Ventilation efficiency during exercise: the delicate balance behind carbon dioxide removal

Jeness Campodonico[1,2], MD, PhD, Robin Willixhofer[1], MD, PhD, Elisabetta Salvioni[1], PhD, Laura Graciela Gochicoa Rangel[3,4], MD, PhD, Rosaura E. Benitez-Perez[3], MD, Massimo Mapelli[1,2], MD, PhD, Piergiuseppe Agostoni[1,2], MD, PhD

1) Centro Cardiologico Monzino, IRCCS, Milan, Italy
2) Department of Clinical Sciences and Community Health, Cardiovascular Section, University of Milan, 20122 Milan, Italy
3) National Institute of Respiratory Diseases, Mexico City, México
4) Instituto de Desarollo e Innovación en Fisiología Respiratoria, Mexico City, México

Corresponding author:

Prof. Piergiuseppe Agostoni, MD, PhD,
Centro Cardiologico Monzino, IRCCS
Department of Clinical Sciences and Community Health, Cardiovascular Section, University of Milan
Via Parea, 4, 20138 Milan, Italy
Phone 0039 02 58002772
E-mail piergiuseppe.agostoni@unimi.it; piergiuseppe.agostoni@ccfm.it

Abstract

Ventilation (VE) efficiency, a cardinal feature of cardiopulmonary diseases, is defined as the amount of VE needed for a given carbon dioxide production (VCO_2). During exercise it is mainly assessed as the relationship between VE and VCO_2 provided that arterial CO_2 pressure is not increased. However, the current understanding of VE efficiency, is limited and interpretative challenges remain for the wider clinical workforce.

This review emphasizes the importance of the VE/VCO_2 relationship, by assessing its exercise physiological mechanisms in health and disease, delving into how different diseases, including heart

failure (HF), chronic obstructive pulmonary disease and pulmonary hypertension, display different profiles of VE efficiency.

Additionally, we discuss different methodologies for analyzing the VE/VCO_2 relationship, including measuring the slope up to and beyond the respiratory compensation point, assessing the ventilatory equivalents for CO_2 ($EqCO_2$) at defined time points, and evaluating the $EqCO_2$ nadir.

Lastly, we aimed to highlight the prognostic implications of identifying specific ventilatory response profiles alongside meet the defined cut-offs based on different methodologies of assessment.

All the provided information is aimed at helping clinicians in understanding the VE efficiency concept, measures and its application in clinical reasoning for improved patient management. Indeed, when assessing a cardiopulmonary exercise test VE efficiency must be assessed, quantified and its causes investigated to allow physicians to modify patients' treatment accordingly.

Ventilation efficiency: definition and physiological relevance

The present review aims to facilitate the assessment of ventilation (VE) efficiency during exercise in both healthy individuals and patients with various diseases, including those with a combination of comorbidities, that may exert similar or opposing effects on VE. In normal subjects during a progressively increasing workload exercise, i.e., a linear workload increase (ramp protocol), oxygen uptake (VO_2), carbon dioxide production (VCO_2) and VE exhibit three kinetic patterns, so that VO_2 increase is linear through the entire exercise while VCO_2 shows 2 linear relationships: the first from the beginning of exercise to the anaerobic threshold (AT) and the second from AT to end of exercise. Differently, VE kinetics, however, are characterized by 3 different and progressively increasing slopes: the first between rest and AT, the second between AT and the respiratory compensation point (RCP), the third between RCP and the exercise endpoint. A final, steeper increase in VE is occasionally observed in

some individuals and named terminal hyperventilation. The driving forces for VE increase during exercise at sea level changes from VCO_2, to H^+ and to heat exchange for terminal hyperventilation (see supplemental fig 1). The latter is a major driver force for VE in fur-coated animals [1-3]. Differently in hypoxia, VO_2 is the driving force for VE increase instead of VCO_2.[4]

Specifically, in normobaric normoxia conditions (sea level), from rest through exercise up to the end of the isocapnic buffering period also known as the second ventilatory threshold or RCP, VE follows the formula [5]:

$$VE = k \times VCO_2/[PaCO_2 \times (1-VD/VT)].$$

This equation can be solved as for $VD/VT = 1 - 863 / PaCO_2 (VE/VCO_2)$ and is graphically outlined in figure 1 where dead space/tidal volume ratio (VD/VT) is plotted on the Y-axis, and the ventilatory equivalent ($EqCO_2$) for carbon dioxide production (VCO_2) which is the ratio of VE corrected for mask dead space VCO_2 is reported on the X-axis. In the same figure isocapnic (constant $PaCO_2$) lines are also presented to indicate different combinations of $PaCO_2$, VE/VCO_2 and VD/VT.

The highest VE efficiency is defined as the lowest VE, which allows the needed CO_2 removal without $PaCO_2$ increase. Therefore, a low efficiency may occur when VE is insufficient, leading to an increase in CO_2 levels in the blood and/or tissues, conversely, when VE is excessive, and waste VE develops. Accordingly, the relationship between absolute VE and VE efficiency follows a U-shaped pattern (figure 2).

Ultimately, the importance of VE for health and disease is best described by examining the acute or chronic impairment of VE regulation leading to insufficient or excessive VE, both of which lead to the subjective sensation of breathlessness (i.e. dyspnea). On the one hand the abnormally heightened ventilatory response results from a complex interaction of reflex dysregulation, cardiopulmonary

constraints, and autonomic dysfunction, ultimately causing a mismatch between metabolic demand and VE. On the other hand, insufficient VE leads to CO_2 accumulation, acid/base imbalance, mental confusion and impairment of vascular regulation. Of note, the physiological consequences of excess VE exhibit significant parallels to adaptations observed in healthy subjects at high altitude. In hypoxic conditions, as also seen in heart failure (HF) and other cardiopulmonary conditions, compensatory hyperventilation, increased pulmonary artery pressure due to hypoxic pulmonary vasoconstriction and autonomic adjustments, which closely resemble the challenges experienced by patients. These mechanisms contribute to alveolar hyperventilation, an increased physiological dead space (VD), which has been linked to disease severity in both HF and chronic obstructive pulmonary disease (COPD)[6-10], and heightened neurochemical afferent signaling, collectively intensifying the perception of breathlessness despite similar levels of exertion. Ultimately, the physiological strain associated with excessive VE, whether in pathological states or high-altitude environments or during intense exercise, manifests as exertional dyspnea, underscoring the impact of low VE efficiency either absolute or relative, on exercise capacity [11, 12] and quality of life [13, 14].

Ventilation efficiency in clinical contexts

The evaluation of VE during exercise has gained a lot of interest in clinical medicine for assessment of "unexplained dyspnea", as well as for patients with cardiovascular and respiratory diseases including HF, chronic obstructive pulmonary disease (COPD), group I and IV pulmonary hypertension (PH)[15], and in the trickiest but not so rare cases where respiratory and cardiovascular diseases (usually HF and COPD or PH) coexist in the same subject. Indeed, VE estimation during exercise provides valuable diagnostic and prognostic information. It is also used to evaluate treatment efficacy and disease progression.[16] Nowadays this is relevant even in diseases where VE abnormalities are not immediately

evident such as hypertrophic cardiomyopathy, where VE efficiency plays a major prognostic role also on top of peak oxygen uptake (VO_2).[17-19] In this clinical context, VE efficiency changes have emerged as a tool to assess treatment efficacy.[20-24]

Figure 1 reports the behaviors during a maximal cardiopulmonary exercise test (CPET) performed with a progressively increasing workload protocol of a normal subject (Blue), and of patients with HF (Red), PH (Green) and COPD (Purple). The lines clearly diverge and show specific ventilatory patterns in each disease.

As stated above, low VE efficiency may occur when VE is inadequate for gas exchange leading to $PaCO_2$ increase or, conversely, when it is excessive, leading to an increased VE. In this case $PaCO_2$ reduces. The former pattern are typically patients affected by respiratory diseases, while the latter are patients with PH. The efficiency of VE may be assessed during exercise by $EqCO_2$ or the slope of the VE vs. VCO_2 relationship albeit with no identical meaning. In fact, it has been proposed that values of both measures are only comparable if the intercept of the relationship between VE and VCO_2 passes the origin, although only happening in approximately 5% of cases [25]. The ratio between VE and VCO_2 and the $EqCO_2$, exhibit a typical pattern during exercise in normal subjects. It decreases at the beginning of exercise due to alveolar capillary recruitment, remains thereafter flat up to the end of the isocapnic buffering period, i.e. up to RCP, where it starts to increase to the end of exercise (figure 3 panel A). The changes of $EqCO_2$ are paralleled by $PetCO_2$ kinetics which reach its highest value at the anaerobic threshold (AT) and stay still till RCP when it starts to decrease (Figure 3 panel B). The value of $PetCO_2$ during the isocapnic buffering period, i.e., between AT and RCP, is the best moment to assess chemoreflex activity during exercise [26]. With respect to VE efficiency, the lower the $EqCO_2$ the higher the VE efficiency, provided that $PaCO_2$ is maintained in the normal range. The lowest $EqCO_2$ value is observed during a progressive workload exercise at or slightly after the AT. This $EqCO_2$ nadir value

progressively increases from lung diseases without PH and/or hypocapnia to condition associated with PH [27] (figure 4, left). In parallel with $EqCO_2$ increase, $PetCO_2$ reduces (figure 4, right). Moreover, the $EqCO_2$ nadir serves as risk stratification of the overall population with higher values being associated with an increased cardiovascular risk burden, showing the applicability in both health and disease [28].

