EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

State of the art

Excess ventilation and exertional dyspnoea in heart failure and pulmonary hypertension

J. Alberto Neder, Devin B. Phillips, Denis E. O'Donnell, Jerome A. Dempsey

Please cite this article as: Neder JA, Phillips DB, O'Donnell DE, *et al*. Excess ventilation and exertional dyspnoea in heart failure and pulmonary hypertension. *Eur Respir J* 2022; in press (https://doi.org/10.1183/13993003.00144-2022).

Excess Ventilation and Exertional Dyspnoea in Heart Failure and Pulmonary Hypertension

J. Alberto Neder, MD, PhD[2], Devin B. Phillips, PhD[2], Denis E. O'Donnell MD[2], Jerome A. Dempsey, PhD[1]

[1] Professor Emeritus, John Rankin Laboratory of Pulmonary Medicine, Dept of Population Health Sciences, University of Wisconsin-Madison, Madison, Wisconsin, USA
[2] Clinical Exercise Physiology and Respiratory Investigation Unit, Division of Respiratory and Critical Care Medicine, Department of Medicine, Queen's University and Kingston Health Sciences Centre, Kingston, Ontario, Canada

Short title (46/50): ***Exertional ventilation in cardiopulmonary disease***

Sources of Funding: None.
Disclosures: None.
Address for correspondence to: Dr. J Alberto Neder MD, PhD, 102 Stuart Street, Kingston, Ontario, Canada K7L 2V6; tel: 1-613-549-6666 (x 3198); fax: 1-613-549-1459; e-mail: alberto.neder@queensu.ca

Total word count: 5486

Take home message (245/256): ***Understanding why patients with heart failure and pulmonary hypertension ventilate excessively during exercise gives unique insights into the seeds of their shortness of breath, creating a rationale for a clinically-relevant therapeutic target.***

Abstract

Increased ventilation relative to metabolic secondary to 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 (r) or preserved (p) ejection fraction, pulmonary arterial hypertension (PAH), and chronic thromboembolic PH (CTEPH). We herein provide the key pieces of information to the caring physician to a) gain unique insights into the seeds of patients' shortness of breath, and b) develop a rationale for therapeutically lessening excess ventilation to mitigate this distressing symptom. Reduced bulk O_2 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 in small-vessel, distal CTEPH. As such, interventions geared to improve central hemodynamics and/or reduce chemosensitivity have been particularly effective in lessening their excess ventilation. In contrast, high filling pressures in HFpEF (a) and impaired lung perfusion leading to ventilation/perfusion mismatch in proximal CTEPH (b) conspire to increase physiological dead space. Accordingly, decreasing pulmonary capillary pressures (a) and mechanically unclogging larger pulmonary vessels (pulmonary endarterectomy and balloon pulmonary angioplasty) (b) 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 non-pharmacological interventions might prove instrumental to alleviate the devastating consequences of these prevalent diseases.

Word count: 250/250

"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)[a] [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]. Recognizing 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][8][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 a) gain unique insights into the seeds of patients' shortness of breath, and b) develop a rationale for therapeutically lessening $\dot{V}E{:}\dot{V}CO_2$ to mitigate this distressing symptom (**Figure 1**). We emphasize pharmacological and non-pharmacological interventions which shed novel light on fundamental mechanisms of disease. Since the sources of ventilatory stimulation may differ depending on mechanisms of hemodynamic impairment and exercise limitation, we contrast HF with reduced (r) versus preserved (p) 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 it has already been reviewed in detail elsewhere.[10][12][13].

[a] We prefer the term "excess ventilation" to 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.

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 ($PaCO_2$) is maintained ($\leftrightarrow$) within ±3 mmHg throughout mild-to-moderate exercise (**Figure 2C**).[14] Such a tight control of $PaCO_2$ 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 ($V_{D_{phys}}$) decreases ($\downarrow$) hyperbolically [3] (**Figure 2A**) because a) V_T increases out of proportion ($\uparrow\uparrow$) to airway "anatomical" V_D and b) the higher compliance of the alveoli over that of the airways, i.e., more air goes to the alveoli than the airways:[15]

$$\leftrightarrow PaCO_2 = \frac{1}{\downarrow \frac{\dot{V}_E}{\dot{V}CO_2} \times \left(1 - \left(\frac{\uparrow V_D}{\uparrow\uparrow V_T}\right)\right)} \quad \textbf{Eq (1)}$$

- Thus, if $\dot{V}_E/\dot{V}CO_2$ did not decrease in tandem with V_D/V_T (compare **Figure 2A** and **Figure 2B**), $\dot{V}_A$:$\dot{V}CO_2$ 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 $PaCO_2$. 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 be alveolar hypoventilation, i.e., a high $PaCO_2$. [14][15] The corollary is that the lower the $PaCO_2$ and the higher the wasted ventilation in the $V_{D_{phys}}$[b], the higher the excess ventilation (**Figure 2**):[16]

$$\uparrow \frac{\dot{V}_E}{\dot{V}CO_2} = \frac{1}{\downarrow PaCO_2 \times \left(1 - \left(\frac{\uparrow V_D}{\downarrow V_T}\right)\right)} \quad \textbf{Eq. (2)}$$

[b] A higher wasted ventilation indicates that a larger total dead space is required to explain the observed impairment in CO_2 elimination. The physiological dead space 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 a) apparatus V_D, b) anatomical V_D, c) alveolar V_D (preserved alveolar ventilation ($\dot{V}A$), no capillary perfusion ($\dot{Q}c$), d) V_D effect (high VA/Qc, usually due to normal $\dot{V}A$ but low $\dot{Q}c$) and e) any contribution of shunt to increase $PaCO_2$. In this context, a) and b) are "series" VD whereas c)-e) 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 (usually 2-3 L/min $\dot{V}_E$ 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 overlapping [28] though the use of % predicted is physiologically sounder as higher values are seen in women and elderly subjects.[29] .

The importance of directly measuring $PaCO_2$ and V_D/V_T in dyspneic patients showing excess ventilation cannot be underestimated. Specifically, end-tidal (ET) PCO_2 should not be used to estimate $PaCO_2$, particularly in patients. For instance, resting $P_{ET}CO_2$ is 3-4 mmHg lower than $PaCO_2$ 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 $V_{D_{phys}}$. During exercise, $P_{ET}CO_2$ is greater than $PaCO_2$ in health (i.e., the $P(a\text{-}ET)CO_2$ difference becomes negative) due to the effects of:[31]

a) increases in pulmonary blood flow with CO_2-enriched mixed venous blood;
b) faster and more homogeneous lung emptying; and, importantly,
c) a larger V_T leading to greater sampling of alveolar gas.

Relating $P_{ET}CO_2$ to $PaCO_2$, therefore, can be particularly informative: whereas impaired perfusion of ventilated areas leading to a high $V_{D_{phys}}$ decreases $P_{ET}CO_2$ out-of-proportion to $PaCO_2$ (i.e., $P_{ET}CO_2$ fails to surpass $PaCO_2$) (a), a narrow $P(a\text{-}ET)CO_2$ coupled with a low $PaCO_2$ implies in alveolar hyperventilation (b).[32] Replacing $PaCO_2$ by $P_{ET}CO_2$ to estimate V_D/V_T in scenario (a) is particularly misleading: the worse the wasted ventilation, the lower the $P_{ET}CO_2$ relative to $PaCO_2$ and, consequently, the larger the V_D/V_T underestimation.[33] Regardless of the underlying cause(s), a lack of increase in $P_{ET}CO_2$ [34] and/or a low peak value [35] signals more advanced PH [34] [35] and HF [36] since both (a) and (b) are markers of disease severity. High $\dot{V}_E$:$\dot{V}CO_2$ and low $P_{ET}CO_2$ (and $PaCO_2$) are also seen in primary hyperventilation:[37] non-cyclical 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 centers and the capacity of the respiratory system to respond appropriately.[40] The patient's ability to translate (a) or not (b) a heightened drive into the mechanical act of breathing (V_T and $\dot{V}_E$) establishes the presence of:[41]

a) "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 are relatively proportional to $\dot{V}_E$; or
b) "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 (HFrEF)

Mechanisms of excess ventilation in HFrEF

Excess ventilation is observed in most dyspneic 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 tachypneic 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 $V_{D_{phys}}$ 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 alveolar ventilation ($\dot{V}_A$)/capillary perfusion ($\dot{Q}c$) due to perfusion abnormalities with or without associated PH[45] [46] may increase V_D, a low V_T seems the dominant factor [47] [48] due to:

a) changes in breathing pattern induced by heightened chemostimulation [49];
b) inspiratory constraints secondary to low lung compliance,[50] and,
c) 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 $P_{ET}CO_2$ on exercise (<1.2 mm Hg) (***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 VD_{phys} 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]

a) 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]
b) heightened afferent stimuli from over sensitized ergorreceptors [57] and excessive metabolite accumulation in the peripheral [58].[59] and respiratory muscles;
c) carotid body-mediated chemoreceptor hypersensitivity [49] [60] and heightened response of the central chemoreceptors to CO_2 [61];
d) associated PH [62] [53] [63] and/or increased pulmonary vascular pressures/right ventricular-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

e) other congestive consequences of the disease, such as increased left atrial pressure [68], J reflex due to interstitial edema,[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 $PaCO_2$ 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 $PaCO_2$ at a given ventilation.[74] A chronically-low $PaCO_2$ may also impair the expected cerebral vasoconstriction; consequently, less H^+ accumulates close to the central chemoreceptors, further de-stabilizing 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 to HFrEF with relatively similar reductions in cardiac index.[77] These data provide important supportive evidence in favor 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 chronic obstructive pulmonary disease (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][80][81] Interestingly, patients with coexistent HFrEF-COPD characteristically present with high $\dot{V}_E$ intercepts than those with HFrEF alone, potentially reflecting a high resting $V_{D_{phys}}$.[82] 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 $\dot{V}_E$.[83] 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 $PaCO_2$ rather than higher $V_{D_{phys}}$ [84], 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 [85] and low dose opiates [86] 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, sympathoexcitation, and mortality in animals with HFrEF.[87] After a case description,[88] a small (N= 10) study in humans found that unilateral resection decreased sympathetic activity and ventilation.[88] 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, altitude) [89] and deleterious consequences to co-morbid respiratory disease and obstructive sleep apnea this approach remains largely experimental.[90] A further complicating issue is the current controversies on the optimum methodology for assessing chemoreceptor sensitivity.[91] The strong anti-adrenergic effect of carvedilol (α-, β_1- and β_2-blocker) provided another evidence of the relevance of carotid bodies in promoting excess ventilation in HFrEF [92]: despite worsening pulmonary gas exchange (likely increasing VD_{phys})[93], carvedilol was more effective than selective β-blockers in decreasing peripheral chemoreceptor activity [94], lessening hyperventilation [95] and $\dot{V}E:\dot{V}CO_2$ [93]. Interestingly, long-term treatment β-blocker reduced the dyspnoea-$\dot{V}E$-slope (less "impeded breathing") [96] suggesting lower lung congestion/higher lung compliance and/or higher inspiratory muscle strength. [92] [97]

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 [98] improved the membrane component of lung diffusing capacity for carbon monoxide (D_{LCO}) [99], decreasing VD/VT and $\dot{V}E:\dot{V}CO_2$ (***Key unanswered questions on $\dot{V}E$-$\dot{V}CO_2$ and exertional dyspnoea;*** **Table 1)**.[100] These salutary effects were ascribed to increased local concentration of

prostaglandins readjusting lung vessel tone and membrane conductance [98] since they were virtually abolished by cyclooxygenase inhibition.[100] The angiotensin II receptor blocker (ARB) losartan - which lacks significant pulmonary vascular effects - did not change $\dot{V}E:\dot{V}CO_2$.[101][102] 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 $\dot{V}E:\dot{V}CO_2$.[103][104] Since the protection by ACEi against alveolar edema varies according to insertion/deletion polymorphism genotypes,[105] they may carry a role in explaining the variability in prevalence and severity of excess ventilation in patients with similar hemodynamic impairment (***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:

a) improved respiratory muscle strength and endurance,[106] particularly when potentiated by inspiratory muscle training [107] [108];
b) decreased peripheral chemoreceptors sensitivity [109] and, potentially, the beneficial consequences of less hyperventilation (higher $PaCO_2$) on the former [37];
c) improved neurovascular control [110] and bulk muscle blood flow and distribution [111] leading to less activation of ergorreceptors [59]; and
d) enhancing muscle "quality" as intramuscular fat, likely disturbing blood flow distribution, [112] strongly predicted the lessening effects of muscle afferent blockade on $\dot{V}E:\dot{V}CO_2$ [113].

