant light on the relative role of high V_{Dphys} versus chemostimulation in increasing $\dot{V}_E$–$\dot{V}_{CO_2}$ in patients with proximal/larger vessel versus distal/smaller vessel disease.

Effects of interventions on excess ventilation in CTEPH

The advent of treatment approaches for central (mechanical unclogging via pulmonary endarterectomy (PEA) [192] and balloon pulmonary angioplasty (BPA) [193]) versus peripheral (e.g. pharmacological treatment with the soluble guanylate cyclase stimulator, riociguat [194]) vascular disease allowed a better understanding of the complex pathophysiology of CTEPH. Marked improvement in $\dot{V}_E/\dot{V}_{CO_2}$ with dramatic reductions in V_{Dphys} and arterial–mixed expired CO_2 difference are usually observed after successful PEA [192] and, to a lesser extent, BPA [193]. Lower heterogeneity in $\dot{V}_A/\dot{Q}_c$ and improved cardiac output may jointly contribute to reducing V_D/V_T after these procedures [195], e.g. ventilation/perfusion imaging successfully predicted the CTEPH patients who benefited the most from BPA [196]. BPA improved V_{Dphys} [193] and reduced the respiratory neural drive [197], a key correlate of exertional dyspnoea across disease states [40], in tandem with a lower $\dot{V}_E$–$\dot{V}_{CO_2}$ in these patients. Despite normalisation of pulmonary haemodynamics, however, dyspnoea and exercise intolerance may persist, a finding related to residual impairment in the O_2 pathway [198] and, in some patients, exertional hypoxaemia (figure 4) [199].

The persistence of exercise-related PH after successful normalisation of resting PAP with BPA or PEA is associated with high $\dot{V}_E$–$\dot{V}_{CO_2}$ and residual dyspnoea which has been interpreted as evidence of nondetected distal disease [200]. Pharmacological treatment (i.e. pulmonary vasodilators) of small-vessel vasculopathy was associated with lower $\dot{V}_E$–$\dot{V}_{CO_2}$ despite higher V_{Dphys}, suggesting a decrease in chemostimulation [200]. In fact, a meta-analysis showed that treatment with riociguat did improve exertional dyspnoea [194], but it remains unknown whether this is a consequence of lower $\dot{V}_E$–$\dot{V}_{CO_2}$. Interestingly, pulmonary vasodilators increased P_{aCO_2}, again in keeping with less chemostimualation; thus, this positive effect outweighs any simultaneous increase in V_{Dphys} and $\dot{V}_A/\dot{Q}_c$ mismatch after treatment [200]. In contrast, others found that patients showing distal CTEPH had higher V_{Dphys} and $\dot{V}_E$–$\dot{V}_{CO_2}$ slope than their counterparts with PAH [201]. In any case, worsening in V_{Dphys} with oral vasodilators has a considerable potential to counterbalance potential decreases in chemostimulation (see section: Key unanswered questions on $\dot{V}_E$–$\dot{V}_{CO_2}$ and exertional dyspnoea; table 1) [201].

Key unanswered questions on $\dot{V}_E$–$\dot{V}_{CO_2}$ and exertional dyspnoea
Mechanistic features
It is rather embarrassing that despite the remarkable advances in our knowledge regarding the cellular and subcellular determinants of disease, we remain oblivious to the mechanisms responsible for the tight $\dot{V}_A/\dot{V}_{CO_2}$ control during exercise both in health and disease [3, 8, 14]. Without clarification of this fundamental issue, we will continue to be limited in our ability to fully understand how HF and PH disturb the control of exercise hyperpnoea. For instance, are there hitherto unidentified sensor(s) of CO_2 flow from the periphery to the lungs? If so, where? In the venous circulation, right heart chambers, pulmonary vasculature, airways or alveoli? How does the respiratory controller "fine tune" ventilation (via V_T and respiratory frequency) to precisely control P_{aCO_2} close to its resting value in the face of a changing V_{Dphys}? Is this achieved via intrinsic estimation of the alveolar V_D (i.e. regions with high $\dot{V}_A/\dot{Q}_c$)? For instance, would a lower rate of CO_2 unloading from the capillary blood to the alveoli in areas with high $\dot{V}_A/\dot{Q}_c$ induce sufficiently large intra- or between-breaths fluctuations in P_{CO_2} of the arterial blood leaving the lungs [202] with subsequent stimulation of the peripheral and/or central chemoreceptors [203]? Is there also a role for central integration [204] in the "fine tuning" process? Alternatively (or complementarily), neural plasticity and adaptive models might be involved: a process of "associative learning" beginning with errors in respiratory control and coincident blood gas fluctuations would be followed by more refined adjustments which ultimately lead to the typical eucapnic response [205]. The emergence of HF or PH (particularly HFrEF and PAH) and the consequent additional afferent stimuli would disturb this long-learned associative process, leading to alveolar hyperventilation (table 1).