Role of the VE/VCO_2 relationship according to different methods of calculation

From a physiological and clinical point of view, the $EqCO_2$ dynamic behavior during exercise is of great interest. Indeed, in PH patients, group I and IV, the $EqCO_2$ is flat, or in case of severe PH, it increases during the effort (figure 2 suppl panel A and B) without a nadir. This respiratory pattern results from the rapid and substantial increase of waste VE which overwhelms the normal VD/VT reduction observed at the beginning of exercise due to alveolar recruitment. This behavior is typical and easily recognizable allowing different probability of PH diagnosis (figure 5, see below for details). Of note, Rocha et al [27] classified COPD patients according to the presence/absence of hypocapnia, and found a higher $EqCO_2$ nadir (42±5) and lower $PetCO_2$ (28±4 mmHg) at peak exercise in hypocapnic compared to non-hypocapnic COPD patients (33±6 and 41±5 mmHg, respectively) [29, 30]. Also, in psychogenic hyperventilation the VE/VCO_2 ratio increase at the beginning of exercise. However, differently from severe PH cases, patients are unable to maintain for the entire exercise this respiratory pattern and after the initial increase VE/VCO_2 reduces till the end of the isocapnic buffering period. The latter is also reduced and, in some cases, absent due to the loss of CO_2 during the initial hyperventilation phase.

In a cohort of dyspneic patients with preserved ejection fraction a higher $EqCO_2$ nadir was associated with lower peak cardiac output, increased pulmonary vascular resistance and greater pulmonary capillary wedge pressure at rest [28]. Further, the nadir predicted cardiovascular hospitalization and death. Similarly, in a broader community-based cohort (Framingham Heart Study), a greater $EqCO_2$ nadir

correlated with greater cardiovascular risk factor burden (smoking, higher risk scores, lower fitness), rendering the VE/VCO_2 relationship of importance also for the overall population. [28] The findings of $EqCO_2$ nadir as a marker of overall cardiac health is further supported by the association of the $EqCO_2$ nadir to heart rate reserve[31] and to heart rate recovery (cardiac autonomic function)[32], which are reduced in non-severe COPD patients with a higher $EqCO_2$ nadir. [32]

On the other end of the spectrum, rare diseases such as idiopathic pulmonary fibrosis, might also benefit from the inclusion of the $EqCO_2$ nadir into prognostic models [33]. Further, there is increased interest in evaluating the prognostic implications of the $EqCO_2$ nadir in the pre-surgical evaluation of patients, due to its better reproducibility compared to the VE/VCO_2 slope.[34]

An alternative approach analyzing $EqCO_2$, or simply the VE/VCO_2 ratio, is to assess it at a specific time point, independent of the AT. While the nadir reflects VE efficiency during submaximal exercise, the lowest $EqCO_2$ at peak exercise may indicate the extent of VE efficiency at maximal exertion (i.e. true hyperventilation counteracting metabolic acidosis). In chronic HF, both methods, evaluating the nadir and assessing the ratio at peak exercise, have been shown to stratify disease severity and predict clinical outcomes, with higher values associated with worse prognosis [29, 30]. While both approaches provide valuable clinical insight, their predictive power differs. The $EqCO_2$ at peak exercise has proven less effective in predicting clinical outcomes compared to the slope, except in clinical scenarios where RCP is not achieved such as,PH or COPD. Conversely, the ratio at AT (i.e., close to the nadir) might offer additional prognostic value when combined with peak data [30]. The value of nadir and peak ratios is also evident in patients with chronic thromboembolic pulmonary hypertension (CTEPH), where it has been shown that both the $EqCO_2$ ratio at peak exercise and the $EqCO_2$ ratio nadir are able to differentiate patients with CTEPH who underwent rehabilitation from controls [35]. In patients with moderate-to-

severe COPD [6], $EqCO_2$ nadir values are often comparable to peak values as patients have no or limited respiratory compensation during exercise due to their obstructive constraints to increase VE. As a matter of fact, peak exercise $EqCO_2$, does not constitute an index of VE efficiency in those who are able to exercise beyond the RCP being dependent on the patient's effort.

Another way to assess the relationship between VE and VCO_2 is by analyzing the slope of their correlation which remains linear during a progressive workload exercise up to the of the end of the isocapnic buffering period. This raises the question on how to measure the VE vs. VCO_2 relationship slope: either from the beginning, but excluding the warm up period due to its high VE variability, to the end of exercise or only to the end of the isocapnic buffering period. The latter is physiologically correct, being, above RCP, VE primarily driven by unbuffered acidosis rather than by VCO_2. However, both methods have been applied with different cut-off values. Recently, Chaumont et al [36] reported a difference of around 4 units, a value that clearly demonstrates the need to specify how VE vs. VCO_2 has been calculated in the CPET report. Furthermore, the VE vs. VCO_2 slope physiologically increases with age and, for the same VCO_2, VE is about 1 L higher in females than in males of the same age. Accordingly, an age- and sex-based normalization of the VE/VCO_2 slope has been proposed [37]. Therefore, a CPET report must specify how VE vs. VCO_2 was calculated, whether using the nadir of the ratio or the slope, and, in case of the slope, the exercise frames considered (until or beyond RCP). Additionally, when the ratio is assessed its specific exercise time point, while when the slope is physiologically built, both the absolute value and the percent of the predicted value should be reported [37]. Indeed, 34 is a common absolute cut off value for HF prognostication using the VE vs. VCO_2 relationship slope calculated up to RCP. However, significantly lower values have been reported [38] (30 ± 6.9) in patients with dilated cardiomyopathy who are more frequently young/-middle-aged males. A few reports analyzed also the VE vs. VCO_2 slope above RCP, to assess waste ventilation development

in this part of effort [28, 39]. A summary on how to report ventilation efficiency data is described in table 1.

Currently there is no convincing evidence to prefer the calculation of the VE vs. VCO_2 slope over the entire curve versus up to RCP, although the latter has a strong physiological basis and importantly can be entirely assessable also in submaximal CPET, these tests are indicated by an early test termination [before achieving a respiratory exchange ratio (RER) of 1.05], due to concomitant conditions, such as orthopedic comorbidities, arrhythmias, cardiac ischemia or insufficient patient effort. As a matter of fact, comparisons between the two methods for measurement have been rarely done (table 2). Of note, as regards the prognostic capacity, the Cohen-Solal group showed a better prognostic power in HF for the slope calculated over the entire exercise duration [29, 40] (table 2).

Setting aside the challenges of slope measurements during a maximal CPET, the possibility of studying the relationship between VE and VCO_2 during submaximal exercise is fascinating. Studies conducted with HF subjects performing daily life activities, have shown that, for the same workload, individuals with more advanced HF exhibit lower absolute VO_2 values but higher $EqCO_2$ [41]. This confirms the predominant role of low VE efficiency as a marker of HF also during the patient's ordinary tasks.

The crucial role of the chemoreceptors in regulating the VE in response to the same amount of VCO_2 also deserves a brief comment. These specialized sensors, located in both the central and peripheral nervous systems, detect changes in arterial CO_2 levels and pH, triggering appropriate respiratory adjustments. Few previous studies [20, 26, 42] have shown that certain pharmacological therapies, such as non-selective β-blockers like carvedilol, can reduce the VE/VCO_2 ratio, most likely by acting at the chemoreceptor level. This effect was not observed with selective β-blockers (bisoprolol and nebivolol) at equivalent doses. These findings suggest that a drug-induced modulation of chemoreceptors and lung (alveolar) β2 receptors [43] may influence VE efficiency by modifying their sensitivity to CO_2, emerging

as a potential area for the development of new pharmacological agents or respiratory devices designed to target these mechanisms [44]. By targeting chemoreceptor sensitivity and low VE efficiency, such treatments could help improve respiratory function and overall quality of life in affected individuals reducing the burden of exertional dyspnea. Finally, VE/VCO_2 increases in response to baro- metabo-receptors activation and to increase right ventricle diastolic stiffness and afterload [45, 46]. Of note, activation of chemo- baro- and metabo- reflexes are linked to increased sympathetic activity affecting negatively prognosis and quality of life.

Clinically, the combined assessment of VE/VCO_2, either as $EqCO_2$ or VE/VCO_2 slope, and $PetCO_2$ has gained a lot of interest being used to judge the presence of pulmonary hypertension. Indeed, in the early days of modern CPET assessment the presence of pulmonary vascular abnormalities as the cause of exercise limitation was possible only through arterial blood gas measurements which still have a relevant clinical role [47]. Specifically, presence of exercise limitation due to pulmonary vascular impairment was considered in case of A) an Alveolar to arterial pO_2 gradient ($\Delta PA\text{-}aO_2$) increasing during exercise to ≥45mmHg, B) a drop in hemoglobin oxygen saturation >3% without $PaCO_2$ rise and C) dead space to tidal volume ratio (VD/VT) using $PaCO_2$ measured by arterial gas analysis increasing during exercise > 30%.[47, 48]Of note it has been proposed to normalize the $\Delta PA\text{-}aO_2$ over VO_2 [49, 50] to better evaluate the O_2 pressure gradient across the alveolar- capillary membrane and the role of lung diffusion impairment.