Of note, the relevance of disturbed peripheral hemodynamics to mitigate excess ventilation has also been highlighted by the positive effects of sildenafil, [114] and respiratory muscle unloading [115] which increased muscle blood flow reducing O_2 extraction at a given O_2 uptake [116]. Part of the beneficial effects of sildenafil on excess ventilation (including EOV) [1] and dyspnoea, however, might be related by lower PH on exertion.[118] Despite all 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 [92] (***Key unanswered questions on $\dot{V}E$-$\dot{V}CO_2$ and exertional dyspnoea;*** **Table 1)**

Heart failure with preserved left ventricular ejection fraction (HFpEF)

Mechanisms of excess ventilation in HFpEF

Heart failure with preserved (≥50%) EF (HFpEF) is characterized by mild systolic dysfunction but pronounced limitations in systolic reserve capacity during the stress of exercise. Increased LV 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, endothelial and skeletal muscle dysfunction, to cause severe exercise intolerance.[119] Despite ample variability, $\dot{V}_E$-$\dot{V}CO_2$ is typically not as elevated or frequent as in HFrEF [119]; nevertheless, the clinical implications of an increased $\dot{V}_E$:$\dot{V}CO_2$ vis-à-vis morbidity (dyspnoea) and mortality are similar.[120]. In fact, a large recent study (N= 1347) found that all-cause mortality and HF hospitalization were increased across the spectrum of HF, including those with mid-range HF, i.e., 50%<LVEF≥40%.[121] Exercise-induced mitral regurgitation was commonly seen in all HF subtypes, being associated with RV-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 $V_{D_{phys}}$ seems to overcome alveolar hyperventilation as the primary etiological mechanism for excess exertional ventilation secondary to (**Figure 3**): [55] [122] [123]

a) impaired RV-pulmonary arterial coupling [66] and right ventricular contractile dysfunction altering pulmonary blood flow, [55] a stiff pulmonary circulation, [124] and impaired gas conductance [125] jointly leading to increased areas of high $\dot{V}_A/\dot{Q}$c and alveolar V_D [126] [127]; and
b) a fast and superficial breathing pattern,[128] likely secondary to excessive J receptor stimulation (vagally-mediated reflexes) [69] associated with high pulmonary capillary wedge pressure,[128] left atrial distention/pulmonary venous hypertension [68], reduced lung compliance due to congestion [129] and, occasionally inspiratory muscle weakness [51].

The few studies that measured $PaCO_2$ during exercise in patients with HFpEF found values slightly lower than expected values but still within the eucapnic range.[55][127] The

sympathetic outflow is characteristically increased in HFpEF from the earlier stages of the disease and the central chemoreflex is enhanced;[130] moreover, acute activation of central chemoreceptors leads to further increases of cardiac sympathetic outflow and impairment in cardiac function in animal models.[131] These data coupled with the known importance of skeletal muscle abnormalities at the limits of exercise tolerance in HFpEF [132] suggest that a role for increased neurochemical input to increase $\dot{V}_E$:$\dot{V}CO_2$ may have been overlooked (***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 VD_{phys} in explaining excess ventilation and higher diastolic pulmonary artery pressure for a given pulmonary capillary wedge pressure (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 to post-capillary PH in HFpEF.[133] Newer strategies focused on improving RV function: adding to impaired aerobic capacity unveils a specific HFpEF phenotype characterized by a greater burden of right-sided heart disease and combined pre- and post-capillary PH.[134] Unfortunately, however, the vasodilators praliciguat [135] and sildenafil [136] failed to decrease $\dot{V}_E$-$\dot{V}CO_2$ slope in these patients. It remains to be tested whether sub-sets of patients would benefit from these medications. Intrinsic pulmonary vasculopathy and micro-vessel remodeling, for example, is more frequently found in the obese/metabolic syndrome phenotype of HFpEF.[137]

Joining echocardiographic measures of RV-pulmonary circulation uncoupling (e.g., low tricuspid annular plane systolic excursion to pulmonary artery systolic pressure ratio)[138] with excess ventilation and other clinical data (e.g., atrial fibrillation, high brain natriuretic peptide, severity of diastolic dysfunction) might prove useful to phenotype HFrEF patients more prone to respond to interventions aimed at improving right side hemodynamics in HFpEF (***Key unanswered questions on $\dot{V}_E$-$\dot{V}CO_2$ and exertional dyspnoea;*** **Table 1)**.[139] A small study found lower $\dot{V}_E$:$\dot{V}CO_2$ and dyspnoea with exertional O_2 supplementation in a non-hypoxemic group of patients with HFpEF and associated PH:[140] whether this was secondary to lower pulmonary vascular pressures and/or decreased peripheral

chemosensitivity remain 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,[141] perhaps with an even greater relative contribution of "peripheral" mechanisms, i.e., improved microvascular and/or skeletal muscle function.[142][143]

Pulmonary arterial hypertension (PAH)

Mechanisms of excess ventilation in PAH

In similarity with HF, the hyperpneic response to exercise is characteristically exacerbated in patients with PAH.[144] [145] 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 pulmonary artery pressure between 20-25 mmHg (***Key unanswered questions on $\dot{V}_E$-$\dot{V}CO_2$ and exertional dyspnoea;* Table 1).**.[146] 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.[147] These authors reported higher dyspnoea scores in PAH compared to 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 over-activation as relevant contributors (**Figure 4**).[148][149] For instance, higher-than-expected ventilation in response to hypoxic and hypercapnic breathing indicates heightened peripheral and central chemosensitivity [150] [151] and microneurographic recordings signal sympathetic hyperactivity with an increase in bursts akin to that observed in HFrEF.[152] Cerebrovascular reactivity to CO_2 might be impaired [153] in tandem with increases in central chemoreceptor sensitivity and exercise $\dot{V}_E$-$\dot{V}CO_2$ [154] 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.[150][155] 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 to those with HFrEF and HFpEF showing more impaired cardiac output [147]; 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:

a) reflexes related to increased filling pressures of the right chambers,[156];

b) baroreflex dysfunction, particularly during blood pressure fluctuations;[157]
c) decreased pulmonary vascular distensibility leading to RV-pulmonary arterial uncoupling,[66];
d) increased pulmonary artery shear stress and/or dilatation,[158];
e) skeletal muscle dysfunction [159] / disease [160] (including inspiratory muscles) and/or deconditioning leading to metaboreflex overactivation [161] [162] and increased central command in the setting of weak muscles [163] ; and
f) low cardiac output due to RV failure [164] and muscle capillary rarefaction [165] impairing muscle oxygenation [166].

Increased V_D/V_T related to extensive vascular remodeling and obliteration has been traditionally thought to decrease $\dot{Q}c$ relative to $\dot{V}_A$,[167] contributing to a high $\dot{V}_E$-$\dot{V}CO_2$ in patients with PAH[168]. An upward displacement of $\dot{V}_E$-$\dot{V}CO_2$ as a function of $PaCO_2$ [169] [7] 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.[170] 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.[171] 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 (IC) may decrease during exercise, indicating dynamic hyperinflation [172] and/or exercise-induced inspiratory muscle weakness [161]: preserved inspiratory muscle function regardless of changes in dynamic IC does suggest the former.[173] Of note, those who showed decreasing IC during exercise have a lower $\dot{V}_E$-$\dot{V}CO_2$ slope, developed a plateau in V_T, and described their respiratory sensations as "unsatisfied inspiration",[174] all findings previously reported in respiratory patients who reach critical inspiratory constraints [175]. Progression of diaphragm dysfunction follows hemodynamic worsening as PH progresses; interestingly, when the severity of RV failure was considered, inspiratory muscle weakness did not independently contribute to exercise intolerance [176]

Effects of interventions on excess ventilation in PAH

The pulmonary arteries and the right atrium are richly innervated with sympathetic fibers. In fact, two interventional studies in severe PAH (pulmonary artery denervation [177] and atrial septostomy [178]) 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 [179] 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 heart failure gene expression and RV remodeling, ultimately lessening excess ventilation (***Key unanswered questions on $\dot{V}_E$-$\dot{V}CO_2$ and exertional dyspnoea;*** **Table 1)**.[180] Interestingly, O_2 supplementation during exercise significantly reduced $\dot{V}_E$-$\dot{V}CO_2$ and increased $PaCO_2$ while V_D/V_T remained unchanged, suggesting a reduction in ventilatory drive despite only modest hypoxemia.[181] Whether this is an expression of lessened carotid body chemoreception [151] remains unclear.

In keeping with the notion that improving central hemodynamics is instrumental to mitigate excess ventilation in PAH, pulmonary vasodilators variably lessened excess ventilation, including the phosphodiesterase inhibitor sildenafil [182] and the prostacyclin analogues iloprost [183] and beraprost [184] In fact, greater decrements in $\dot{V}_E$:$\dot{V}CO_2$ were found in the subset of patients showing greater hemodynamic improvement in response to calcium-channel blockers,[185] Moreover, failure to normalize central hemodynamics, PaO_2, and $\dot{V}_E$:$\dot{V}CO_2$ after "treatment optimization" with combination therapy largely explained residual exertional dyspnoea in PAH.[186] Although altered lung mechanics might not be critical to peak exercise capacity [147] their sensory consequences may have a relevant contributory role in the decision of patients to stop exercising (**Figure 4**) [187]. Whether enhanced lung emptying with inhaled bronchodilators and/or improved inspiratory muscle strength may decrease exertional dyspnoea in these patients remain to be demonstrated (***Key unanswered questions on $\dot{V}_E$-$\dot{V}CO_2$ and exertional dyspnoea;*** **Table 1)**.

Chronic thromboembolic pulmonary hypertension (CTEPH)

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 these patients than PAH.[188] In fact, depicting $\dot{V}_E/\dot{V}CO_2$ (y) against $PaCO_2$ [169] [7] showed CTEPH patients lying above (higher $V_{D_{phys}}$) and to the right (higher $PaCO_2$) relative to those with PAH. [189] The classical explanation for increased $V_{D_{phys}}$ 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 (under or overperfused pulmonary zones).[189] Variable hypoxemia, 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.[190] (**Figure 4**) It is noteworthy that patients with chronic thromboembolic disease without resting PH also show high $V_{D_{phys}}$ and $\dot{V}_E:\dot{V}CO_2$, albeit to a lesser extent than patients with overt CTEPH.[191] In similarity with PAH, some patients with CTEPH may present with dynamic decreases in IC which may constrain the limits for V_T expansion.[192] 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 lower VT and higher dyspnoea-$\dot{V}_E$ relationship.[192] As discussed below, the distinct effect of some interventions shed relevant light on the relative role of high $V_{D_{phys}}$ 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)[193] and balloon pulmonary angioplasty (BPA))[194] versus peripheral (e.g., pharmacological treatment with the soluble guanylate cyclase stimulator, riociguat)[195] 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 $V_{D_{phys}}$ and arterial-mixed expired CO_2 difference are usually observed after successful PEA

[193] and, to a lesser extent, BPA[194]. 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 [196]; for instance, ventilation/perfusion imaging successfully predicted the CTEPH patients who benefited the most from BPA.[197] BPA improved $V_{D_{phys}}$ [194] and reduced the respiratory neural drive [198] – 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 normalization of pulmonary hemodynamics, however, dyspnoea and exercise intolerance may persist, a finding related to residual impairment in the O_2 pathway [199] and, in some patients, exertional hypoxemia [200] (**Figure 4**).