Implications for exertional dyspnoea
It is rather surprising that dyspnoea remains a "soft end-point" in cardiovascular research since almost every study on the clinical relevance of $\dot{V}_E$–$\dot{V}_{CO_2}$ in HF or PH is justified based on its putative link with exertional dyspnoea (in addition to mortality). Despite the mounting evidence that the presence and severity of peak dyspnoea is an important predictor of poor patient-related outcomes in HF [206, 207], no study to date has prospectively established exertional dyspnoea as the primary outcome. Unfortunately, careful quantification of the intensity and quality of dyspnoea is rare: no published study simultaneously related serial exertional dyspnoea readings with their putative neurochemical and haemodynamic determinants. Multimodality exercise assessment in evaluating exertional dyspnoea has been cogently

TABLE 1 Key unanswered questions on the determinants, respiratory-sensory consequences and effects of interventions on excess exertional ventilation in heart failure (HF) and pulmonary hypertension (PH)

Ventilatory control during exercise

- Are there hitherto unknown CO_2 receptors in the right chambers, pulmonary vasculature and airways that can precisely match $\dot{V}_A$ to $\dot{V}_{CO_2}$?
- If such receptors do not exist, how does the respiratory controller "know" the instantaneous V_{Dphys} to control P_{aCO_2} close to the resting values?
- Is there a role for neural/behavioural mechanisms of ventilatory control in "fine tuning" exercise hyperpnoea in health and disease?
- Does alveolar hyperventilation in HFrEF and PAH follow a downward shift in P_{aCO_2} set-point or is a low P_{aCO_2} a "passive" consequence of increased neurochemical stimulation/receptor sensitivity?
- What are the exact sources of increased afferent stimulation in the presence of central haemodynamic abnormalities signalling RV–PA uncoupling and/or PH across diseases?
- Do specific insertion/deletion polymorphisms of ACE genotypes carry a role in explaining the variability in prevalence and severity of excess ventilation in HFrEF?
- What are the relative contributions of low lung compliance *versus* increased reflex stimulation in decreasing V_T, and consequently increasing V_{Dphys}, in patients with HFpEF?
- How is the severity of excess exertional ventilation modulated by the different haemodynamic phenotypes of HFpEF?
- Does "stagnant hypoxia" (as seen in HFrEF) play a role in chronic carotid body sensitisation in HFpEF and, potentially, PAH?

Exertional dyspnoea

- Does dyspnoea increase in tandem with, or out of proportion to, respiratory neural drive and $\dot{V}_E–\dot{V}_{CO_2}$?
- How are dyspnoea intensity and quality influenced by their putative neurochemical, gas exchange and haemodynamic determinants?
- Is periodic breathing associated with worsening dyspnoea at a given $\dot{V}_E–\dot{V}_{CO_2}$?
- Is there a discernible relationship between changes in dyspnoea intensity and quality with decrements in neurochemical afference *versus* V_{Dphys}?
- Is dyspnoea perception increased by coexistent prevalent symptoms on exertion, such as heightened leg discomfort?
- Do submaximal dyspnoea readings (*versus* work rate and/or $\dot{V}_E$) add to peak dyspnoea scores to predict negative clinical outcomes?
- What is the influence of common comorbidities (*e.g.* obesity, hypertension, diabetes mellitus and atrial fibrillation) on dyspnoea perception?
- What is the minimal clinically important difference for dyspnoea reduction during submaximal exercise (according to different scales)?
- How can exertional dyspnoea be used as a main outcome in clinical trials involving pharmacological and nonpharmacological interventions?