Later the Wasserman group proposed a different approach to this issue. Indeed, Yasunobu et al. demonstrated that in a CPET on a cycloergometer with a progressively increasing workload that the likelihood of PH increased as $PetCO_2$ reduced and $EqCO_2$ increased [51] (Figure 5). Similar results were reported by Ferrazza et al. on a treadmill exercise [52]. More recently, Pezzuto et al. showed in a large

multicenter study that in PH patients (group I and IV) the relationship between VE vs. VCO_2 slope and $PetCO_2$ is directly linked to pulmonary pressure values [53]. Of relevant interest are the physiological consequence of VE efficiency which may be assessed by evaluating the pressure gradient between arterial PCO_2 and end tidal pCO_2 ($\Delta Pa\text{-}etCO_2$). The latter is directly linked to VE / perfusion abnormalities in the lung [54]. The highest $\Delta Pa\text{-}etCO_2$ values, obtained by simultaneous measurements of respiratory and arterial blood gases, are observed in case of PH, pulmonary embolism and HF, particularly in patients with preserved ejection fraction HF. Indeed, a high $\Delta Pa\text{-}etCO_2$ indicates the presence of lung regions ventilated with little to no perfusion and/or a relevant increase during exercise of VD/VT usually mediated by increase of reflex VE. The latter is frequently observed in HFpEF [55]. A similar approach may be utilized for the assessment of O_2 exchange at the alveolar capillary membrane level. In such a case 3 elements come into play, namely the alveolar-arterial pO_2 gradient ($\Delta A\text{-}aPO_2$), alongside VO_2 and alveolar capillary diffusion abnormalities. Accordingly, VO_2 can increase by expanding the gas exchange surface; however, for a given surface area, it can only rise by increasing the $\Delta A\text{-}aPO_2$. An upper limit for the $\Delta A\text{-}aPO_2$ at 25 mmHg has been suggested during acute hypoxia exposure [56]. On the other side, at rest, in case of severely reduced lung diffusion, reduction of resting VO_2 has been shown by Morosin et al [49].

Alternative assessment to ventilation efficiency during exercise.

Two other parameters have been proposed for low VE efficiency analysis, the O_2 ventilatory equivalent ($EqVO_2$) and the O_2 uptake efficiency slope (OUES). The former is calculated as the ratio of VE/VO_2 corrected for mask dead space ventilation while the latter is the rate of VO_2 increase in response to VE increase during incremental exercise. Since this relationship is not linear the VO_2 increase is plotted against the logarithm of VE increase. OUES has been proposed by Baba et al in 1996 [57] and is

frequently utilized in clinical and research setting [58]. It should be underlined that OUES has a limited physiological sense since artificially transform a curvilinear relationship into a linear-one [59].

Clinical applications

The analysis of the VE vs. VCO_2 linear relationship offers more information on top of the slope. Indeed, all the linear relationships are represented by the equation $Y = aX + b$, where $Y = VE$, $X = VCO_2$, a = slope and b = the intercept on the Y-axis, which corresponds to the VE value extrapolated at $VCO_2 = 0$. In a multicenter study, Apostolo et al [60] showed that the Y-axis intercept allows to separate HF patients from HF+COPD or COPD, while the slope was unable to do it. In brief, in HF patients, a Y-axis intercept greater than 4.07L in the VE vs. VCO_2 relationship suggests that the concomitant presence of lung disease is likely.

At this point, a schema of the VE vs. VCO_2 relationship including slope and Y-intercept in different disease is helpful. VE is the sum of alveolar and dead space VE, with the former following a linear relationship with its extrapolation close to the origin of the VE (Y-) and VCO_2 (X-) axis. The presence of dead space VE, i.e. VE not participating to gas exchange, which progressively reduces in a normal subject as exercise increases, explains the presence of a positive Y-intercept (figure 6). The Y-intercept can be upshifted if an external dead space is added [60, 61]. However, it must be underlined that the Y-axis intercept is not directly representing the dead space, but is influenced by the amount of dead space at rest and by its changes during exercise: a high (>4.07 L) value, excluding well trained subjects and athletes, suggests an increased dead space at rest, as in COPD; a low value (around 0 or negative) is suggestive of dead space development during effort, as in PH and in HF, particularly in case of HF with preserved ejection fraction[62]. Examples of exercise behavior of VE and its partitioning, alveolar and

dead space VE, vs. VCO_2 are reported in figure 6 for COPD, HF and PH case, in panel C, D and E, respectively.

An elevation of VE/VCO_2, slope or ratio, is frequently observed in HF and particularly in patients with preserved ejection fraction where ventilatory abnormalities may be one of the few abnormal findings [55, 63]. $EqCO_2$ has a pivotal role in HF severity and prognosis assessment, being also included in the current recommendation for heart transplant referral [64]. In the MECKI score data set, which now includes 8464 HF patients the average VE/VCO_2 slope was 33.4±8.0 equal to 127±30% pred. Grouping patients according to the classical cut off value of 34 clearly separate prognosis with an AUC = 0.622. However, with HF being a multifaced syndrome, it is more appropriate to evaluate VE/VCO_2 as just one – albeit crucial - of the prognostic tools. The MECKI score demonstrated that VE/VCO_2 is an independent prognostic factor which significantly adds power to our capability to assess HF prognosis (figure 3 suppl) [17, 64, 65].

Importantly, new HF therapies have been shown to positively impact low VE efficiency, in addition to targeting multiple other mechanisms. In this regard, prospective studies, have demonstrated that sacubitril/valsartan and SGLT2 inhibitors (gliflozins) can reduce the VE/VCO_2 slope, alongside beneficial effects on biomarkers, cardiac remodeling, and NYHA class improvement [66-68]. Similarly, in hypertrophic obstructive cardiomyopathy mavacamten and aficamten showed in parallel with a peak VO_2 increase a reduction of VE/VCO_2 slope [23, 24]. Moreover, improvement of VE efficiency has been reported with exercise and inspiratory muscles training [69, 70].

It must be underlined that a low VE efficiency is also present when VE increase is not enough for VCO_2 elimination and $PaCO_2$ increases (see figure 2) as it happens in patients with severe COPD [71]. In such cases the VE/VCO_2 slope is not able to pick up this setting albeit the Y-intercept is high. A few authors proposed for this condition a new approach to evaluate low VE efficiency based on complex calculations

[72]. Specifically, similarly to OUES it is possible to calculate VCO_2 vs log VE (ηVE) and compare the observed value vs a theoretical maximum ηVE [73]. This approach must be validated in the clinical setting but, due to its intrinsic difficult physiological background, it is unlikely that it will become popular [74].

Future prospective and knowledge gaps.

A systematic assessment of VE efficiency in specific cardiorespiratory diseases is definitively needed. For instance, in HF a precise definition, clinical and prognostic meaning of ventilation efficiency according to LVEF phenotypes is still lacking, Similarly the effects of treatment strategies is only imperfectively known. Moreover, few other research gaps should be underlined. First, we need to define what is the daily and inter laboratory variability of VE efficiency measurements, either $EqCO_2$ or VE/VCO_2 slope, as well as of other parameters associated with VE efficiency. This is relevant for normal subjects as well as for patients with different diseases. Second, we still do not know when and whether a change in VE efficiency is associated to a change in patients' prognosis, and third whether on this regard differences in methods to assess VE efficiency exist. Finally, how to assess VE efficiency in patients with exercise induced oscillatory breathing (EOV) is at present unknown, albeit differences between subjects with EOV lasting for the entire exercise vs. those in whom EOV disappears during effort suggest the presence of variable VE efficiency [75].

Conclusion.

In brief, when assessing VE efficiency during exercise it is mandatory to report which parameter you are using for the VE vs. VCO_2 relationship, $EqCO_2$ or slope and, in case of the former, the exercise time point and, in case of the latter, how you calculated it. Adding $PetCO_2$ significantly increase the VE

efficiency assessment as more advances parameters which imply arterial gas measurements do, such as ΔPa-etCO_2 and ΔA-aPO_2. Moreover, we need to report the quantification of low VE efficiency and its causes to allow physicians to modify patients' treatment accordingly aiming to improve VE efficiency.

Author contribution:

J.C., R.W., E.S., L.G.G.R., R.E.B.P., M.M., P.A, reviewed the literature and contributed to the writing and discussion for scientific content of the present review. R.W., E.S. prepared figures and tables. Being this paper a review paper no other activities were expected.

Conflict of interest

None

Data Availability

Due to the nature of the paper (review) no raw data are linked to the present review.

Funding: This research was supported by the Italian Ministry of Health-Ricerca Corrente to Centro Cardiologico Monzino IRCCS (CUP= B43C24000090001).

Ethical Approval:

Due to the nature of the paper (review) no ethical approval was needed.

Acknowledgments

None.