The persistence of exercise-related PH after successful normalization of resting pulmonary arterial pressure 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 non-detected distal disease.[201] Pharmacological treatment (i.e. pulmonary vasodilators) of small vessel vasculopathy was associated with lower $\dot{V}_E:\dot{V}CO_2$ despite higher $V_{D_{phys}}$, suggesting a decrease in chemostimulation.[201] In fact, a meta-analysis showed that treatment with riociguat did improve exertional dyspnoea [195] but it remains unknown whether this is consequence of lower $\dot{V}_E:\dot{V}CO_2$. Interestingly, pulmonary vasodilators increased $PaCO_2$, again in keeping with less chemostimualation; thus, this positive effect outweighs any simultaneous increase in $V_{D_{phys}}$ and $\dot{V}_A/\dot{Q}$c mismatch after treatment. [201] In contrast, others found that patients showing distal CTEPH had higher $V_{D_{phys}}$ and $\dot{V}_E$-$\dot{V}CO_2$ slope than their counterparts with PAH.[202] In any case, worsening in $V_{D_{phys}}$ with oral vasodilators has a considerable potential to counterbalance potential decreases in chemostimulation (***Key unanswered questions on $\dot{V}_E$-$\dot{V}CO_2$ and exertional dyspnoea;*** **Table 1)**.[202]

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 sub-cellular 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 persist 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 $PaCO_2$ close to its resting value in the face of a changing VD_{phys}? 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 $PaCO_2$ of the arterial blood leaving the lungs [203] with subsequent stimulation of the peripheral and/or central chemoreceptors?[204] Is there also a role for central integration [205] 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.[206] 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,[207] [208] 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 hemodynamic determinants. Multimodality exercise assessment in evaluating exertional dyspnoea has been cogently advocated[209]: coupling technologically advanced techniques (including invasive hemodynamics and imaging)[13] with a parallel quantitative and qualitative characterization

of the symptom is paramount.[210] 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) [211] differ across these diseases, e.g. "air hunger or unsatisfied inspiration" instead of "work/effort" signaling heightened chemostimulation?[212] If so, do they have a distinct impact on 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 $V_{D_{phys}}$? 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 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.[92] Adding other pieces of information to excess ventilation might prove valuable, e.g., non-selective anti-adrenergics rather than β-selectives showing unordinary high sympathetic tonus, [94] ACEi rather than ARBs in those with low $D_{L_{CO}}$, [99] sildenafil for patients showing PH [118] in association with impaired muscle extraction [114]. Despite the associative evidence herein presented, we should recognize that it remains unknown whether $\dot{V}_E$:$\dot{V}CO_2$ decrease to a larger extent in response to interventions aimed at reducing alveolar hyperventilation compared to those which primarily improve $V_{D_{phys}}$ in HFrEF, PAH, and small-vessel CTEPH. Similarly, it is unclear whether $\dot{V}_E$:$\dot{V}CO_2$ decrease to a larger extent in response to interventions aimed at decreasing $V_{D_{phys}}$ compared to 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 remodeling predispose obese patients with metabolic syndrome to derive greater benefit from pulmonary vasodilators? [137] 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' hemodynamic consequences of high pulmonary arterial pressures 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, [172] is there a role for bronchodilators (particularly anti-muscarinics) in lessening their dyspnoea? Conversely, patients in the early stages of PAH showing marked excess ventilation may benefit from a parsimonious use of anti-adrenergics. More studies are required to test the effects of PAH medications in the sub-set of dyspneic patients with post-pulmonary embolism syndrome or overt CTEPH showing excess ventilation but apparently no residual thromboembolic disease (**Table 1**).[213]

Conclusions

Excess ventilation (high $\dot{V}E:\dot{V}CO_2$), signaling alveolar hyperventilation and/or increased "wasted" ventilation (high $V_{D_{phys}}$), 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 cardiac output limitation (a) and/or RV-PA uncoupling and RV failure (b) 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 hemodynamics and/or reduce chemosensitivity have shown the largest beneficial effects to excess ventilation in these patient populations. In contrast, high filling pressures (a), impaired lung perfusion leading to $\dot{V}_A/\dot{Q}$c mismatch (b) and a low V_T (c) conspire to increase $V_{D_{phys}}$ 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 (pulmonary endarterectomy and balloon pulmonary angioplasty) 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 randomized controlled trials on pharmacological and non-pharmacological interventions aimed at improving these key patient-centered outcomes.

References

1. West, JB. Essays on the History of Respiratory Physiology. New York: Springer@American Physiological Society; 2015.

2. Whipp BJ, Ward SA, Wasserman K. Ventilatory responses to exercise and their control in man. *Am. Rev. Respir. Dis.* 1984; 129: S17-20.

3. Forster HV, Haouzi P, Dempsey JA. Control of breathing during exercise. *Compr Physiol* 2012; 2: 743–777.

4. Sue DY. Excess ventilation during exercise and prognosis in chronic heart failure. *Am. J. Respir. Crit. Care Med.* 2011; 183: 1302–1310.

5. O'Donnell DE, Milne KM, Vincent SG, Neder JA. Unraveling the Causes of Unexplained Dyspnoea: The Value of Exercise Testing. *Clin. Chest Med.* 2019; 40: 471–499.

6. Mahler DA. Evaluation of Dyspnoea in the Elderly. *Clin. Geriatr. Med.* 2017; 33: 503–521.

7. Naeije R, Faoro V. The great breathlessness of cardiopulmonary diseases. *Eur. Respir. J.* 2018; 51.

8. Dempsey JA, Smith CA. Pathophysiology of human ventilatory control. *Eur. Respir. J.* 2014; 44: 495–512.

9. Stickland MK, Neder JA, Guenette JA, O'Donnell DE, Jensen D. Using Cardiopulmonary Exercise Testing to Understand Dyspnoea and Exercise Intolerance in Respiratory Disease. *Chest* 2022; : S0012-3692(22)00145-3.

10. Myers J, Arena R, Cahalin LP, Labate V, Guazzi M. Cardiopulmonary Exercise Testing in Heart Failure. *Curr Probl Cardiol* 2015; 40: 322–372.

11. Naeije R, Faoro V. The breathlessness of pulmonary hypertension. *Int J Cardiol* 2018; 259: 183–184.

12. Arena R, Sietsema KE. Cardiopulmonary exercise testing in the clinical evaluation of patients with heart and lung disease. *Circulation* 2011; 123: 668–680.

13. Guazzi M, Bandera F, Ozemek C, Systrom D, Arena R. Cardiopulmonary Exercise Testing: What Is its Value? *J. Am. Coll. Cardiol.* 2017; 70: 1618–1636.

14. Whipp BJ. Control of the exercise hyperpnea: the unanswered question. *Adv Exp Med Biol* 2008; 605: 16–21.

15. Whipp BJ. The hyperpnea of dynamic muscular exercise. *Exerc Sport Sci Rev* 1977; 5: 295–311.

16. Whipp BJ, Ward SA. Cardiopulmonary coupling during exercise. *J. Exp. Biol.* 1982; 100: 175–193.

17. Wasserman K, Whipp BJ, Koyl SN, Beaver WL. Anaerobic threshold and respiratory gas exchange during exercise. *J Appl Physiol* 1973; 35: 236–243.

18. Arena R, Myers J, Aslam SS, Varughese EB, Peberdy MA. Technical considerations related to the minute ventilation/carbon dioxide output slope in patients with heart failure. *Chest* 2003; 124: 720–727.

19. Ferreira EVM, Ota-Arakaki JS, Ramos RP, Barbosa PB, Almeida M, Treptow EC, Valois FM, Nery LE, Neder JA. Optimizing the evaluation of excess exercise ventilation for prognosis assessment in pulmonary arterial hypertension. *Eur J Prev Cardiol* 2014; 21: 1409–1419.

20. Sun X-G, Hansen JE, Garatachea N, Storer TW, Wasserman K. Ventilatory efficiency during exercise in healthy subjects. *Am. J. Respir. Crit. Care Med.* 2002; 166: 1443–1448.

21. Lewthwaite H, Elsewify O, Niro F, Bourbeau J, Guenette JA, Maltais F, Marciniuk DD, O'Donnell DE, Smith BM, Stickland MK, Tan WC, Jensen D, CanCOLD Collaborative Research Group, Canadian Respiratory Research Network. Normative Cardiopulmonary Exercise Test Responses at the Ventilatory Threshold in Canadian Adults 40 to 80 Years of Age. *Chest* 2021; 159: 1922–1933.

22. Neder JA, Nery LE, Peres C, Whipp BJ. Reference values for dynamic responses to incremental cycle ergometry in males and females aged 20 to 80. *Am. J. Respir. Crit. Care Med.* 2001; 164: 1481–1486.

23. Salvioni E, Corrà U, Piepoli M, Rovai S, Correale M, Paolillo S, Pasquali M, Magrì D, Vitale G, Fusini L, Mapelli M, Vignati C, Lagioia R, Raimondo R, Sinagra G, Boggio F, Cangiano L, Gallo G, Magini A, Contini M, Palermo P, Apostolo A, Pezzuto B, Bonomi A, Scardovi AB, Filardi PP, Limongelli G, Metra M, Scrutinio D, Emdin M, et al. Gender and age normalization and ventilation efficiency during exercise in heart failure with reduced ejection fraction. *ESC Heart Fail* 2020; 7: 371–380.

24. Arena R, Myers J, Abella J, Peberdy MA, Bensimhon D, Chase P, Guazzi M. Development of a ventilatory classification system in patients with heart failure. *Circulation* 2007; 115: 2410–2417.

25. Woods PR, Taylor BJ, Frantz RP, Johnson BD. A pulmonary hypertension gas exchange severity (PH-GXS) score to assist with the assessment and monitoring of pulmonary arterial hypertension. *Am J Cardiol* 2012; 109: 1066–1072.

26. Myers J, Oliveira R, Dewey F, Arena R, Guazzi M, Chase P, Bensimhon D, Peberdy MA, Ashley E, West E, Cahalin LP, Forman DE. Validation of a cardiopulmonary exercise test score in heart failure. *Circ Heart Fail* 2013; 6: 211–218.

27. Neder JA, Alharbi A, Berton DC, Alencar MCN, Arbex FF, Hirai DM, Webb KA, O'Donnell DE. Exercise Ventilatory Inefficiency Adds to Lung Function in Predicting Mortality in COPD. *COPD* 2016; 1–9.

28. Alencar MC, Arbex F, O'Donnell DE, Neder JA. Does exercise ventilatory inefficiency predict poor outcome in heart failure patients with COPD? *J Cardiopulm Rehab Prev* 2016;36(6):454-459.

29. Agostoni P, Sciomer S, Palermo P, Contini M, Pezzuto B, Farina S, Magini A, De Martino F, Magrì D, Paolillo S, Cattadori G, Vignati C, Mapelli M, Apostolo A, Salvioni E. Minute ventilation/carbon dioxide production in chronic heart failure. *Eur Respir Rev* 2021; 30.

30. Yamanaka MK, Sue DY. Comparison of arterial-end-tidal PCO2 difference and dead space/tidal volume ratio in respiratory failure. *Chest* 1987; 92: 832–835.

31. Neder JA, Ramos RP, Ota-Arakaki JS, Hirai DM, D'Arsigny CL, O'Donnell D. Exercise intolerance in pulmonary arterial hypertension. The role of cardiopulmonary exercise testing. *Ann Am Thorac Soc* 2015; 12: 604–612.

32. Weatherald J, Sattler C, Garcia G, Laveneziana P. Ventilatory response to exercise in cardiopulmonary disease: the role of chemosensitivity and dead space. *Eur. Respir. J.* 2018; 51.

33. Lewis DA, Sietsema KE, Casaburi R, Sue DY. Inaccuracy of noninvasive estimates of VD/VT in clinical exercise testing. *Chest* 1994; 106: 1476–1480.

34. Ramos RP, Ferreira EVM, Valois FM, Cepeda A, Messina CMS, Oliveira RK, Araújo ATV, Teles CA, Neder JA, Nery LE, Ota-Arakaki JS. Clinical usefulness of end-tidal CO2profiles during incremental exercise in patients with chronic thromboembolic pulmonary hypertension. *Respir Med* 2016; 120: 70–77.

35. Weatherald J, Boucly A, Montani D, Jaïs X, Savale L, Humbert M, Sitbon O, Garcia G, Laveneziana P. Gas Exchange and Ventilatory Efficiency During Exercise in Pulmonary Vascular Diseases. *Arch Bronconeumol (Engl Ed)* 2020; 56: 578–585.

36. Tanabe Y, Hosaka Y, Ito M, Ito E, Suzuki K. Significance of end-tidal P(CO(2)) response to exercise and its relation to functional capacity in patients with chronic heart failure. *Chest* 2001; 119: 811–817.

37. Jack S, Rossiter HB, Pearson MG, Ward SA, Warburton CJ, Whipp BJ. Ventilatory responses to inhaled carbon dioxide, hypoxia, and exercise in idiopathic hyperventilation. *Am. J. Respir. Crit. Care Med.* 2004; 170: 118–125.

38. Watson M, Ionescu MF, Sylvester K, Fuld J. Minute ventilation/carbon dioxide production in patients with dysfunctional breathing. *Eur Respir Rev* 2021; 30: 200182.

39. Neder JA, Hirai DM, Jones JH, Zelt JT, Berton DC, O'Donnell DE. A 56-Year-Old, Otherwise Healthy Woman Presenting With Light-headedness and Progressive Shortness of Breath. *Chest* 2016; 150: e23-27.

40. Mahler DA, O'Donnell DE. Recent advances in dyspnoea. *Chest* 2015; 147: 232–241.

41. O'Donnell DE, Milne KM, James MD, de Torres JP, Neder JA. Dyspnoea in COPD: New Mechanistic Insights and Management Implications. *Adv Ther* 2020; 37: 41–60.

42. Phillips DB, Neder JA, Elbehairy AF, Milne KM, James MD, Vincent SG, Day AG, DE-Torres JP, Webb KA, O'Donnell DE, Canadian Respiratory Research Network. Qualitative Components of Dyspnoea during Incremental Exercise across the COPD Continuum. *Med Sci Sports Exerc* 2021; 53: 2467–2476.

43. Wasserman K, Zhang YY, Gitt A, Belardinelli R, Koike A, Lubarsky L, Agostoni PG. Lung function and exercise gas exchange in chronic heart failure. *Circulation* 1997; 96: 2221–2227.

44. Agostoni P, Cattadori G, Bussotti M, Apostolo A. Cardiopulmonary interaction in heart failure. *Pulm Pharmacol Ther* 2007; 20: 130–134.