Effects of interventions

- Does $\dot{V}_E–\dot{V}_{CO_2}$ decrease to a larger extent in response to interventions aimed at reducing alveolar hyperventilation compared with those which primarily improve V_{Dphys} in HFrEF, PAH and small-vessel CTEPH?
- Does $\dot{V}_E–\dot{V}_{CO_2}$ decrease to a larger extent in response to interventions aimed at decreasing V_{Dphys} compared with those which primarily reduced alveolar hyperventilation in HFpEF and large-vessel CTEPH?
- Is there an independent (or auxiliary) role for excess ventilation in helping establish the best pharmacological treatment for dyspnoeic patients with HFrEF?
- Are HFrEF patients showing low D_{LCO} (signalling impaired pulmonary gas exchange) particularly prone to respond to ACE inhibitors rather than ARBs?
- Is the unduly high $\dot{V}_E–\dot{V}_{CO_2}$ in combined pre- and post-capillary PH a reflection of the added negative haemodynamic effects of the former or only a mere reflection of more advanced HF?
- Is sildenafil particularly effective in lessening excess ventilation in HFrEF showing PH and impaired muscle O_2 extraction?
- Is $\dot{V}_E–\dot{V}_{CO_2}$ consistently increased in patients in the early stages of PH, *i.e.* those showing mPAP between 20 and 25 mmHg?
- Is there a role for pharmacological or nonpharmacological modulation of the adrenergic tonus in the early stages of PAH?
- What does explain the marked variability of the effects of pulmonary vasodilators on excess ventilation in patients with PH?
- Does the beneficial effect of pulmonary vasodilation (or lack thereof) on excess ventilation and dyspnoea differ between treatment target pathways (*e.g.* nitric oxide, endothelin and prostacyclin) and between cardiocirculatory disease entities?
- Can a high $\dot{V}_E–\dot{V}_{CO_2}$ (alone or in association with a low P_{ETCO_2}) help in selecting patients with small-vessel, distal CTEPH or even dyspnoeic post-pulmonary embolism patients showing persistent perfusion deficits to receive pulmonary vasodilators?

$\dot{V}_A$: alveolar ventilation; $\dot{V}_{CO_2}$: CO_2 output; V_{Dphys}: physiological dead space; P_{aCO_2}: arterial CO_2 partial pressure; HFrEF: HF with reduced ejection fraction; PAH: pulmonary arterial hypertension; RV: right ventricle; PA: pulmonary artery; PH: pulmonary hypertension; ACE: angiotensin-converting enzyme; V_T: tidal volume; HFpEF: HF with preserved ejection fraction; $\dot{V}_E$: minute ventilation; CTEPH: chronic thromboembolic pulmonary hypertension; D_{LCO}: diffusing capacity of the lung for CO; ARB: angiotensin receptor blocker; mPAP: mean pulmonary arterial pressure; P_{ETCO_2}: end-tidal partial pressure for CO_2.

advocated [208]: coupling technologically advanced techniques (including invasive haemodynamics and imaging) [13] with a parallel quantitative and qualitative characterisation of the symptom is paramount [209]. Detailed studies relating more accurate indexes of inspiratory neural drive, such as diaphragm electromyography, to $\dot{V}_E–\dot{V}_{CO_2}$ and dyspnoea in HF and PH are lacking. Does the language of dyspnoea (dyspnoea descriptors) [40] differ across these diseases, *e.g.* "air hunger or unsatisfied inspiration" instead of "work/effort" signalling heightened chemostimulation [210]? If so, do they have a distinct impact on the patient's decision to stop exercising (affective domain)? Are the sensory consequences of a given decrease in $\dot{V}_E–\dot{V}_{CO_2}$ similar when reached *via* less chemosensitivity *versus* lower V_{Dphys}? If not, we may need to consider that there are some therapeutic strategies that might be more beneficial to improving exercise tolerance than others depending on the dominant mechanism of excess ventilation. Finally, does EOV

cause worse dyspnoea at a given $\dot{V}_E$–$\dot{V}_{CO_2}$? If so, lessening the frequency or amplitude of ventilatory oscillations may have relevant effects on HFrEF morbidity, even if mortality is not substantially altered (table 1).