References

1. Brazile, T.L., B.D. Levine, and K.M. Shafer, Cardiopulmonary Exercise Testing. NEJM Evid, 2025; 4: EVIDra2400390.
2. Brazile, T.L., B.D. Levine, and K.M. Shafer, Physiological Principles of Exercise. NEJM Evid, 2025; 4: EVIDra2400363.
3. Wasserman, K., B. Whipp, K. Sietsema, D. Sue, W. Stringer, and S. Ward, *Principles of exercise testing and interpretation, sixth edition (pp. 8-58)*. 2020, Wolters Kluer: Philadelphia. p. 600.
4. Sato, M., J.W. Severinghaus, F.L. Powell, F.D. Xu, and M.J. Spellman, Jr., Augmented hypoxic ventilatory response in men at altitude. J Appl Physiol (1985), 1992; 73: 101-107.
5. Wasserman, K., B. Whipp, K. Sietsema, D. Sue, W. Stringer, and S. Ward, *Principles of exercise testing and interpretation, sixth edition (pp. 576-577)*. 2020, Wolters Kluer: Philadelphia. p. 600.
6. Neder, J.A., D.C. Berton, F.F. Arbex, M.C. Alencar, A. Rocha, P.A. Sperandio, et al., Physiological and clinical relevance of exercise ventilatory efficiency in COPD. Eur Respir J, 2017; 49.
7. O'Donnell, D.E., P. Laveneziana, K. Webb, and J.A. Neder, Chronic obstructive pulmonary disease: clinical integrative physiology. Clin Chest Med, 2014; 35: 51-69.
8. Woods, P.R., T.P. Olson, R.P. Frantz, and B.D. Johnson, Causes of breathing inefficiency during exercise in heart failure. J Card Fail, 2010; 16: 835-842.
9. Kee, K., C. Stuart-Andrews, M.J. Ellis, J.P. Wrobel, K. Nilsen, M. Sharma, et al., Increased Dead Space Ventilation Mediates Reduced Exercise Capacity in Systolic Heart Failure. Am J Respir Crit Care Med, 2016; 193: 1292-1300.
10. Robertson, H.T., Gas exchange consequences of left heart failure. Compr Physiol, 2011; 1: 621-634.
11. Richalet, J.P., E. Hermand, and F.J. Lhuissier, Cardiovascular physiology and pathophysiology at high altitude. Nat Rev Cardiol, 2024; 21: 75-88.
12. Neder, J.A., D.B. Phillips, D.E. O'Donnell, and J.A. Dempsey, Excess ventilation and exertional dyspnoea in heart failure and pulmonary hypertension. Eur Respir J, 2022; 60.
13. Currow, D.C., S. Chang, E.D. Grande, D.H. Ferreira, S. Kochovska, I. Kinchin, et al., Quality of Life Changes With Duration of Chronic Breathlessness: A Random Sample of Community-Dwelling People. J Pain Symptom Manage, 2020; 60: 818-827 e814.
14. Currow, D.C., E. Dal Grande, D. Ferreira, M.J. Johnson, N. McCaffrey, and M. Ekstrom, Chronic breathlessness associated with poorer physical and mental health-related quality of life (SF-12) across all adult age groups. Thorax, 2017; 72: 1151-1153.
15. Humbert, M., G. Kovacs, M.M. Hoeper, R. Badagliacca, R.M.F. Berger, M. Brida, et al., 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J, 2022; 43: 3618-3731.
16. Cahalin, L.P., P. Chase, R. Arena, J. Myers, D. Bensimhon, M.A. Peberdy, et al., A meta-analysis of the prognostic significance of cardiopulmonary exercise testing in patients with heart failure. Heart Fail Rev, 2013; 18: 79-94.
17. McDonagh, T.A., M. Metra, M. Adamo, R.S. Gardner, A. Baumbach, M. Bohm, et al., 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J, 2021; 42: 3599-3726.
18. Heidenreich, P.A., B. Bozkurt, D. Aguilar, L.A. Allen, J.J. Byun, M.M. Colvin, et al., 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation, 2022; 145: e895-e1032.
19. Mikic, L., A. Ristic, N. Markovic Nikolic, M. Tesic, D.G. Jakovljevic, R. Arena, et al., The Role of Cardiopulmonary Exercise Testing in Hypertrophic Cardiomyopathy. Medicina (Kaunas), 2023; 59.

20. Contini, M., A. Apostolo, G. Cattadori, S. Paolillo, A. Iorio, E. Bertella, et al., Multiparametric comparison of CARvedilol, vs. NEbivolol, vs. BIsoprolol in moderate heart failure: the CARNEBI trial. Int J Cardiol, 2013; 168: 2134-2140.
21. Maron, M.S., A. Masri, M.E. Nassif, R. Barriales-Villa, M. Arad, N. Cardim, et al., Aficamten for Symptomatic Obstructive Hypertrophic Cardiomyopathy. N Engl J Med, 2024; 390: 1849-1861.
22. Desai, M.Y., A.T. Owens, T. Abraham, I. Olivotto, P. Garcia-Pavia, R.D. Lopes, et al., Mavacamten in Symptomatic Nonobstructive Hypertrophic Cardiomyopathy. N Engl J Med, 2025; 393: 961-972.
23. Lee, M.M.Y., A. Masri, M.E. Nassif, R. Barriales-Villa, T.P. Abraham, B.L. Claggett, et al., Aficamten and Cardiopulmonary Exercise Test Performance: A Substudy of the SEQUOIA-HCM Randomized Clinical Trial. JAMA Cardiol, 2024; 9: 990-1000.
24. Wheeler, M.T., I. Olivotto, P.M. Elliott, S. Saberi, A.T. Owens, M.S. Maurer, et al., Effects of Mavacamten on Measures of Cardiopulmonary Exercise Testing Beyond Peak Oxygen Consumption: A Secondary Analysis of the EXPLORER-HCM Randomized Trial. JAMA Cardiol, 2023; 8: 240-247.
25. Sun, X.G., J.E. Hansen, N. Garatachea, T.W. Storer, and K. Wasserman, Ventilatory efficiency during exercise in healthy subjects. Am J Respir Crit Care Med, 2002; 166: 1443-1448.
26. Agostoni, P., A. Apostolo, G. Cattadori, E. Salvioni, G. Berna, L. Antonioli, et al., Effects of beta-blockers on ventilation efficiency in heart failure. Am Heart J, 2010; 159: 1067-1073.
27. Rocha, A., F.F. Arbex, P.A. Sperandio, A. Souza, L. Biazzim, F. Mancuso, et al., Excess Ventilation in Chronic Obstructive Pulmonary Disease-Heart Failure Overlap. Implications for Dyspnea and Exercise Intolerance. Am J Respir Crit Care Med, 2017; 196: 1264-1274.
28. Nayor, M., V. Xanthakis, M. Tanguay, J.B. Blodgett, R.V. Shah, M. Schoenike, et al., Clinical and Hemodynamic Associations and Prognostic Implications of Ventilatory Efficiency in Patients With Preserved Left Ventricular Systolic Function. Circ Heart Fail, 2020; 13: e006729.
29. Bard, R.L., B.W. Gillespie, N.S. Clarke, T.G. Egan, and J.M. Nicklas, Determining the best ventilatory efficiency measure to predict mortality in patients with heart failure. J Heart Lung Transplant, 2006; 25: 589-595.
30. Myers, J., R. Arena, R.B. Oliveira, D. Bensimhon, L. Hsu, P. Chase, et al., The lowest VE/VCO2 ratio during exercise as a predictor of outcomes in patients with heart failure. J Card Fail, 2009; 15: 756-762.
31. Brubaker, P.H. and D.W. Kitzman, Chronotropic incompetence: causes, consequences, and management. Circulation, 2011; 123: 1010-1020.
32. Shi, M., S. Qumu, S. Wang, Y. Peng, L. Yang, K. Huang, et al., Abnormal heart rate responses to exercise in non-severe COPD: relationship with pulmonary vascular volume and ventilatory efficiency. BMC Pulm Med, 2024; 24: 183.
33. Vainshelboim, B., J. Oliveira, B.D. Fox, and M.R. Kramer, The Prognostic Role of Ventilatory Inefficiency and Exercise Capacity in Idiopathic Pulmonary Fibrosis. Respir Care, 2016; 61: 1100-1109.
34. Kristenson, K., J. Hylander, M. Boros, A. Fyrenius, and K. Hedman, Ventilatory efficiency in combination with peak oxygen uptake improves risk stratification in patients undergoing lobectomy. JTCVS Open, 2022; 11: 317-326.
35. Xi, Q., Z. Zhao, Z. Liu, X. Ma, Q. Luo, and W. Liu, The lowest VE/VCO(2) ratio best identifies chronic thromboembolic pulmonary hypertension. Thromb Res, 2014; 134: 1208-1213.
36. Chaumont, M., K. Forton, A. Gillet, D. Tcheutchoua Nzokou, and M. Lamotte, How Does the Method Used to Measure the VE/VCO(2) Slope Affect Its Value? A Cross-Sectional and Retrospective Cohort Study. Healthcare (Basel), 2023; 11.
37. Salvioni, E., U. Corrà, M. Piepoli, S. Rovai, M. Correale, S. Paolillo, 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.
38. Baracchini, N., D. Zaffalon, M. Merlo, S. Baschino, G. Barbati, B. Pezzuto, et al., Prognostic value of cardiopulmonary exercise testing repetition during follow-up of clinically stable patients with severe dilated cardiomyopathy. A preliminary study. Int J Cardiol, 2023; 390: 131252.