45. Sullivan MJ, Higginbotham MB, Cobb FR. Increased exercise ventilation in patients with chronic heart failure: intact ventilatory control despite hemodynamic and pulmonary abnormalities. *Circulation* 1988; 77: 552–559.

46. Johnson RL. Gas exchange efficiency in congestive heart failure. *Circulation* 2000; 101: 2774–2776.

47. Woods PR, Olson TP, Frantz RP, Johnson BD. Causes of breathing inefficiency during exercise in heart failure. *J. Card. Fail.* 2010; 16: 835–842.

48. Smith JR, Olson TP. Ventilatory constraints influence physiological dead space in heart failure. *Exp. Physiol.* 2019; 104: 70–80.

49. Ponikowski P, Banasiak W. Chemosensitivity in chronic heart failure. *Heart Fail Monit* 2001; 1: 126–131.

50. Agostoni P, Pellegrino R, Conca C, Rodarte JR, Brusasco V. Exercise hyperpnea in chronic heart failure: relationships to lung stiffness and expiratory flow limitation. *J. Appl. Physiol.* 2002; 92: 1409–1416.

51. Hamazaki N, Masuda T, Kamiya K, Matsuzawa R, Nozaki K, Maekawa E, Noda C, Yamaoka-Tojo M, Ako J. Respiratory muscle weakness increases dead-space ventilation ratio aggravating ventilation-perfusion mismatch during exercise in patients with chronic heart failure. *Respirology* 2019; 24: 154–161.

52. Guazzi M, Borlaug BA. Pulmonary hypertension due to left heart disease. *Circulation* 2012; 126: 975–990.

53. Lim HS, Theodosiou M. Exercise ventilatory parameters for the diagnosis of reactive pulmonary hypertension in patients with heart failure. *J Card Fail* 2014; 20: 650–657.

54. Wensel R, Georgiadou P, Francis DP, Bayne S, Scott AC, Genth-Zotz S, Anker SD, Coats AJS, Piepoli MF. Differential contribution of dead space ventilation and low arterial pCO2 to exercise hyperpnea in patients with chronic heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am. J. Cardiol.* 2004; 93: 318–323.

55. Van Iterson EH, Johnson BD, Borlaug BA, Olson TP. Physiological dead space and arterial carbon dioxide contributions to exercise ventilatory inefficiency in patients with reduced or preserved ejection fraction heart failure. *Eur. J. Heart Fail.* 2017; 19: 1675–1685.

56. Amann M, Dempsey JA. Locomotor muscle fatigue modifies central motor drive in healthy humans and imposes a limitation to exercise performance. *J. Physiol. (Lond.)* 2008; 586: 161–173.

57. Floras JS, Ponikowski P. The sympathetic/parasympathetic imbalance in heart failure with reduced ejection fraction. *Eur. Heart J.* 2015; 36: 1974–1982b.

58. Ponikowski PP, Chua TP, Francis DP, Capucci A, Coats AJ, Piepoli MF. Muscle ergoreceptor overactivity reflects deterioration in clinical status and cardiorespiratory reflex control in chronic heart failure. *Circulation* 2001; 104: 2324–2330.

59. Piepoli MF, Crisafulli A. Pathophysiology of human heart failure: importance of skeletal muscle myopathy and reflexes. *Exp Physiol* 2014; 99: 609–615.

60. Toledo C, Andrade DC, Lucero C, Schultz HD, Marcus N, Retamal M, Madrid C, Del Rio R. Contribution of peripheral and central chemoreceptors to sympatho-excitation in heart failure. *J Physiol* 2017; 595: 43–51.

61. Narkiewicz K, Pesek CA, van de Borne PJ, Kato M, Somers VK. Enhanced sympathetic and ventilatory responses to central chemoreflex activation in heart failure. *Circulation* 1999; 100: 262–267.

62. Taylor BJ, Shapiro BP, Johnson BD. Exercise intolerance in heart failure: The important role of pulmonary hypertension. *Exp Physiol* 2020; 105: 1997–2003.

63. Guazzi M, Cahalin LP, Arena R. Cardiopulmonary exercise testing as a diagnostic tool for the detection of left-sided pulmonary hypertension in heart failure. *J Card Fail* 2013; 19: 461–467.

64. Maron BA, Kovacs G, Vaidya A, Bhatt DL, Nishimura RA, Mak S, Guazzi M, Tedford RJ. Cardiopulmonary Hemodynamics in Pulmonary Hypertension and Heart Failure: JACC Review Topic of the Week. *J Am Coll Cardiol* 2020; 76: 2671–2681.

65. Legris V, Thibault B, Dupuis J, White M, Asgar AW, Fortier A, Pitre C, Bouabdallaoui N, Henri C, O'Meara E, Ducharme A, EARTH Investigators. Right ventricular function and its coupling to pulmonary circulation predicts exercise tolerance in systolic heart failure. *ESC Heart Fail* 2022; 9: 450–464.

66. Bandera F, Barletta M, Fontana M, Boveri S, Ghizzardi G, Alfonzetti E, Ambrogi F, Guazzi M. Exercise-induced mitral regurgitation and right ventricle to pulmonary circulation uncoupling across the heart failure phenotypes. *Am J Physiol Heart Circ Physiol* 2021; 320: H642–H653.

67. Paintal AS. Vagal sensory receptors and their reflex effects. *Physiol Rev* 1973; 53: 159–227.

68. Millar PJ, Murai H, Floras JS. Paradoxical muscle sympathetic reflex activation in human heart failure. *Circulation* 2015; 131: 459–468.

69. Widdicombe JG. The J Reflex. *J Physiol* 1998; 511: 2.

70. Bainbridge FA. The influence of venous filling upon the rate of the heart. *J Physiol* 1915; 50: 65–84.

71. Haouzi P, Chenuel B, Huszczuk A. Sensing vascular distension in skeletal muscle by slow conducting afferent fibers: neurophysiological basis and implication for respiratory control. *J. Appl. Physiol.* 2004; 96: 407–418.

72. Ponikowski P, Chua TP, Anker SD, Francis DP, Doehner W, Banasiak W, Poole-Wilson PA, Piepoli MF, Coats AJ. Peripheral chemoreceptor hypersensitivity: an ominous sign in patients with chronic heart failure. *Circulation* 2001; 104: 544–549.

73. Hall MJ, Xie A, Rutherford R, Ando S, Floras JS, Bradley TD. Cycle length of periodic breathing in patients with and without heart failure. *Am J Respir Crit Care Med* 1996; 154: 376–381.

74. Dempsey JA. Central sleep apnea: misunderstood and mistreated! *F1000Res* 2019; 8: F1000 Faculty Rev-981.

75. Xie A, Skatrud JB, Khayat R, Dempsey JA, Morgan B, Russell D. Cerebrovascular response to carbon dioxide in patients with congestive heart failure. *Am. J. Respir. Crit. Care Med.* 2005; 172: 371–378.

76. Guazzi M, Arena R, Halle M, Piepoli MF, Myers J, Lavie CJ. 2016 Focused Update: Clinical Recommendations for Cardiopulmonary Exercise Testing Data Assessment in Specific Patient Populations. *Circulation* 2016 Jun 14;133(24):e694-711. doi: 10.1161/CIR.0000000000000406.

77. Vicenzi M, Deboeck G, Faoro V, Loison J, Vachiery J-L, Naeije R. Exercise oscillatory ventilation in heart failure and in pulmonary arterial hypertension. *Int. J. Cardiol.* 2016; 202: 736–740.

78. Leite JJ, Mansur AJ, de Freitas HFG, Chizola PR, Bocchi EA, Terra-Filho M, Neder JA, Lorenzi-Filho G. Periodic breathing during incremental exercise predicts mortality in patients with chronic heart failure evaluated for cardiac transplantation. *J. Am. Coll. Cardiol.* 2003; 41: 2175–2181.

79. Apostolo A, Laveneziana P, Palange P, Agalbato C, Molle R, Popovic D, Bussotti M, Internullo M, Sciomer S, Bonini M, Alencar MC, Godinas L, Arbex F, Garcia G, Neder JA, Agostoni P. Impact of chronic obstructive pulmonary disease on exercise ventilatory efficiency in heart failure. *Int. J. Cardiol.* 2015; 189: 134–140.

80. Arbex FF, Alencar MC, Souza A, Mazzuco A, Sperandio PA, Rocha A, Hirai DM, Mancuso F, Berton DC, Borghi-Silva A, Almeida DR, O'Donnell DE, Neder JA. Exercise Ventilation in COPD: Influence of Systolic Heart Failure. *COPD* 2016; : 1–8.

81. Smith JR, Van Iterson EH, Johnson BD, Borlaug BA, Olson TP. Exercise ventilatory inefficiency in heart failure and chronic obstructive pulmonary disease. *Int. J. Cardiol.* 2018; .

82. Agostoni P, Cattadori G, Bussotti M, Apostolo A. Cardiopulmonary interaction in heart failure. *Pulm Pharmacol Ther* 2007; 20: 130–134.

83. Rocha A, Arbex FF, Alencar MCN, Sperandio PA, Hirai DM, Berton DC, O'Donnell DE, Neder JA. Physiological and sensory consequences of exercise oscillatory ventilation in heart failure-COPD. *Int. J. Cardiol.* 2016; 224: 447–453.

84. Rocha A, Arbex FF, Sperandio PA, Souza A, Biazzim L, Mancuso F, Berton DC, Hochhegger B, Alencar MCN, Nery LE, O'Donnell DE, Neder JA. Excess Ventilation in COPD-heart Failure Overlap: Implications for Dyspnoea and Exercise Intolerance. *Am. J. Respir. Crit. Care Med.* 2017;196:1264-1274.

85. Chua TP, Ponikowski PP, Harrington D, Chambers J, Coats AJ. Contribution of peripheral chemoreceptors to ventilation and the effects of their suppression on exercise tolerance in chronic heart failure. *Heart* 1996; 76: 483–489.

86. Chua TP, Harrington D, Ponikowski P, Webb-Peploe K, Poole-Wilson PA, Coats AJ. Effects of dihydrocodeine on chemosensitivity and exercise tolerance in patients with chronic heart failure. *J Am Coll Cardiol* 1997; 29: 147–152.

87. Del Rio R, Marcus NJ, Schultz HD. Carotid chemoreceptor ablation improves survival in heart failure: rescuing autonomic control of cardiorespiratory function. *J Am Coll Cardiol* 2013; 62: 2422–2430.

88. Niewiński P, Janczak D, Rucinski A, Jazwiec P, Sobotka PA, Engelman ZJ, Fudim M, Tubek S, Jankowska EA, Banasiak W, Hart ECJ, Paton JFR, Ponikowski P. Carotid body removal for treatment of chronic systolic heart failure. *Int J Cardiol* 2013; 168: 2506–2509.

89. Niewinski P, Tubek S, Paton JFR, Banasiak W, Ponikowski P. Oxygenation pattern and compensatory responses to hypoxia and hypercapnia following bilateral carotid body resection in humans. *J Physiol* 2021; 599: 2323–2340.

90. Niewinski P. Carotid body modulation in systolic heart failure from the clinical perspective. *J Physiol* 2017; 595: 53–61.

91. Keir DA, Duffin J, Floras JS. Measuring Peripheral Chemoreflex Hypersensitivity in Heart Failure. *Front Physiol* 2020; 11: 595486.

92. Contini M. Cardiopulmonary Exercise Test as a Tool to Choose Therapy in Heart Failure. *Ann Am Thorac Soc* 2017; 14: S67–S73.

93. Kataoka M, Satoh T, Yoshikawa T, Nakamura I, Kohno T, Yoshizawa A, Anzai T, Ogawa S. Comparison of the effects of carvedilol and metoprolol on exercise ventilatory efficiency in patients with congestive heart failure. *Circ J* 2008; 72: 358–363.

94. Agostoni P, Contini M, Cattadori G, Apostolo A, Sciomer S, Bussotti M, Palermo P, Fiorentini C. Lung function with carvedilol and bisoprolol in chronic heart failure: is beta selectivity relevant? *Eur. J. Heart Fail.* 2007; 9: 827–833.

95. Agostoni P, Apostolo A, Cattadori G, Salvioni E, Berna G, Antonioli L, Vignati C, Schina M, Sciomer S, Bussotti M, Palermo P, Fiorentini C, Contini M. Effects of beta-blockers on ventilation efficiency in heart failure. *Am. Heart J.* 2010; 159: 1067–1073.

96. Witte KKA, Thackray S, Nikitin NP, Cleland JGF, Clark AL. The effects of long-term beta-blockade on the ventilatory responses to exercise in chronic heart failure. *Eur J Heart Fail* 2005; 7: 612–617.

97. Wolk R, Johnson BD, Somers VK, Allison TG, Squires RW, Gau GT, Olson LJ. Effects of beta-blocker therapy on ventilatory responses to exercise in patients with heart failure. *J Card Fail* 2005; 11: 333–339.