Effects of interventions

There is little controversy on the clinical importance of excess ventilation in HFrEF [10, 12, 13]; much work, however, is needed to include $\dot{V}_E$–$\dot{V}_{CO_2}$ in the pharmacological treatment of high-risk patients [91]. Adding other pieces of information to excess ventilation might prove valuable, *e.g.* nonselective antiadrenergics rather than β-selectives in those showing unusually high sympathetic tonus [93], ACEi rather than ARBs in those with low D_{LCO} [98] and sildenafil for patients showing PH [117] in association with impaired muscle extraction [113]. Despite the associative evidence presented herein, we should recognise that it remains unknown whether $\dot{V}_E$–$\dot{V}_{CO_2}$ decreases to a larger extent in response to interventions aimed at reducing alveolar hyperventilation compared with those which primarily improve V_{Dphys} in HFrEF, PAH and small-vessel CTEPH. Similarly, it is unclear whether $\dot{V}_E$–$\dot{V}_{CO_2}$ decreases to a larger extent in response to interventions aimed at decreasing V_{Dphys} compared with those which primarily reduced alveolar hyperventilation in HFpEF and large-vessel CTEPH. Studies with specific HFpEF phenotypes are lacking: do intrinsic pulmonary vasculopathy and micro-vessel remodelling predispose obese patients with metabolic syndrome to derive greater benefit from pulmonary vasodilators [136]? The large variability on the effects of vasodilators in PAH and PH secondary to HF is puzzling: can the patient response (or lack thereof) to pulmonary vasodilation help illuminate the pathophysiological underpinning of excess ventilation? Is the greater $\dot{V}_E$–$\dot{V}_{CO_2}$ in HF patients with combined pre- and post-capillary PH reflective of the "superimposed" haemodynamic consequences of high PAPs or a mere consequence of more advanced HF? Given the growing evidence that some patients with PAH and excess ventilation present with expiratory flow limitation and dynamic hyperinflation [171], is there a role for bronchodilators (particularly antimuscarinics) in lessening their dyspnoea? Conversely, patients in the early stages of PAH showing marked excess ventilation may benefit from a parsimonious use of antiadrenergics. More studies are required to test the effects of PAH medications in the subset of dyspnoeic patients with post-pulmonary embolism syndrome or overt CTEPH showing excess ventilation but apparently no residual thromboembolic disease (table 1) [211].

Conclusions

Excess ventilation (high $\dot{V}_E$–$\dot{V}_{CO_2}$), signalling alveolar hyperventilation and/or increased "wasted" ventilation (high V_{Dphys}), has become an important physiological biomarker (figure 1) across the spectrum of HF and PH severity. Evidence accrued to date indicates that reduced bulk O_2 transfer induced by 1) cardiac output limitation and/or 2) right ventricle–pulmonary artery uncoupling and right ventricle failure increases neurochemical afferent stimulation and (largely chemo-) receptor sensitivity, causing alveolar hyperventilation in HFrEF, PAH and in most patients with small-vessel, distal CTEPH. Approaches to improving central haemodynamics and/or reduce chemosensitivity have shown the largest beneficial effects to excess ventilation in these patient populations. In contrast, 1) high filling pressures, 2) impaired lung perfusion leading to $\dot{V}_A/\dot{Q}_c$ mismatch and 3) a low V_T conspire to increase V_{Dphys} in HFpEF and in most patients with proximal CTEPH. Treatment strategies focused on decreasing pulmonary capillary pressures in HFpEF and mechanically unclogging larger pulmonary vessels (PEA and BPA) in CTEPH have been associated with larger decrements in excess ventilation and dyspnoea. Advancing the knowledge on the complex relationship between excess exertional ventilation and dyspnoea would then set the stage for large randomised controlled trials on pharmacological and nonpharmacological interventions aimed at improving these key patient-centred outcomes.

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