39. Paolillo, S., S. Farina, M. Bussotti, A. Iorio, P. PerroneFilardi, M.F. Piepolil, et al., Exercise testing in the clinical management of patients affected by pulmonary arterial hypertension. Eur J Prev Cardiol, 2012; 19: 960-971.
40. Tabet, J.Y., F. Beauvais, G. Thabut, J.M. Tartiere, D. Logeart, and A. Cohen-Solal, A critical appraisal of the prognostic value of the VE/VCO2 slope in chronic heart failure. Eur J Cardiovasc Prev Rehabil, 2003; 10: 267-272.
41. Mapelli, M., E. Salvioni, A. Bonomi, P. Gugliandolo, F. De Martino, C. Vignati, et al., How Patients With Heart Failure Perform Daily Life Activities: An Innate Energy-Saving Strategy. Circ Heart Fail, 2020; 13: e007503.
42. Campodonico, J., M. Contini, M. Alimento, M. Mapelli, E. Salvioni, I. Mattavelli, et al., Physiology of exercise and heart failure treatments: cardiopulmonary exercise testing as a tool for choosing the optimal therapeutic strategy. Eur J Prev Cardiol, 2023; 30: ii54-ii62.
43. Paolillo, S., R. Pellegrino, E. Salvioni, M. Contini, A. Iorio, F. Bovis, et al., Role of alveolar β2-adrenergic receptors on lung fluid clearance and exercise ventilation in healthy humans. PLoS One, 2013; 8: e61877.
44. Contini, M., E. Spadafora, S. Barbieri, P. Gugliandolo, E. Salvioni, A. Magini, et al., Effects of β(2)-receptor stimulation by indacaterol in chronic heart failure treated with selective or non-selective β-blockers: a randomized trial. Sci Rep, 2020; 10: 7101.
45. Rodrigues Sousa, S., J. Nunes Caldeira, and C. Rodrigues, COPD phenotypes by computed tomography and ventilatory response to exercise. Pulmonology, 2024; 30: 222-229.
46. Tello, K., A. Dalmer, R. Vanderpool, H.A. Ghofrani, R. Naeije, F. Roller, et al., Impaired right ventricular lusitropy is associated with ventilatory inefficiency in pulmonary arterial hypertension. Eur Respir J, 2019; 54.
47. Agostoni, P.G. and J. Butler, *Cardiac evaluation*, in *Murray JF, Nadel JA, eds. Textbook of Respiratory Medicine.* . 1994, WB Saunders Company: Philadelphia, London, Toronto, Montreal, Sydney, Tokyo. p. 943–962.
48. Agostoni, P., D.D. Smith, R.B. Schoene, H.T. Robertson, and J. Butler, Evaluation of breathlessness in asbestos workers. Results of exercise testing. Am Rev Respir Dis, 1987; 135: 812-816.
49. Morosin, M., C. Vignati, A. Novi, E. Salvioni, F. Veglia, M. Alimento, et al., The alveolar to arterial oxygen partial pressure difference is associated with pulmonary diffusing capacity in heart failure patients. Respir Physiol Neurobiol, 2016; 233: 1-6.
50. Smith, D.D. and P.G. Agostoni, The discriminatory value of the P(A-a)O2 during exercise in the detection of asbestosis in asbestos exposed workers. Chest, 1989; 95: 52-55.
51. Yasunobu, Y., R.J. Oudiz, X.G. Sun, J.E. Hansen, and K. Wasserman, End-tidal PCO2 abnormality and exercise limitation in patients with primary pulmonary hypertension. Chest, 2005; 127: 1637-1646.
52. Ferrazza, A.M., D. Martolini, G. Valli, and P. Palange, Cardiopulmonary exercise testing in the functional and prognostic evaluation of patients with pulmonary diseases. Respiration, 2009; 77: 3-17.
53. Pezzuto, B., R. Badagliacca, M. Muratori, S. Farina, M. Bussotti, M. Correale, et al., Role of cardiopulmonary exercise test in the prediction of hemodynamic impairment in patients with pulmonary arterial hypertension. Pulm Circ, 2022; 12: e12044.
54. Wasserman, K., Y.Y. Zhang, A. Gitt, R. Belardinelli, A. Koike, L. Lubarsky, et al., Lung function and exercise gas exchange in chronic heart failure. Circulation, 1997; 96: 2221-2227.
55. Agostoni, P. and M. Guazzi, Exercise ventilatory inefficiency in heart failure: some fresh news into the roadmap of heart failure with preserved ejection fraction phenotyping. Eur J Heart Fail, 2017; 19: 1686-1689.
56. Agostoni, P.G., M. Bussotti, P. Palermo, and M. Guazzi, Does lung diffusion impairment affect exercise capacity in patients with heart failure? Heart, 2002; 88: 453-459.

57. Baba, R., M. Nagashima, M. Goto, Y. Nagano, M. Yokota, N. Tauchi, et al., Oxygen uptake efficiency slope: a new index of cardiorespiratory functional reserve derived from the relation between oxygen uptake and minute ventilation during incremental exercise. J Am Coll Cardiol, 1996; 28: 1567-1572.
58. Akkerman, M., M. van Brussel, E. Hulzebos, L. Vanhees, P.J. Helders, and T. Takken, The oxygen uptake efficiency slope: what do we know? J Cardiopulm Rehabil Prev, 2010; 30: 357-373.
59. Agostoni, P., P. Gugliandolo, and J. Campodonico, Inside OUES: fact or fiction? Eur J Prev Cardiol, 2019; 26: 174-176.
60. Apostolo, A., P. Laveneziana, P. Palange, C. Agalbato, R. Molle, D. Popovic, et al., Impact of chronic obstructive pulmonary disease on exercise ventilatory efficiency in heart failure. International Journal of Cardiology, 2015; 189: 134-140.
61. Gargiulo, P., A. Apostolo, P. Perrone-Filardi, S. Sciomer, P. Palange, and P. Agostoni, A non invasive estimate of dead space ventilation from exercise measurements. PLoS One, 2014; 9: e87395.
62. De Martino, F. and P. Agostoni, Insight Ventilation Perfusion Inefficiency in Patients With Heart Failure With Preserved Ejection Fraction. Chest, 2022; 162: 1233-1235.
63. Gong, J., R.R.T. Castro, J.P. Caron, C.P. Bay, J. Hainer, A.R. Opotowsky, et al., Usefulness of ventilatory inefficiency in predicting prognosis across the heart failure spectrum. ESC Heart Fail, 2022; 9: 293-302.
64. Peled, Y., A. Ducharme, M. Kittleson, N. Bansal, J. Stehlik, S. Amdani, et al., International Society for Heart and Lung Transplantation Guidelines for the Evaluation and Care of Cardiac Transplant Candidates-2024. J Heart Lung Transplant, 2024; 43: 1529-1628.e1554.
65. Agostoni, P., S. Paolillo, M. Mapelli, P. Gentile, E. Salvioni, F. Veglia, et al., Multiparametric prognostic scores in chronic heart failure with reduced ejection fraction: a long-term comparison. Eur J Heart Fail, 2018; 20: 700-710.
66. Mapelli, M., I. Mattavelli, S. Paolillo, E. Salvioni, D. Magri, A. Galotta, et al., Effects of sacubitril/valsartan on exercise capacity: a prognostic improvement that starts during uptitration. Eur J Clin Pharmacol, 2023; 79: 1173-1184.
67. Mantegazza, V., V. Volpato, M. Mapelli, V. Sassi, E. Salvioni, I. Mattavelli, et al., Cardiac Reverse Remodelling by 2D and 3D Echocardiography in Heart Failure Patients Treated with Sacubitril/Valsartan. Diagnostics (Basel), 2021; 11.
68. Mapelli, M., I. Mattavelli, E. Salvioni, A. Bonomi, N. Capra, P. Palermo, et al., Looking into the Kinetics of NT-proBNP and sST2 Changes in Patients with Heart Failure Treated with Sacubitril/Valsartan: A Hint to Different Therapeutic Pathways. Drugs R D, 2023; 23: 397-402.
69. Li, H., L. Tao, Y. Huang, Z. Li, and J. Zhao, Inspiratory muscle training in patients with heart failure: A systematic review and meta-analysis. Front Cardiovasc Med, 2022; 9: 993846.
70. Cipriano, G., Jr., V.T. Cipriano, V.Z. da Silva, G.F. Cipriano, G.R. Chiappa, A.C. de Lima, et al., Aerobic exercise effect on prognostic markers for systolic heart failure patients: a systematic review and meta-analysis. Heart Fail Rev, 2014; 19: 655-667.
71. Muller, P.T., G.R. Chiappa, P. Laveneziana, R. Ewert, and J.A. Neder, Lung mechanical constraints: the Achilles' heel of excess exertional ventilation for prognosis assessment? J Appl Physiol (1985), 2023; 134: 378-382.
72. Ramos, R.P., M.C. Alencar, E. Treptow, F. Arbex, E.M. Ferreira, and J.A. Neder, Clinical usefulness of response profiles to rapidly incremental cardiopulmonary exercise testing. Pulm Med, 2013; 2013: 359021.
73. Muller, P.T. and E.F. Saraiva, Ventilatory inefficiency during graded exercise in COPD: A pragmatic approach. Clin Physiol Funct Imaging, 2021; 41: 103-109.
74. de Campos, G.G.O., L.S. Goelzer, T.R.L. Augusto, G.W. Barbosa, G.R. Chiappa, E.H. van Iterson, et al., Comparable Ventilatory Inefficiency at Maximal and Submaximal Performance in COPD vs. CHF subjects: An Innovative Approach. Arq Bras Cardiol, 2024; 121: e20230578.
75. Cunha, G.J.L., S. Maltes, B.M.L. Rocha, D. Nina, C. Aguiar, M.J. Andrade, et al., Beyond exercise oscillatory ventilations: the prognostic impact of loop gain in heart failure. Eur J Prev Cardiol, 2023.