98. Guazzi M, Agostoni P, Guazzi MD. Modulation of alveolar-capillary sodium handling as a mechanism of protection of gas transfer by enalapril, and not by losartan, in chronic heart failure. *J. Am. Coll. Cardiol.* 2001; 37: 398–406.

99. Guazzi M, Agostoni P. Angiotensin-converting enzyme inhibition restores the diffusing capacity for carbon monoxide in patients with chronic heart failure by improving the molecular diffusion across the alveolar capillary membrane. *Clin Sci (Lond)* 1999; 96: 17–22.

100. Guazzi M, Marenzi G, Alimento M, Contini M, Agostoni P. Improvement of alveolar-capillary membrane diffusing capacity with enalapril in chronic heart failure and counteracting effect of aspirin. *Circulation* 1997; 95: 1930–1936.

101. Guazzi M, Melzi G, Agostoni P. Comparison of changes in respiratory function and exercise oxygen uptake with losartan versus enalapril in congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1997; 80: 1572–1576.

102. Guazzi M, Palermo P, Pontone G, Susini F, Agostoni P. Synergistic efficacy of enalapril and losartan on exercise performance and oxygen consumption at peak exercise in congestive heart failure. *Am J Cardiol* 1999; 84: 1038–1043.

103. Dos Santos MR, Alves M-J de NN, Jordão CP, Pinto CEN, Correa KTS, de Souza FR, da Fonseca GWP, Tomaz Filho J, Costa M, Pereira RMR, Negrão CE, Barretto ACP. Sacubitril/valsartan versus enalapril on exercise capacity in patients with heart failure with reduced ejection fraction: A randomized, double-blind, active-controlled study. *Am Heart J* 2021; 239: 1–10.

104. Halle M, Schöbel C, Winzer EB, Bernhardt P, Mueller S, Sieder C, Lecker LSM. A randomized clinical trial on the short-term effects of 12-week sacubitril/valsartan vs. enalapril on peak oxygen consumption in patients with heart failure with reduced ejection fraction: results from the ACTIVITY-HF study. *Eur J Heart Fail* 2021; 23: 2073–2082.

105. Contini M, Compagnino E, Cattadori G, Magrì D, Camera M, Apostolo A, Farina S, Palermo P, Gertow K, Tremoli E, Fiorentini C, Agostoni P. ACE-Inhibition Benefit on Lung Function in Heart Failure is Modulated by ACE Insertion/Deletion Polymorphism. *Cardiovasc Drugs Ther* 2016; 30: 159–168.

106. Muza SR, Levine L, Latzka WA, Sawka MN. Inspiratory resistance effects on exercise breathing pattern relationships to chemoresponsiveness. *Int J Sports Med* 1996; 17: 344–350.

107. McConnell AK, Lomax M. The influence of inspiratory muscle work history and specific inspiratory muscle training upon human limb muscle fatigue. *J Physiol* 2006; 577: 445–457.

108. Trevizan PF, Antunes-Correa LM, Lobo DML, Oliveira PA, de Almeida DR, Abduch MCD, Mathias Junior W, Hajjar LA, Kalil Filho R, Negrão CE. Effects of inspiratory muscle training combined with aerobic exercise training on neurovascular control in chronic heart failure patients. *ESC Heart Fail* 2021; 8: 3845–3854.

109. Martin BJ, Weil JV, Sparks KE, McCullough RE, Grover RF. Exercise ventilation correlates positively with ventilatory chemoresponsiveness. *J Appl Physiol Respir Environ Exerc Physiol* 1978; 45: 557–564.

110. Antunes-Correa LM, Kanamura BY, Melo RC, Nobre TS, Ueno LM, Franco FGM, Roveda F, Braga AM, Rondon MUPB, Brum PC, Barretto ACP, Middlekauff HR, Negrao CE. Exercise training improves neurovascular control and functional capacity in heart failure patients regardless of age. *Eur J Prev Cardiol* 2012; 19: 822–829.

111. Negrao CE, Middlekauff HR, Gomes-Santos IL, Antunes-Correa LM. Effects of exercise training on neurovascular control and skeletal myopathy in systolic heart failure. *Am. J. Physiol. Heart Circ. Physiol.* 2015; 308: H792–H802.

112. Vettor R, Milan G, Franzin C, Sanna M, De Coppi P, Rizzuto R, Federspil G. The origin of intermuscular adipose tissue and its pathophysiological implications. *Am J Physiol Endocrinol Metab* 2009; 297: E987-998.

113. Keller-Ross ML, Johnson BD, Carter RE, Joyner MJ, Eisenach JH, Curry TB, Olson TP. Improved Ventilatory Efficiency with Locomotor Muscle Afferent Inhibition is Strongly Associated with Leg Composition in Heart Failure. *Int. J. Cardiol.* 2016; 202: 159–166.

114. Sperandio PA, Oliveira MF, Rodrigues MK, Berton DC, Treptow E, Nery LE, Almeida DR, Neder JA. Sildenafil improves microvascular O_2 delivery-to-utilization matching and accelerates exercise O_2 uptake kinetics in chronic heart failure. *Am. J. Physiol. Heart Circ. Physiol.* 2012; 303: H1474-1480.

115. Borghi-Silva A, Carrascosa C, Oliveira CC, Barroco AC, Berton DC, Vilaça D, Lira-Filho EB, Ribeiro D, Nery LE, Neder JA. Effects of respiratory muscle unloading on leg muscle oxygenation and blood volume during high-intensity exercise in chronic heart failure. *Am. J. Physiol. Heart Circ. Physiol.* 2008; 294: H2465-2472.

116. Poole DC, Richardson RS, Haykowsky MJ, Hirai DM, Musch TI. Exercise limitations in heart failure with reduced and preserved ejection fraction. *J. Appl. Physiol.* 2018; 124: 208–224.

117. Guazzi M, Vicenzi M, Arena R. Phosphodiesterase 5 inhibition with sildenafil reverses exercise oscillatory breathing in chronic heart failure: a long-term cardiopulmonary exercise testing placebo-controlled study. *Eur. J. Heart Fail.* 2012; 14: 82–90.

118. Guazzi M, Myers J, Peberdy MA, Bensimhon D, Chase P, Arena R. Ventilatory efficiency and dyspnoea on exertion improvements are related to reduced pulmonary pressure in heart failure patients receiving Sildenafil. *Int. J. Cardiol.* 2010; 144: 410–412.

119. Borlaug BA. The pathophysiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol* 2014; 11: 507–515.

120. Guazzi M, Labate V, Cahalin LP, Arena R. Cardiopulmonary exercise testing reflects similar pathophysiology and disease severity in heart failure patients with reduced and preserved ejection fraction. *Eur J Prev Cardiol* 2014; 21: 847–854.

121. Gong J, Castro RRT, Caron JP, Bay CP, Hainer J, Opotowsky AR, Mehra MR, Maron BA, Di Carli MF, Groarke JD, Nohria A. Usefulness of ventilatory inefficiency in predicting prognosis across the heart failure spectrum. *ESC Heart Fail* 2022; 9: 293–302.

122. Guazzi M, Villani S, Generati G, Ferraro OE, Pellegrino M, Alfonzetti E, Labate V, Gaeta M, Sugimoto T, Bandera F. Right Ventricular Contractile Reserve and Pulmonary Circulation Uncoupling During Exercise Challenge in Heart Failure: Pathophysiology and Clinical Phenotypes. *JACC Heart Fail* 2016; 4: 625–635.

123. Nayor M, Xanthakis V, Tanguay M, Blodgett JB, Shah RV, Schoenike M, Sbarbaro J, Farrell R, Malhotra R, Houstis NE, Velagaleti RS, Moore SA, Baggish AL, O'Connor GT, Ho JE, Larson MG, Vasan RS, Lewis GD. Clinical and Hemodynamic Associations and Prognostic Implications of Ventilatory Efficiency in Patients With Preserved Left Ventricular Systolic Function. *Circ Heart Fail* 2020; 13: e006729.

124. Tsujinaga S, Iwano H, Chiba Y, Ishizaka S, Sarashina M, Murayama M, Nakabachi M, Nishino H, Yokoyama S, Okada K, Kaga S, Anzai T. Heart Failure With Preserved Ejection Fraction vs. Reduced Ejection Fraction - Mechanisms of Ventilatory Inefficiency During Exercise in Heart Failure. *Circ Rep* 2020; 2: 271–279.

125. Fermoyle CC, Stewart GM, Borlaug BA, Johnson BD. Simultaneous Measurement of Lung Diffusing Capacity and Pulmonary Hemodynamics Reveals Exertional Alveolar-Capillary Dysfunction in Heart Failure With Preserved Ejection Fraction. *J Am Heart Assoc* 2021; 10: e019950.

126. Petersson J, Glenny RW. Gas exchange and ventilation-perfusion relationships in the lung. *Eur. Respir. J.* 2014; 44: 1023–1041.

127. Smith JR, Borlaug BA, Olson TP. Exercise Ventilatory Efficiency in Older and Younger Heart Failure Patients With Preserved Ejection Fraction. *J Card Fail* 2019; 25: 278–285.

128. Obokata M, Olson TP, Reddy YNV, Melenovsky V, Kane GC, Borlaug BA. Haemodynamics, dyspnoea, and pulmonary reserve in heart failure with preserved ejection fraction. *Eur Heart J* 2018; 39: 2810–2821.

129. Reddy YNV, Obokata M, Wiley B, Koepp KE, Jorgenson CC, Egbe A, Melenovsky V, Carter RE, Borlaug BA. The haemodynamic basis of lung congestion during exercise in heart failure with preserved ejection fraction. *Eur Heart J* 2019; 40: 3721–3730.

130. Andrade DC, Arce-Alvarez A, Toledo C, Díaz HS, Lucero C, Quintanilla RA, Schultz HD, Marcus NJ, Amann M, Del Rio R. Revisiting the physiological effects of exercise training on autonomic regulation and chemoreflex control in heart failure: does ejection fraction matter? *Am J Physiol Heart Circ Physiol* 2018; 314: H464–H474.

131. Del Rio R, Andrade DC, Toledo C, Diaz HS, Lucero C, Arce-Alvarez A, Marcus NJ, Schultz HD. Carotid Body-Mediated Chemoreflex Drive in The Setting of low and High Output Heart Failure. *Sci Rep* 2017; 7: 8035.

132. Dhakal BP, Malhotra R, Murphy RM, Pappagianopoulos PP, Baggish AL, Weiner RB, Houstis NE, Eisman AS, Hough SS, Lewis GD. Mechanisms of exercise intolerance in heart failure with preserved ejection fraction: the role of abnormal peripheral oxygen extraction. *Circ Heart Fail* 2015; 8: 286–294.

133. Oakland HT, Joseph P, Elassal A, Cullinan M, Heerdt PM, Singh I. Diagnostic utility of sub-maximum cardiopulmonary exercise testing in the ambulatory setting for heart failure with preserved ejection fraction. *Pulm Circ* 2020; 10: 2045894020972273.

134. Guazzi M, Dixon D, Labate V, Beussink-Nelson L, Bandera F, Cuttica MJ, Shah SJ. RV Contractile Function and its Coupling to Pulmonary Circulation in Heart Failure With Preserved Ejection Fraction: Stratification of Clinical Phenotypes and Outcomes. *JACC Cardiovasc Imaging* 2017; 10: 1211–1221.

135. Udelson JE, Lewis GD, Shah SJ, Zile MR, Redfield MM, Burnett J, Parker J, Seferovic JP, Wilson P, Mittleman RS, Profy AT, Konstam MA. Effect of Praliciguat on Peak Rate of Oxygen Consumption in Patients With Heart Failure With Preserved Ejection Fraction: The CAPACITY HFpEF Randomized Clinical Trial. *JAMA* 2020; 324: 1522–1531.

136. Hussain I, Mohammed SF, Forfia PR, Lewis GD, Borlaug BA, Gallup DS, Redfield MM. Impaired Right Ventricular-Pulmonary Arterial Coupling and Effect of Sildenafil in Heart Failure With Preserved Ejection Fraction: An Ancillary Analysis

From the Phosphodiesterase-5 Inhibition to Improve Clinical Status And Exercise Capacity in Diastolic Heart Failure (RELAX) Trial. *Circ Heart Fail* 2016; 9: e002729.

137. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence Supporting the Existence of a Distinct Obese Phenotype of Heart Failure With Preserved Ejection Fraction. *Circulation* 2017; 136: 6–19.

138. Guazzi M, Bandera F, Pelissero G, Castelvecchio S, Menicanti L, Ghio S, Temporelli PL, Arena R. Tricuspid annular plane systolic excursion and pulmonary arterial systolic pressure relationship in heart failure: an index of right ventricular contractile function and prognosis. *Am J Physiol Heart Circ Physiol* 2013; 305: H1373-1381.

139. Guazzi M, Naeije R, Arena R, Corrà U, Ghio S, Forfia P, Rossi A, Cahalin LP, Bandera F, Temporelli P. Echocardiography of Right Ventriculoarterial Coupling Combined With Cardiopulmonary Exercise Testing to Predict Outcome in Heart Failure. *Chest* 2015; 148: 226–234.

140. Müller J, Lichtblau M, Saxer S, Calendo L-R, Carta AF, Schneider SR, Berlier C, Furian M, Bloch KE, Schwarz EI, Ulrich S. Effect of Breathing Oxygen-Enriched Air on Exercise Performance in Patients With Pulmonary Hypertension Due to Heart Failure With Preserved Ejection Fraction: A Randomized, Placebo-Controlled, Crossover Trial. *Front Med (Lausanne)* 2021; 8: 692029.

141. Donelli da Silveira A, Beust de Lima J, da Silva Piardi D, Dos Santos Macedo D, Zanini M, Nery R, Laukkanen JA, Stein R. High-intensity interval training is effective and superior to moderate continuous training in patients with heart failure with preserved ejection fraction: A randomized clinical trial. *Eur J Prev Cardiol* 2020; 27: 1733–1743.

142. Pandey A, Parashar A, Kumbhani D, Agarwal S, Garg J, Kitzman D, Levine B, Drazner M, Berry J. Exercise training in patients with heart failure and preserved ejection fraction: meta-analysis of randomized control trials. *Circ Heart Fail* 2015; 8: 33–40.

143. Kitzman DW, Brubaker PH, Herrington DM, Morgan TM, Stewart KP, Hundley WG, Abdelhamed A, Haykowsky MJ. Effect of endurance exercise training on endothelial function and arterial stiffness in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. *J. Am. Coll. Cardiol.* 2013; 62: 584–592.

144. Babu AS, Arena R, Myers J, Padmakumar R, Maiya AG, Cahalin LP, Waxman AB, Lavie CJ. Exercise intolerance in pulmonary hypertension: mechanism, evaluation and clinical implications. *Expert Rev Respir Med* 2016; 10: 979–990.

145. Naeije R, Richter MJ, Rubin LJ. The physiologic basis of pulmonary arterial hypertension. *Eur Respir J.* 2021 Nov 4;2102334. doi: 10.1183/13993003.02334-2021.

146. Raza F, Dharmavaram N, Hess T, Dhingra R, Runo J, Chybowski A, Kozitza C, Batra S, Horn EM, Chesler N, Eldridge M. Distinguishing exercise intolerance in early-stage pulmonary hypertension with invasive exercise hemodynamics: Rest VE /VCO2 and ETCO2 identify pulmonary vascular disease. *Clin Cardiol* 2022; Apr 14. doi: 10.1002/clc.23831. Online ahead of print..

147. Deboeck G, Niset G, Lamotte M, Vachiéry JL, Naeije R. Exercise testing in pulmonary arterial hypertension and in chronic heart failure. *Eur Respir J* 2004; 23: 747–751.

148. Wensel R, Jilek C, Dörr M, Francis DP, Stadler H, Lange T, Blumberg F, Opitz C, Pfeifer M, Ewert R. Impaired cardiac autonomic control relates to disease severity in pulmonary hypertension. *Eur Respir J* 2009; 34: 895–901.

149. Naeije R, Borne P van de. Clinical relevance of autonomic nervous system disturbances in pulmonary arterial hypertension. *Eur Respir J*; 2009; 34: 792–794.

150. Farina S, Bruno N, Agalbato C, Contini M, Cassandro R, Elia D, Harari S, Agostoni P. Physiological insights of exercise hyperventilation in arterial and chronic thromboembolic pulmonary hypertension. *Int. J. Cardiol.* 2018; 259: 178–182.

151. Paula-Ribeiro M, Ribeiro IC, Aranda LC, Silva TM, Costa CM, Ramos RP, Ota-Arakaki JS, Cravo SL, Nery LE, Stickland MK, Silva BM. Carotid chemoreflex activity restrains post-exercise cardiac autonomic control in healthy humans and in patients with pulmonary arterial hypertension. *J Physiol* 2019; 597: 1347–1360.

152. Velez-Roa S, Ciarka A, Najem B, Vachiery J-L, Naeije R, van de Borne P. Increased sympathetic nerve activity in pulmonary artery hypertension. *Circulation* 2004; 110: 1308–1312.

153. Treptow E, Oliveira MF, Soares A, Ramos RP, Medina L, Lima R, Alencar MC, Ferreira EV, Ota-Arakaki JS, Tufik S, Nery LE, Bittencourt LR, Neder JA. Cerebral microvascular blood flow and CO2 reactivity in pulmonary arterial hypertension. *Respir Physiol Neurobiol* 2016; 233: 60–65.

154. Malenfant S, Brassard P, Paquette M, Le Blanc O, Chouinard A, Nadeau V, Allan PD, Tzeng Y-C, Simard S, Bonnet S, Provencher S. Compromised Cerebrovascular Regulation and Cerebral Oxygenation in Pulmonary Arterial Hypertension. *J Am Heart Assoc* 2017; 6.

155. Hoeper MM, Pletz MW, Golpon H, Welte T. Prognostic value of blood gas analyses in patients with idiopathic pulmonary arterial hypertension. *Eur. Respir. J.* 2007; 29: 944–950.

156. Linden RJ. Reflexes from receptors in the heart. *Cardiology* 1976; 61 suppl 1: 7–30.

157. Paula-Ribeiro M, Ribeiro IC, Aranda LC, Silva TM, Costa CM, Ramos RP, Ota-Arakaki J, Cravo SL, Nery LE, Stickland MK, Silva BM. Cardiac baroreflex dysfunction in patients with pulmonary arterial hypertension at rest and during orthostatic stress: Role of the peripheral chemoreflex. *J Appl Physiol (1985)* 2021; .

158. Fukui S, Ogo T, Goto Y, Ueda J, Tsuji A, Sanda Y, Kumasaka R, Arakawa T, Nakanishi M, Fukuda T, Takaki H, Yasuda S, Ogawa H, Nakanishi N. Exercise intolerance and ventilatory inefficiency improve early after balloon pulmonary angioplasty in patients with inoperable chronic thromboembolic pulmonary hypertension. *International Journal of Cardiology* 2015; 180: 66–68.

159. Batt J, Ahmed SS, Correa J, Bain A, Granton J. Skeletal muscle dysfunction in idiopathic pulmonary arterial hypertension. *Am J Respir Cell Mol Biol* 2014; 50: 74–86.

160. Marra AM, Arcopinto M, Bossone E, Ehlken N, Cittadini A, Grünig E. Pulmonary arterial hypertension-related myopathy: an overview of current data and future perspectives. *Nutr Metab Cardiovasc Dis* 2015; 25: 131–139.

161. Meyer FJ, Lossnitzer D, Kristen AV, Schoene AM, Kübler W, Katus HA, Borst MM. Respiratory muscle dysfunction in idiopathic pulmonary arterial hypertension. *Eur. Respir. J.* 2005; 25: 125–130.

162. Malenfant S, Lebret M, Breton-Gagnon É, Potus F, Paulin R, Bonnet S, Provencher S. Exercise intolerance in pulmonary arterial hypertension: insight into central and peripheral pathophysiological mechanisms. *Eur Respir Rev* 2021; 30: 200284.

163. Mainguy V, Maltais F, Saey D, Gagnon P, Martel S, Simon M, Provencher S. Effects of a rehabilitation program on skeletal muscle function in idiopathic pulmonary arterial hypertension. *J Cardiopulm Rehabil Prev* 2010; 30: 319–323.

164. Waxman AB. Exercise physiology and pulmonary arterial hypertension. *Prog Cardiovasc Dis* 2012; 55: 172–179.

165. Malenfant S, Potus F, Mainguy V, Leblanc E, Malenfant M, Ribeiro F, Saey D, Maltais F, Bonnet S, Provencher S. Impaired Skeletal Muscle Oxygenation and Exercise Tolerance in Pulmonary Hypertension. *Med Sci Sports Exerc* 2015; 47: 2273–2282.

166. Barbosa PB, Ferreira EMV, Arakaki JSO, Takara LS, Moura J, Nascimento RB, Nery LE, Neder JA. Kinetics of skeletal muscle O2 delivery and utilization at the onset of heavy-intensity exercise in pulmonary arterial hypertension. *Eur J Appl Physiol* 2011; 111: 1851–1861.

167. Dantzker DR, Bower JS. Mechanisms of gas exchange abnormality in patients with chronic obliterative pulmonary vascular disease. *J Clin Invest* 1979; 64: 1050–1055.

168. Sun XG, Hansen JE, Oudiz RJ, Wasserman K. Exercise pathophysiology in patients with primary pulmonary hypertension. *Circulation* 2001; 104: 429–435.

169. Johnson RL. Gas exchange efficiency in congestive heart failure II. *Circulation* 2001; 103: 916–918.

170. Dantzker DR, D'Alonzo GE, Bower JS, Popat K, Crevey BJ. Pulmonary gas exchange during exercise in patients with chronic obliterative pulmonary hypertension. *Am Rev Respir Dis* 1984; 130: 412–416.

171. Robertson HT. Dead space: the physiology of wasted ventilation. *Eur. Respir. J.* 2015; 45: 1704–1716.

172. Laveneziana P, Garcia G, Joureau B, Nicolas-Jilwan F, Brahimi T, Laviolette L, Sitbon O, Simonneau G, Humbert M, Similowski T. Dynamic respiratory mechanics and exertional dyspnoea in pulmonary arterial hypertension. *Eur. Respir. J.* 2013; 41: 578–587.

173. Laveneziana P, Humbert M, Godinas L, Joureau B, Malrin R, Straus C, Jaïs X, Sitbon O, Simonneau G, Similowski T, Garcia G. Inspiratory muscle function, dynamic hyperinflation and exertional dyspnoea in pulmonary arterial hypertension. *Eur Respir J* 2015; 45: 1495–1498.

174. Boucly A, Morélot-Panzini C, Garcia G, Weatherald J, Jaïs X, Savale L, Montani D, Humbert M, Similowski T, Sitbon O, Laveneziana P. Intensity and quality of exertional dyspnoea in patients with stable pulmonary hypertension. *Eur. Respir. J.* 2019; .

175. Laveneziana P, Webb KA, Ora J, Wadell K, O'Donnell DE. Evolution of dyspnoea during exercise in chronic obstructive pulmonary disease: impact of critical volume constraints. *Am. J. Respir. Crit. Care Med.* 2011; 184: 1367–1373.

176. Spiesshoefer J, Herkenrath S, Mohr M, Randerath W, Tuleta I, Diller GP, Emdin M, Young P, Henke C, Florian AR, Yilmaz A, Boentert M, Giannoni A. Diaphragm function does not independently predict exercise intolerance in patients with precapillary pulmonary hypertension after adjustment for right ventricular function. *Biosci Rep* 2019; 39: BSR20190392.

177. Xie Y, Liu N, Xiao Z, Yang F, Zeng Y, Yang Z, Xia Y, Chen Z, Xiao Y. The progress of pulmonary artery denervation. *Cardiol J* 2021; .

178. Ciarka A, Vachièry J-L, Houssière A, Gujic M, Stoupel E, Velez-Roa S, Naeije R, van de Borne P. Atrial septostomy decreases sympathetic overactivity in pulmonary arterial hypertension. *Chest* 2007; 131: 1831–1837.

179. Roncato G, da Fontoura FF, Spilimbergo FB, Meyer GMB, Watte G, de Vargas WO, Casali KR, Berton DC, Rigatto K. Parasympathetic modulation withdrawal improves functional capacity in pulmonary arterial hypertension. *Respir Physiol Neurobiol* 2021; 287: 103620.

180. Badagliacca R, Mercurio V, Romeo E, Correale M, Masarone D, Papa S, Tocchetti CG, Agostoni P, Members of the Study Group on Right and Left Heart Failure of the Italian Society of Cardiology. Beta-blockers in pulmonary arterial hypertension: Time for a second thought? *Vascul Pharmacol* 2022; 144: 106974.

181. Ulrich S, Hasler ED, Saxer S, Furian M, Müller-Mottet S, Keusch S, Bloch KE. Effect of breathing oxygen-enriched air on exercise performance in patients with precapillary pulmonary hypertension: randomized, sham-controlled cross-over trial. *Eur. Heart J.* 2017; 38: 1159–1168.

182. Oudiz RJ, Roveran G, Hansen JE, Sun X-G, Wasserman K. Effect of sildenafil on ventilatory efficiency and exercise tolerance in pulmonary hypertension. *Eur. J. Heart Fail.* 2007; 9: 917–921.

183. Wensel R, Opitz CF, Ewert R, Bruch L, Kleber FX. Effects of iloprost inhalation on exercise capacity and ventilatory efficiency in patients with primary pulmonary hypertension. *Circulation* 2000; 101: 2388–2392.