76. Wasserman, K., *Cardiopulmonary Exercise Testing and Cardiovascular Health*. 2002: Whiley. 246.
77. Barron, A., N. Dhutia, J. Mayet, A.D. Hughes, D.P. Francis, and R. Wensel, Test-retest repeatability of cardiopulmonary exercise test variables in patients with cardiac or respiratory disease. Eur J Prev Cardiol, 2014; 21: 445-453.
78. Leonardi, B., F. Sollazzo, F. Gentili, M. Bianco, E. Pomiato, S.S. Kikina, et al., Cardiopulmonary Exercise Testing after Surgical Repair of Tetralogy of Fallot-Does Modality Matter? J Clin Med, 2024; 13.
79. Arena, R., J. Myers, S.S. Aslam, E.B. Varughese, and M.A. Peberdy, Technical considerations related to the minute ventilation/carbon dioxide output slope in patients with heart failure. Chest, 2003; 124: 720-727.
80. Ingle, L., K. Goode, S. Carroll, R. Sloan, C. Boyes, J.G. Cleland, et al., Prognostic value of the VE/VCO2 slope calculated from different time intervals in patients with suspected heart failure. Int J Cardiol, 2007; 118: 350-355.
81. Groepenhoff, H., A. Vonk-Noordegraaf, A. Boonstra, M.D. Spreeuwenberg, P.E. Postmus, and H.J. Bogaard, Exercise testing to estimate survival in pulmonary hypertension. Med Sci Sports Exerc, 2008; 40: 1725-1732.
82. Ferreira, E.V., J.S. Ota-Arakaki, R.P. Ramos, P.B. Barbosa, M. Almeida, E.C. Treptow, et al., Optimizing the evaluation of excess exercise ventilation for prognosis assessment in pulmonary arterial hypertension. Eur J Prev Cardiol, 2014; 21: 1409-1419.

Figure legend

Figure 1 illustrates the relationship between the dead space to tidal volume ratio and ventilation efficiency assessed as ventilatory equivalents for CO_2: ventilation to carbon dioxide production. Ventilation is corrected for mask dead space. Isopleth curves represents different levels of arterial carbon dioxide partial pressures in mmHg. The trajectories are different conditions, including normal subjects (blue), chronic obstructive pulmonary disease (purple), heart failure (red), and primary pulmonary hypertension (green). The reported trajectories are representative of the behavior during exercise of patients with different diseases. These trajectories may slightly vary with different disease severity. Abbreviations: COPD, chronic obstructive pulmonary disease; $EqCO_2$: ventilatory equivalents for CO_2; HF, heart failure; $PaCO_2$, arterial partial pressure of carbon dioxide; PH, pulmonary hypertension; V_D/V_T, dead space-to-tidal volume ratio.

Figure 2 illustrates the relationship between ventilation (VE, L/min) and ventilation efficiency, depicted as a U-shaped curve, highlighting the optimal VE range and the progressive decline in ventilation

efficiency at both extremes. Different efficiency zones are marked by colored dots, representing various levels of ventilation efficiency. The dark blue dot indicates low VE with low efficiency, while the light blue dot signifies low VE with moderate inefficiency. The green dot represents the point of optimal efficiency, where VE is most effective. As VE increases, efficiency declines, with the orange dot showing high VE with moderate inefficiency and the red dot indicating high VE with low efficiency. Abbreviations: VE, Ventilation; Ineff., ventilatory inefficiency.

Figure 3 illustrates the characteristic pattern of ventilation efficiency and gas exchange during exercise in normal subjects. (A) The ventilatory equivalent for carbon dioxide initially decreases due to alveolar capillary recruitment, remains stable throughout the isocapnic buffering period, and increases after the respiratory compensation point until the end of exercise. (B) The end-tidal carbon dioxide partial pressure reaches its peak at the anaerobic threshold, remaining stable until the RCP, and then declining thereafter. Abbreviations: AT, anaerobic threshold; $EqCO_2$: ventilatory equivalents for CO_2; $PetCO_2$, end-tidal carbon dioxide partial pressure; RCP, respiratory compensation point.

Figure 4 illustrates the relationship between the VE/VCO_2 ratio at nadir (left panel) and $PetCO_2$ at the same workload (right panel) across different physiological and pathological states. In the left panel, the VE/VCO_2 nadir increases from left to right, with healthy individuals having the lowest values, followed by COPD, COPD + HF, HF, and PH, which exhibits the lowest ventilation efficiency. In the right panel, $PetCO_2$ decreases from left to right, with healthy individuals having the highest values, followed by COPD, COPD + HF, HF, and PH, which has the lowest values. This visualization highlights the progressive decline in ventilation efficiency and gas exchange capacity in cardiopulmonary diseases. Abbreviations: VE/VCO_2, ventilation to carbon dioxide production; $PetCO_2$, end-tidal partial pressure of carbon dioxide; COPD, chronic obstructive pulmonary disease; HF, heart failure; PH, pulmonary hypertension.

Figure 5 illustrates the relationship between end-tidal carbon dioxide partial pressure and the VE/VCO_2 ratio, both at the anaerobic threshold, assessing the likelihood of pulmonary vasculopathy in patients with exertional dyspnea of unknown cause. The hyperbolic curve represents the probability of pulmonary hypertension, with graded likelihood categories based on comparisons with normal subjects. Abbreviations: AT, anaerobic threshold; $PetCO_2$, end-tidal carbon dioxide partial pressure; PPH, primary pulmonary hypertension; VE/VCO_2, ventilation to carbon dioxide production relationship. Reproduced from. Yasunobu et al 2005 [51]

Figure 6 illustrates the VE/VCO_2 relationship and the Y-axis intercept concept. Ventilation (VE) has two components: alveolar (VE_{Alv}) and dead space ventilation (VE_{DS}), VE_{Alv} follows a linear trend. In healthy individuals (A) the positive Y-intercept results from VE_{DS}, which normally decreases with exercise. Differently, an increased Y-intercept suggests high resting dead space, as seen when adding an external dead space (B) or in COPD (C), while a low or negative value indicates dead space development during exercise, typical of PH (E) and HF (D Abbreviations: COPD, chronic obstructive pulmonary disease; HF, heart failure; PH, pulmonary hypertension; VE, ventilation; VE_{Alv}, alveolar ventilation; VE_{DS}, dead space ventilation; VCO_2, carbon dioxide production. Reproduced from Apostolo et al., 2015 [60]

Central illustration This central illustration outlines the stratification of dyspnea using cardiopulmonary exercise testing (CPET) with a focus on ventilation efficiency. Patients presenting with shortness of breath and signs of low ventilation efficiency, whether due to excessive or insufficient ventilation, undergo CPET as a standardized diagnostic tool. During CPET, ventilation efficiency is assessed through two key parameters: the VE/VCO_2 slope and the VE/VCO_2 ratio. The VE/VCO_2 slope can be evaluated up to the respiratory compensation point (RCP), across the full exercise range, and by its y-intercept. In

parallel, the VE/VCO_2 ratio can be examined at its nadir, at the anaerobic threshold (AT), and at peak exercise. Abbreviations: AT, anaerobic threshold; CPET, cardiopulmonary exercise testing; RCP, respiratory compensation point; VE, minute ventilation; VCO_2, carbon dioxide production

Table 1: Reporting Format for Ventilation efficiency assessed by Cardiopulmonary Exercise Testing

Reporting Element		
Method used	VE/VCO_2 ratio	VE/VCO_2 slope
Reference point / segment	• Nadir	• Start to RCP • Start to End of Exercise (RER<1.05) • Start to End of Exercise (RER≥1.05)
Numerical value	[Insert value]	[Insert value]
Reference cut-off	Not applicable	≥34
% of predicted based on Salvioni et al. [37]	Not applicable	[Insert %]
Graphical representation	Nadir identified visually: Yes / No	Linear slope confirmed: Yes / No
RCP status	Not applicable	Detected / Not reached

Table 1 provides a standardized template for reporting ventilation efficiency, based on either the VE/VCO_2 ratio (nadir) or the VE/VCO_2 slope. The table includes guidance for reporting the reference point, numerical values, reference cut-offs, percent predicted, graphical verification, and RCP status. Abbreviations: RCP, respiratory compensation point; RER, respiratory exchange ratio; VCO_2, carbon dioxide output; VE, minute ventilation.