184. Nagaya N, Shimizu Y, Satoh T, Oya H, Uematsu M, Kyotani S, Sakamaki F, Sato N, Nakanishi N, Miyatake K. Oral beraprost sodium improves exercise capacity and ventilatory efficiency in patients with primary or thromboembolic pulmonary hypertension. *Heart* 2002; 87: 340–345.

185. Tang Y, Yao L, Liu Z, Ma X, Luo Q, Zhao Z, Huang Z, Tu L, Gao L, Jin Q, Ni X, Xiong C. Effect of calcium channel blockers evaluated by cardiopulmonary exercise testing in idiopathic pulmonary arterial hypertension responding to acute pulmonary vasoreactivity testing. *Pulm Pharmacol Ther* 2017; 43: 26–31.

186. Nishizaki M, Ogawa A, Matsubara H. Response to exercise in patients with pulmonary arterial hypertension treated with combination therapy. *ERJ Open Res* 2021; 7: 00725–02020.

187. Naeije R. Lung mechanics and exertional dyspnoea in pulmonary arterial hypertension. *Respiration* 2014; 88: 16–17.

188. Zhai Z, Murphy K, Tighe H, Wang C, Wilkins MR, Gibbs JSR, Howard LS. Differences in ventilatory inefficiency between pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. *Chest* 2011; 140: 1284–1291.

189. Weatherald J, Philipenko B, Montani D, Laveneziana P. Ventilatory efficiency in pulmonary vascular diseases. *Eur Respir Rev* 2021; 30: 200214.

190. Mélot C, Naeije R. Pulmonary vascular diseases. *Compr Physiol* 2011; 1: 593–619.

191. Held M, Kolb P, Grün M, Jany B, Hübner G, Grgic A, Holl R, Schaefers H-J, Wilkens H. Functional Characterization of Patients with Chronic Thromboembolic Disease. *Respiration* 2016; 91: 503–509.

192. Rolim JV, Ota-Arakaki JS, Ferreira EVM, Figliolino GAM, Ivanaga I, Vieira EB, Fonseca AXC, Messina CMS, Costa CM, Neder JA, Nery LE, Ramos RP. Inspiratory muscle weakness contributes to exertional dyspnoea in chronic thromboembolic pulmonary hypertension. *PLoS ONE* 2018; 13: e0204072.

193. Iwase T, Nagaya N, Ando M, Satoh T, Sakamaki F, Kyotani S, Takaki H, Goto Y, Ohkita Y, Uematsu M, Nakanishi N, Miyatake K. Acute and chronic effects of surgical thromboendarterectomy on exercise capacity and ventilatory efficiency in patients with chronic thromboembolic pulmonary hypertension. *Heart* 2001; 86: 188–192.

194. Blanquez-Nadal M, Piliero N, Guillien A, Doutreleau S, Salvat M, Thony F, Pison C, Augier C, Bouvaist H, Aguilaniu B, Degano B. Exercise hyperventilation and pulmonary gas exchange in chronic thromboembolic pulmonary hypertension: Effects of balloon pulmonary angioplasty. *J Heart Lung Transplant* 2021; : S1053-2498(21)02504-3.

195. Ying M, Song J, Gu S, Zhao R, Li M. Efficacy and safety of riociguat in the treatment of chronic thromboembolic pulmonary arterial hypertension: A meta-analysis. *Medicine (Baltimore)* 2021; 100: e26211.

196. Kapitan KS, Clausen JL, Moser KM. Gas exchange in chronic thromboembolism after pulmonary thromboendarterectomy. *Chest* 1990; 98: 14–19.

197. Wang L, Han X, Wang M, Ma X, Zhang H, Yan C, Fang W. Ventilation/perfusion imaging predicts response to balloon pulmonary angioplasty in patients with chronic thromboembolic pulmonary hypertension. *Ann Nucl Med* 2022; Feb 22. doi: 10.1007/s12149-022-01731-x. Online ahead of print.

198. Blanquez-Nadal M, Piliero N, Guillien A, Salvat M, Thony F, Augier C, Bouvaist H, Degano B. Neural respiratory drive in chronic thromboembolic pulmonary hypertension: Effect of balloon pulmonary angioplasty. *Respir Physiol Neurobiol* 2022; 299: 103857.

199. Howden EJ, Ruiz-Carmona S, Claeys M, De Bosscher R, Willems R, Meyns B, Verbelen T, Maleux G, Godinas L, Belge C, Bogaert J, Claus P, La Gerche A, Delcroix M, Claessen G. Oxygen Pathway Limitations in Patients With Chronic Thromboembolic Pulmonary Hypertension. *Circulation* 2021; 143: 2061–2073.

200. Matsuoka Y, Taniguchi Y, Miwa K, Sumimoto K, Tsuboi Y, Onishi H, Yanaka K, Emoto N, Hirata K. Assessment of oxygenation after balloon pulmonary angioplasty for patients with inoperable chronic thromboembolic pulmonary hypertension. *Int J Cardiol* 2021; 333: 188–194.

201. Charalampopoulos A, Gibbs JSR, Davies RJ, Gin-Sing W, Murphy K, Sheares KK, Pepke-Zaba J, Jenkins DP, Howard LS. Exercise physiological responses to drug treatments in chronic thromboembolic pulmonary hypertension. *J. Appl. Physiol.* 2016; 121: 623–628.

202. Godinas L, Sattler C, Lau EM, Jaïs X, Taniguchi Y, Jevnikar M, Weatherald J, Sitbon O, Savale L, Montani D, Simonneau G, Humbert M, Laveneziana P, Garcia G. Dead-space ventilation is linked to exercise capacity and survival in distal chronic thromboembolic pulmonary hypertension. *J. Heart Lung Transplant.* 2017; 36: 1234–1242.

203. Ward SA. Ventilation/carbon dioxide output relationships during exercise in health. *Eur Respir Rev* 2021; 30.

204. Neder JA. Residual Exertional Dyspnoea in Cardiopulmonary Disease. *Ann Am Thorac Soc* 2020; 17: 1516–1525.

205. Guyenet PG, Stornetta RL, Souza GMPR, Abbott SBG, Shi Y, Bayliss DA. The Retrotrapezoid Nucleus: Central Chemoreceptor and Regulator of Breathing Automaticity. *Trends Neurosci* 2019; 42: 807–824.

206. Mitchell GS, Babb TG. Layers of exercise hyperpnea: modulation and plasticity. *Respir Physiol Neurobiol* 2006; 151: 251–266.

207. Chase P, Arena R, Myers J, Abella J, Peberdy MA, Guazzi M, Kenjale A, Bensimhon D. Prognostic usefulness of dyspnoea versus fatigue as reason for exercise test termination in patients with heart failure. *Am J Cardiol* 2008; 102: 879–882.

208. Guazzi M, Myers J, Peberdy MA, Bensimhon D, Chase P, Arena R. Maximal dyspnoea on exertion during cardiopulmonary exercise testing is related to poor prognosis and echocardiography with tissue Doppler imaging in heart failure. *Congest Heart Fail* 2009; 15: 277–283.

209. Anand V, Bradley D, Frye RL, Borlaug BA. Things Are Not Always as They Seem: Multimodality Exercise Assessment in the Evaluation of Dyspnoea. *Circulation* 2021; 143: 2502–2507.

210. Banzett RB, Schwartzstein RM. Dyspnoea: Don't Just Look, Ask! *Am. J. Respir. Crit. Care Med.* 2015; 192: 1404–1406.

211. Mahler DA, O'Donnell DE. Recent advances in dyspnoea. *Chest* 2015; 147: 232–241.

212. Banzett RB, Lansing RW, Reid MB, Adams L, Brown R. "Air hunger" arising from increased PCO2 in mechanically ventilated quadriplegics. *Respir Physiol* 1989; 76: 53–67.

213. Boon GJAM, Huisman MV, Klok FA. Determinants and Management of the Post-Pulmonary Embolism Syndrome. *Semin Respir Crit Care Med* 2021; 42: 299–307.

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 $V_{D_{phys}}$ to control $PaCO_2$ close to the resting values?
• Is there are a role for neural/behavioral mechanisms of ventilatory control in "fine-tuning" exercise hyperpnea in health and disease?
• Does alveolar hyperventilation in HFrEF and PAH follow a downward shift in $PaCO_2$ set-point or a low $PaCO_2$ is a "passive" consequence of increased neurochemical stimulation/receptor sensitivity?
• What are the exact sources of increased afferent stimulation in the presence of central hemodynamic abnormalities signaling RV-pulmonary arterial 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 $V_{D_{phys}}$ in patients with HFpEF?
• How is the severity of excess exertional ventilation modulated by the different hemodynamic phenotypes of HFpEF?
• Does "stagnant hypoxia" (as seen in HFrEF) play a role in chronic carotid body sensitization 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 hemodynamic 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 $V_{D_{phys}}$?
• 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 co-morbidities (e.g., obesity, hypertension, diabetes mellitus, atrial fibrillation) on dyspnoea perception?
• What is the minimal clinically important difference for dyspnoea reduction during submaximal exercise (according to different scales)?
• How best use exertional dyspnoea as a main outcome in clinical trials involving pharmacological and non-pharmacological 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 to those which primarily improve $V_{D_{phys}}$ 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 $V_{D_{phys}}$ compared to 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 dyspneic patients with HFrEF?
- Are HFrEF patients showing low D_{LCO} (signaling impaired pulmonary gas exchange) particularly prone to respond to ACE inhibitors rather than angiotensin receptor blockers?
- Is the unduly high $\dot{V}E:\dot{V}CO_2$ in combined pre- and post-capillary PH a reflection of the added negative hemodynamics effects of the former or only a mere reflect 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 20-25 mmhg?
- Is there a role for pharmacological or non-pharmacological 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 $P_{ET}CO_2$) help in selecting patients with small vessel, distal CTEPH or even dyspneic post-pulmonary embolism patients showing persistent perfusion deficits to receive pulmonary vasodilators?

Abbreviations and symbols: ACE: angiotensin-converting enzyme; CTEPH: chronic thromboembolic pulmonary hypertension; D_{LCO}: lung diffusing capacity for carbon monoxide; EMGdi: diaphragm electromyography; HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction;; mPAP: mean pulmonary arterial pressure; Pa: arterial partial pressure; PAH: pulmonary arterial hypertension; RV: right ventricle; $\dot{V}A$: alveolar ventilation; $\dot{V}E$: minute ventilation; $\dot{V}CO_2$: carbon dioxide output; $V_{D_{phys}}$: physiological dead space.

Figure Legends

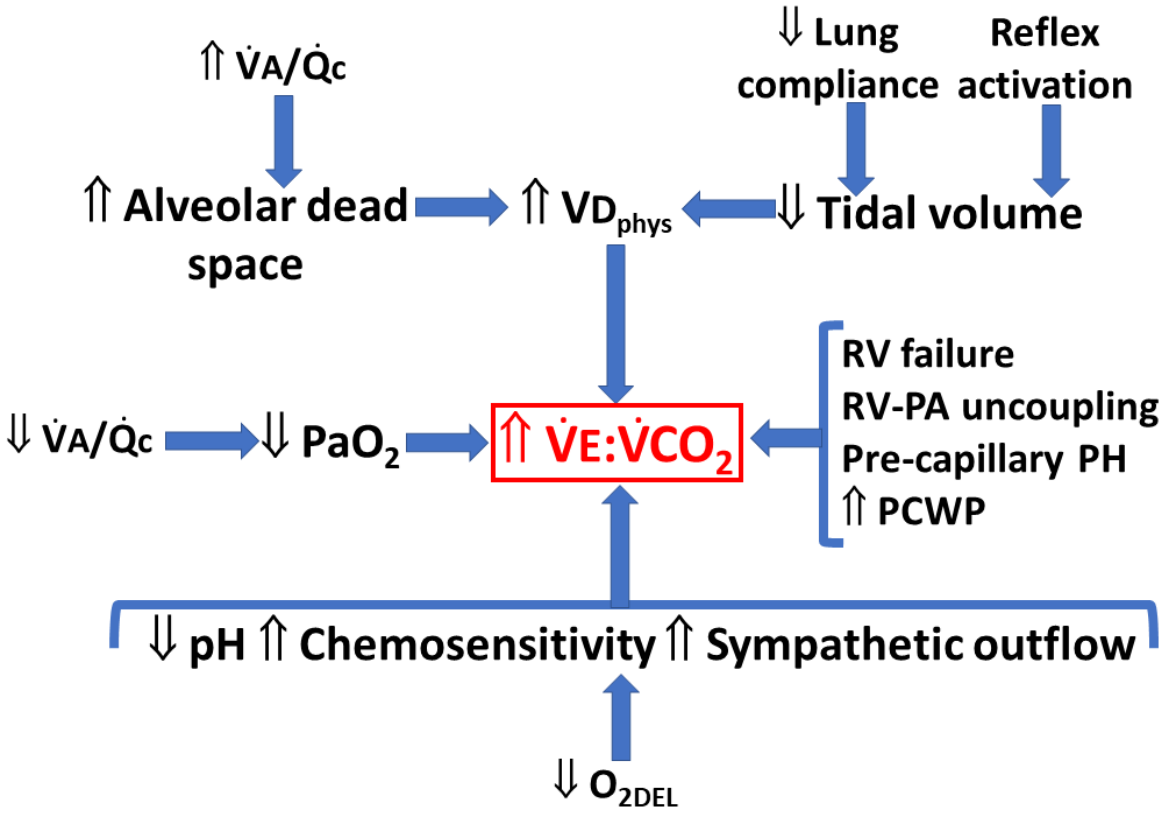

Figure 1. Main abnormalities in cardiopulmonary interactions that may interfere with the ventilatory control system during exercise, leading to excess exertional ventilation (increased ventilation ($\dot{V}_E$):pulmonary carbon dioxide output ($\dot{V}CO_2$) relationship) in patients with cardiac and/or pulmonary vascular disease See text for elaboration.
Symbols and *Abbreviations*: ⇑: increased; ⇓: decreased; $_{DEL}$= delivery; PA: pulmonary artery; Pa: arterial partial pressure; PCWP: pulmonary capillary wedge pressure; PH: pulmonary hypertension; $\dot{Q}$c: capillary perfusion; RV: right ventricle; $\dot{V}_A$: alveolar ventilation; $\dot{V}_E$: minute ventilation; $\dot{V}CO_2$: carbon dioxide output; VD_{phys}: physiological dead space.