Table 2: Comparison of VE/VCO_2 Slope Measurement Methods Across Cardiopulmonary Conditions

Disease	**Study**	**Number of patients (n)**	**VE/VCO_2 slope – measured until RCP**	**VE/VCO_2 slope – measured beyond RCP**	**Approx. difference between measurements**
Unknown/Mixed	Chaumont et al.[36]	308	33 (29-37)	37 (33-41)	4
	Nayor et al.[28]	FHS: 1936	24.8 ± 3.1	27.6 ± 3.5	3
		MGH-ExS: 493	31.7 ± 7.0	35.7 ± 7.7	4
	Barron et al.[77]	93	35.1	37.2	2
Tetralogy of Fallot	Leonardi et al.[78]	57	28.5 (IQR: 4.6)	32.2 (IQR 4.5)	4
Heart Failure	Arena et al. [79]	188	29.9 ± 6.8	32.5 ± 8.0	2.6 ± 4.1*
	Ingle et al.[80]	394	29.9 ± 6.8	32.1 ± 7.8	2
	Tabet et al.[40]	97	31.8 ± 7.5	39.3 ± 11.6	8

Pulmonary Hypertension	Groepenhoff et al.[81]	115	44.6 ± 11.3	48.5 ± 12.6	4
	Ferreira et al.[82]	84	56 ± 25	59 ± 21	3

Table 2 compares VE/VCO_2 slopes across different cardiopulmonary conditions and measurement methods. The VE/VCO_2 slope, a key CPET parameter, reflects ventilation efficiency and varies depending on whether it is measured up to the respiratory compensation point (RCP) or beyond it. Abbreviations: AT, anaerobic threshold; FHS, Framingham Heart Study; IQR, interquartile range; MGH-ExS, Massachusetts General Hospital Exercise Study; RCP, respiratory compensation point; VE/VCO_2, ventilation to carbon dioxide production. * *Reported mean and standard deviation by Arena et al.*

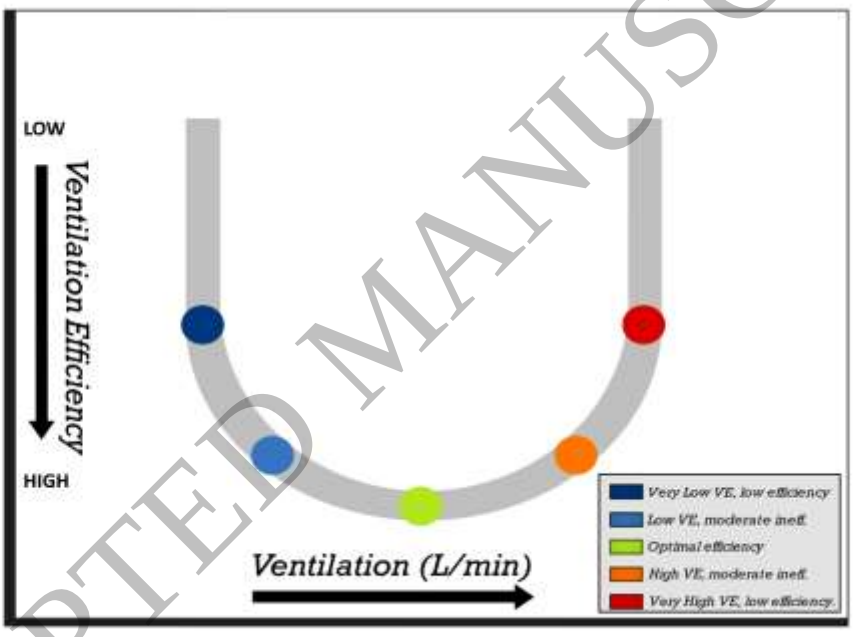


Figure 1
339x190 mm (x DPI)

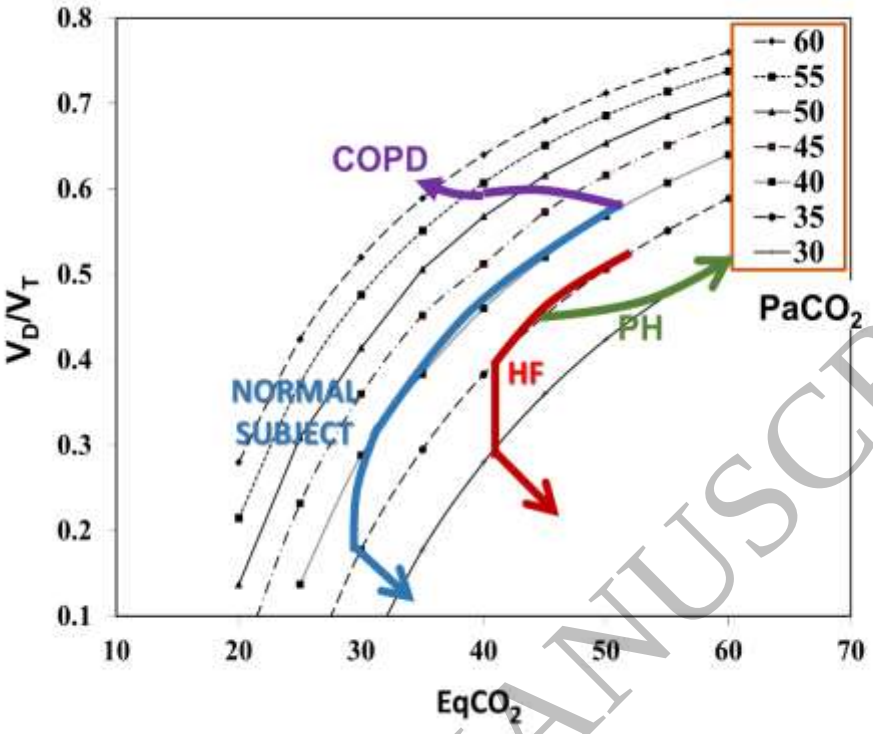


Figure 2
339x190 mm (x DPI)

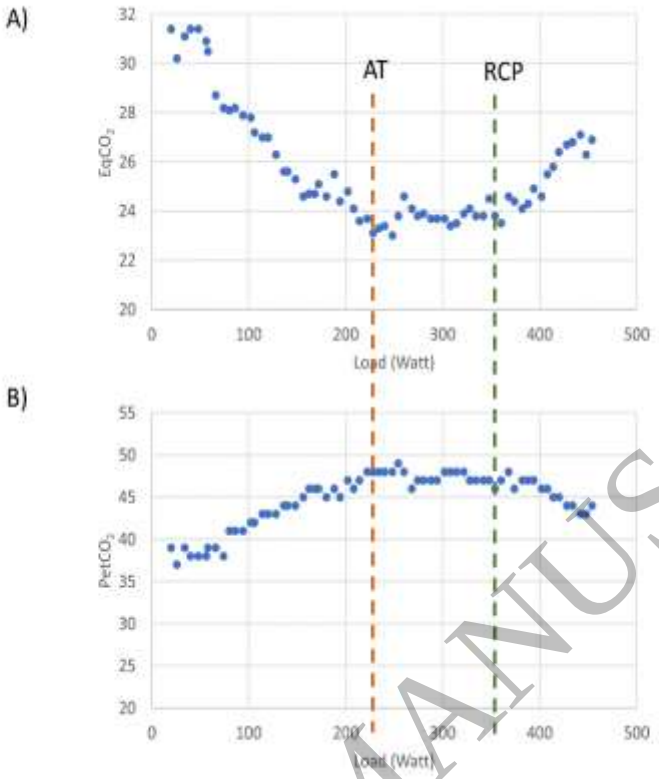


Figure 3
339x190 mm (x DPI)