* We avoid the term "ventilatory inefficiency" to refer to an increased $\dot{V}_E$:$\dot{V}CO_2$ since a) there is no "inefficiency" (in fact, quite the opposite) when a high $\dot{V}_E$:$\dot{V}CO_2$ is associated with hypocapnia, and b) a high VD_{phys} exposes gas exchange, not "ventilatory", inefficiency.

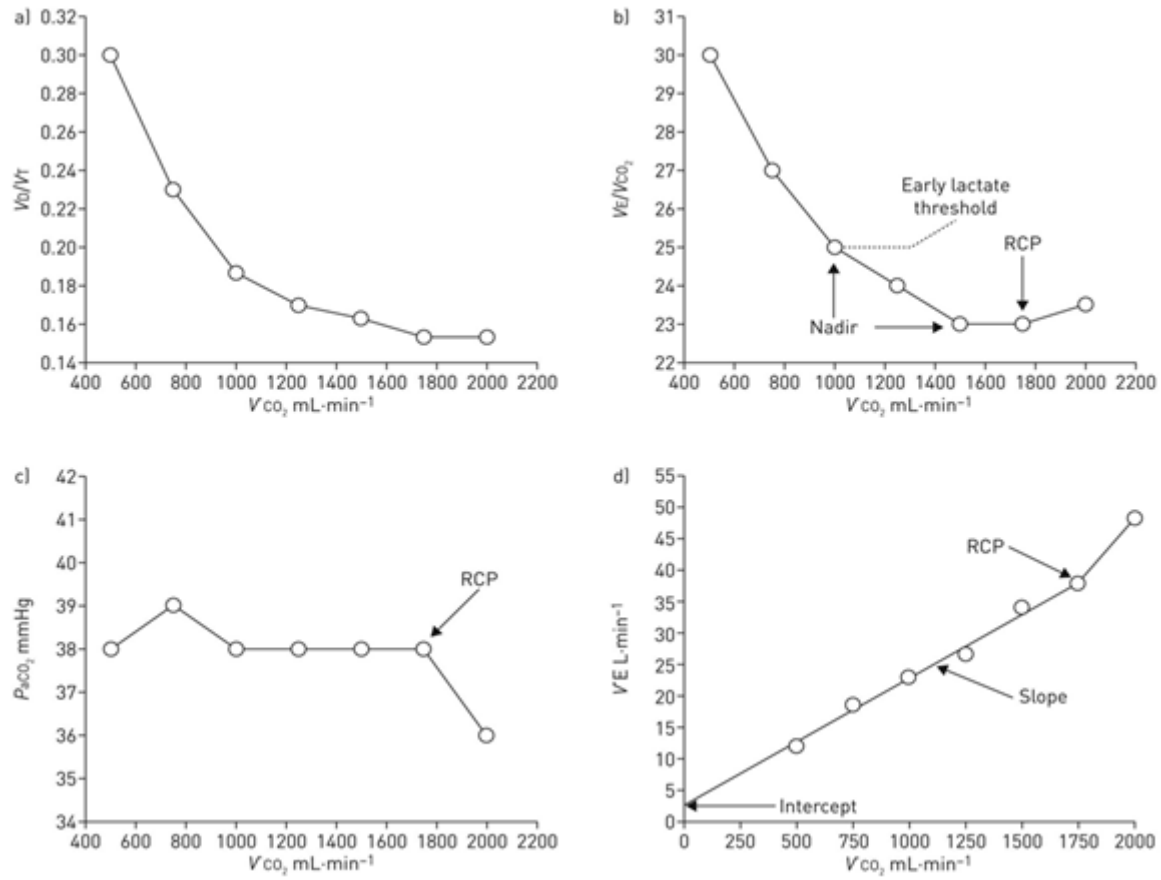

Figure 2. Selected ventilatory and gas exchange responses to incremental CPET in a young healthy male. Proportional decreases in dead space (V_D)/tidal volume (V_T) (a) and ventilation ($\dot{V}_E$)/carbon dioxide output ($\dot{V}CO_2$) (b) ratios maintain arterial carbon dioxide partial pressure ($PaCO_2$) close to resting value during mild-to-moderate exercise (c). 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 (d). Thus, the lowest (nadir) $\dot{V}_E/\dot{V}CO_2$ closely approximates slope plus intercept. $\dot{V}_E$-$\dot{V}CO_2$ 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 acidemia. Note the increases in nadir when the lactate threshold is reached at a low exercise intensity, i.e., before the stabilization of $\dot{V}_E/\dot{V}CO_2$. See text for further elaboration.

Reproduced, with permission from the publisher from:

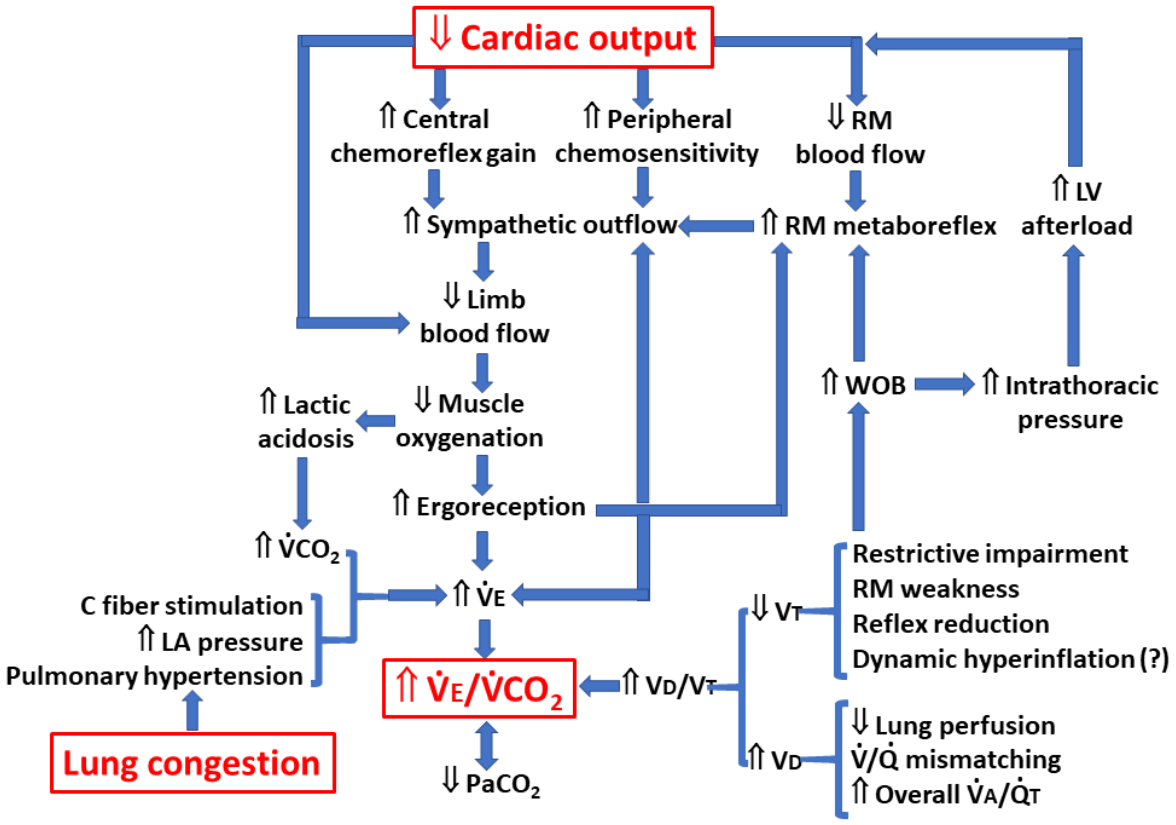

Figure 3. The main mechanisms linking the fundamental pathophysiological features of heart failure (low cardiac output and lung congestion) with excess exertional ventilation, i.e., high ventilation ($\dot{V}_E$):carbon dioxide output ($\dot{V}CO_2$) relationship. The relative importance of individual mechanisms varies according to disease phenotype, i.e., heart failure with reduced versus preserved ejection fraction. See text for elaboration.

Symbols and *Abbreviations*: ⇑: increased; ⇓: decreased; LA: left atrium; LV: left ventricle; RM: respiratory muscles; Pa: arterial partial pressure; $\dot{Q}_T$: cardiac output; $\dot{V}_A$: alveolar ventilation; V_D: dead space; V_T: tidal volume; WOB: work of breathing

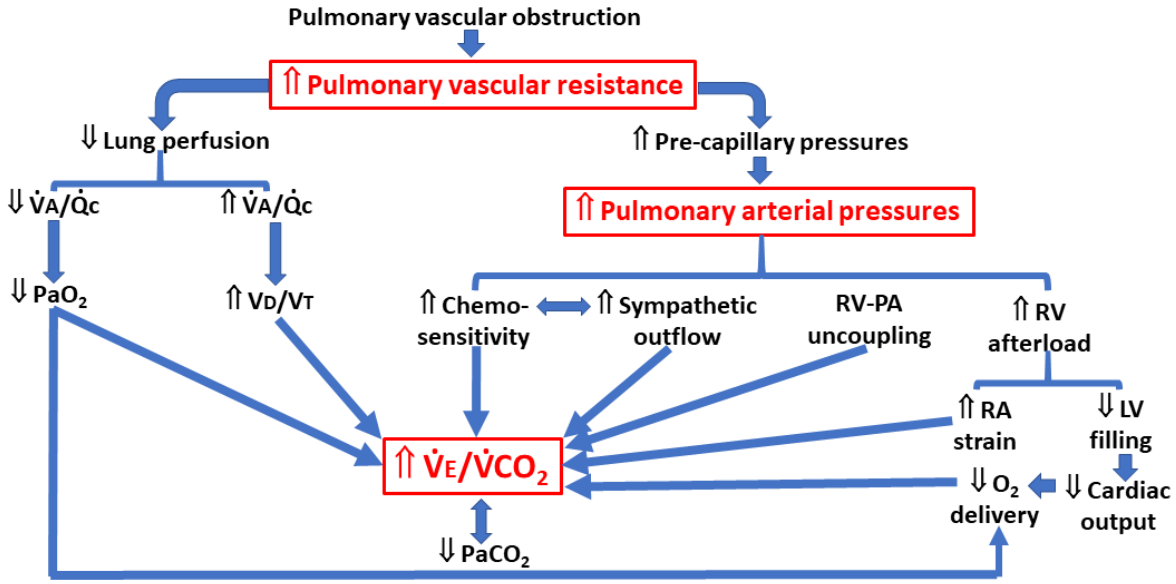

Figure 4. The main mechanisms linking the fundamental pathophysiological features of pulmonary hypertension (increased pulmonary vascular resistance and pulmonary arterial pressures) with excess exertional ventilation, i.e., high ventilation ($\dot{V}_E$):pulmonary carbon dioxide output ($\dot{V}CO_2$) relationship. The relative importance of individual mechanisms varies in pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH). See text for elaboration.

Symbols and *Abbreviations*: ⇑: increased; ⇓: decreased; LV: left ventricle; RA: right atrium; RV: right ventricle; Pa: arterial partial pressure; PA: pulmonary artery; $\dot{Q}c$: capillary perfusion; $\dot{V}_A$: alveolar ventilation; V_D: dead space volume; V_T: tidal volume.