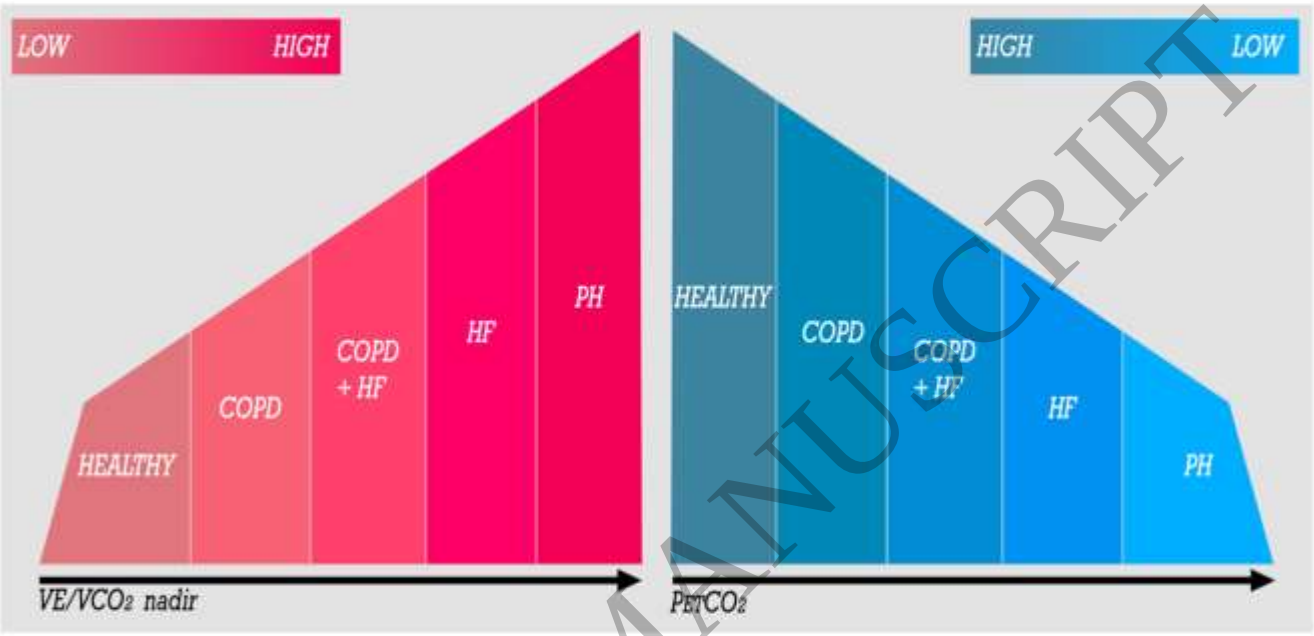


Figure 4
339x190 mm (x DPI)

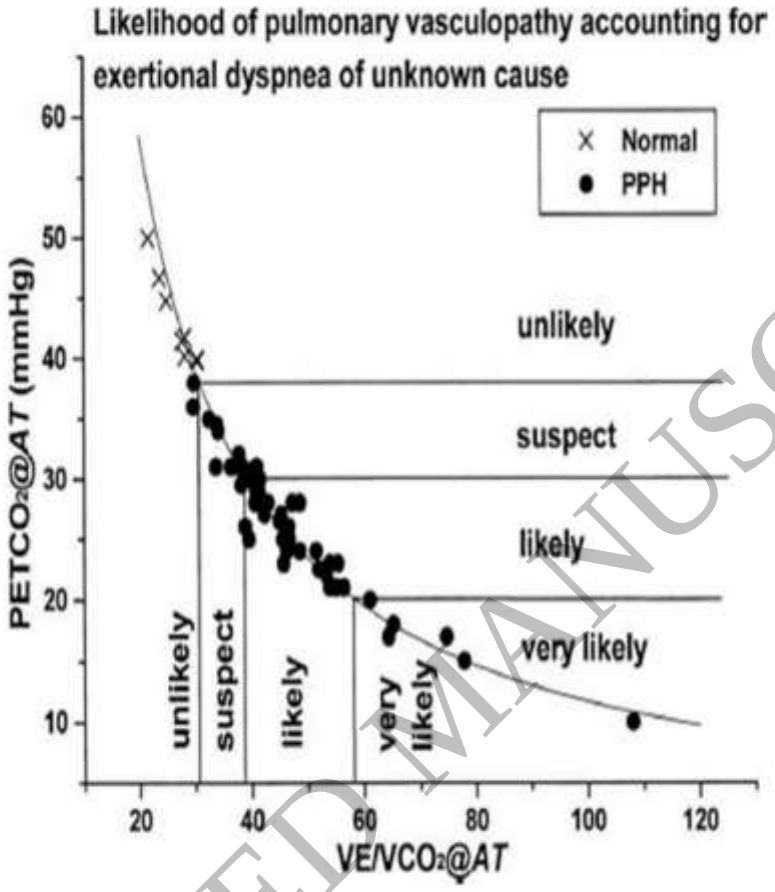


Figure 5
339x190 mm (x DPI)

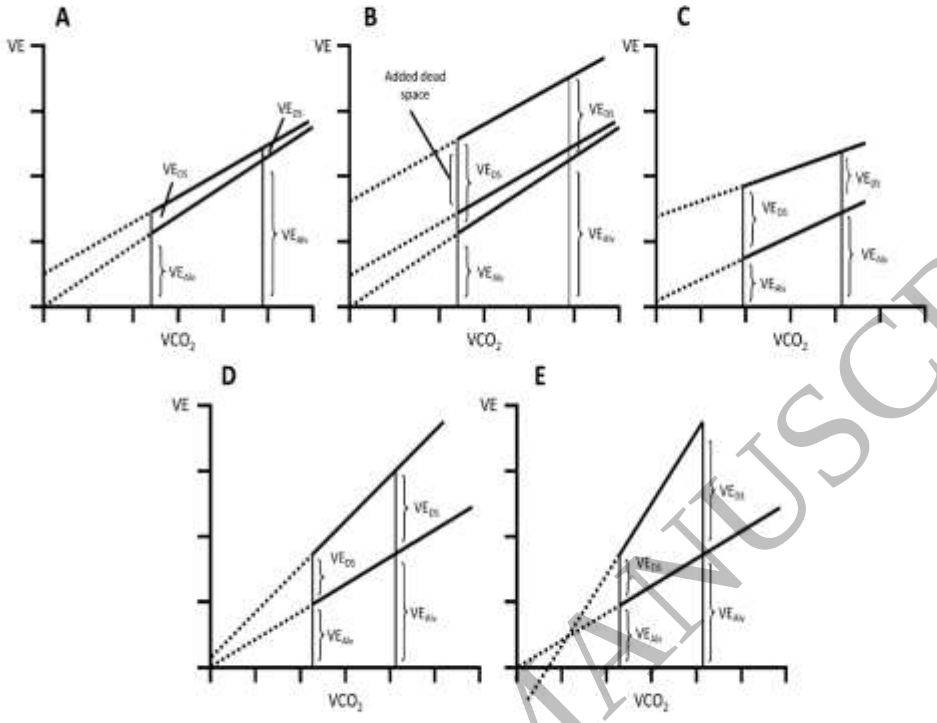
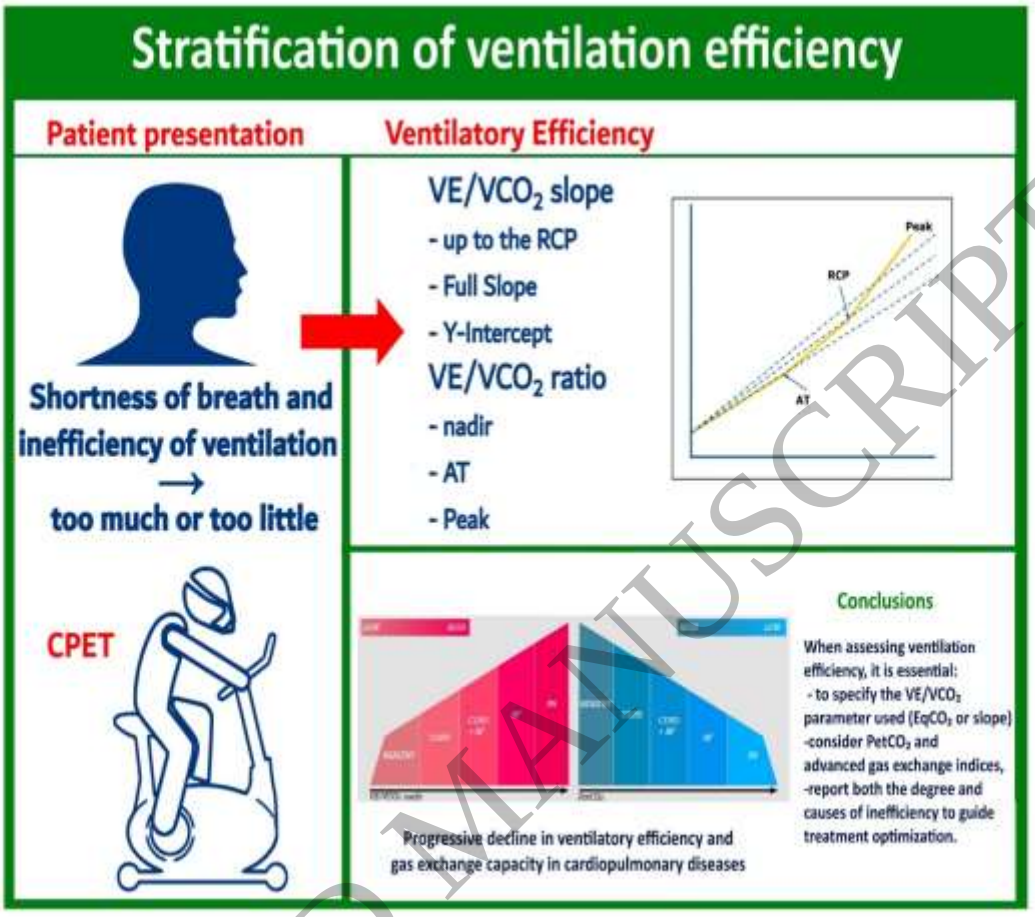


Figure 6
339x190 mm (x DPI)



Graphical Abstract
339x190 mm (x DPI)