



Ventilation/carbon dioxide output relationships during exercise in health

Susan A. Ward

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Edited by Pierantonio Laveneziana and Paolo Palange

Human Bio-Energetics Research Centre, Crickhowell, Powys, UK.

Corresponding author: Susan A. Ward (saward@dsl.pipex.com)



Shareable abstract (@ERSpublications)

The efficiency of CO₂ clearance at the lungs in exercise is estimated from the relationship between ventilation and CO₂ elimination rate. It is compromised in lung and cardiovascular disease, stressing breathing and shortness of breath, and therefore impairing exercise capacity. <https://bit.ly/3gYY866>

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Abstract

“Ventilatory efficiency” is widely used in cardiopulmonary exercise testing to make inferences regarding the normality (or otherwise) of the arterial CO₂ tension (P_{aCO_2}) and physiological dead-space fraction of the breath (V_D/V_T) responses to rapid-incremental (or ramp) exercise. It is quantified as: 1) the slope of the linear region of the relationship between ventilation (V_E) and pulmonary CO₂ output (V'_{CO_2}); and/or 2) the ventilatory equivalent for CO₂ at the lactate threshold ($V_E/V'_{CO_2} \hat{L}T$) or its minimum value ($V_E/V'_{CO_2} \min$), which occurs soon after $\hat{L}T$ but before respiratory compensation. Although these indices are normally numerically similar, they are not equally robust. That is, high values for $V_E/V'_{CO_2} \hat{L}T$ and $V_E/V'_{CO_2} \min$ provide a rigorous index of an elevated V_D/V_T when P_{aCO_2} is known (or can be assumed) to be regulated. In contrast, a high $V_E-V'_{CO_2}$ slope on its own does not, as account has also to be taken of the associated normally positive and small V_E intercept. Interpretation is complicated by factors such as: the extent to which P_{aCO_2} is actually regulated during rapid-incremental exercise (as is the case for steady-state moderate exercise); and whether $V_E/V'_{CO_2} \hat{L}T$ or $V_E/V'_{CO_2} \min$ provide accurate reflections of the true asymptotic value of V_E/V'_{CO_2} , to which the $V_E-V'_{CO_2}$ slope approximates at very high work rates.

Introduction

“Ventilatory efficiency”, the ventilation (V_E) associated with eliminating a given level of metabolically produced CO₂ as pulmonary CO₂ output (V'_{CO_2}), is a construct that has evolved from the discipline of cardiopulmonary exercise testing (CPET), whereby the integrated system function of muscle metabolism, the circulation and heart, pulmonary gas exchange and ventilation are interrogated and monitored in real time (typically breath-by-breath) by means of a rapid-incremental or ramp exercise test [1–3]. Fundamental to any mechanistic consideration of ventilatory efficiency is that V_E during moderate exercise (*i.e.* below the lactate threshold, $\hat{L}T$; *i.e.* estimated, rather than directly measured), with work rates not eliciting a sustained metabolic acidosis) operates as if it is coupled to the requirement for clearing the associated endogenous CO₂ load accruing from aerobic metabolism, to regulate arterial CO₂ tension (P_{aCO_2}) at or close to its resting value (reviewed in [4–8]). Exactly how this apparently CO₂-linked control is mediated remains tantalisingly elusive, however, not the least because of the absence of a significant sustained P_{aCO_2} error signal that could stimulate the carotid body and central chemoreflexes (reviewed in [6–8]). It had been suggested that V_E is driven, largely if not entirely, by the “CO₂ flow to the lungs”, *i.e.* the product of venous return and the mixed-venous CO₂ content [9]. Subsequently, a logical imprecision in this reasoning was identified by WHIPP [10]: “Such proposals, however, fail to meet the P_{aCO_2} -regulatory demands of the control. That is, any such control link will depend not on the rate at which CO₂ is brought to the lung per



unit time but that *minus* the rate at which CO₂ leaves the lung in the pulmonary arterial blood". The precise substrate of such a CO₂-linked mechanism has, to date, remained obscure.

It is important to recognise that P_{aCO_2} regulation during moderate exercise is expressed through the transform not only of the proportional matching of V'_E to V'_{CO_2} but also of the physiological dead space fraction of the breath (V_D/V_T) [7, 8, 10]:

$$P_{aCO_2} = 863 / ((V'_E / V'_{CO_2}) \cdot (1 - V_D / V_T)) \quad (1)$$

where 863 is the constant that corrects for the different conditions of reporting gas volumes (standard temperature and pressure, dry; body temperature and pressure, saturated) and transformation of fractional concentration to partial pressure; and V'_E / V'_{CO_2} is the ventilatory equivalent for CO₂.

At higher work rates engendering a metabolic (largely lactic) acidosis, V'_E has the further imperatives of a) clearing the additional CO₂ resulting from bicarbonate-buffering of the metabolic acidosis and b) generating respiratory compensation to constrain the falling arterial pH (pH_a) [5, 7, 8, 11–14]. This can usefully be expressed through a modification of the Henderson–Hasselbalch equation (*i.e.* $pH = pK + \log([HCO_3^-] / \alpha \cdot P_{aCO_2})$) by substituting for P_{aCO_2} from equation 1:

$$pH_a = pK' + \underbrace{(\log([HCO_3^-]_a / 25.9))}_{\text{metabolic acid-base "set-point"}} \cdot \underbrace{(V'_E / V'_{CO_2})}_{\text{"ventilatory control"}} \cdot \underbrace{(1 - V_D / V_T)}_{\text{pulmonary gas-exchange "efficiency" operators}} \quad (2)$$

where pK' is the negative logarithm of the carbonic acid ionisation constant; $[HCO_3^-]_a$ is arterial bicarbonate concentration; and α is the CO₂ solubility coefficient (0.03 mmol·mmHg⁻¹). The bracketed terms represent (from left to right): metabolic acid–base “set-point”, “ventilatory control” and pulmonary gas-exchange “efficiency” operators [8]. Thus, the effectiveness of respiratory compensation depends not only on V'_E / V'_{CO_2} increasing absolutely, but also relative to V_D / V_T .

The V'_E – V'_{CO_2} relationship

The significance of P_{aCO_2} and V_D / V_T in setting the V'_E requirements during exercise is illustrated by re-arranging equation 1 in terms of V'_E :

$$V'_E = 863 \cdot V'_{CO_2} / P_{aCO_2} \cdot (1 - V_D / V_T) \quad (3)$$

which, when viewed at level of the alveolar gas-exchange process, simplifies to:

$$V'_A = 863 \cdot V'_{CO_2} / P_{aCO_2} \quad (4)$$

where V'_A is alveolar ventilation.

Over a wide work-rate range, expressing V'_E as a function of V'_{CO_2} normally results in a linear relationship (figure 1a):

$$V'_E = m \cdot V'_{CO_2} + c \quad (5)$$

where m is the slope (*i.e.* $\Delta V'_E / \Delta V'_{CO_2}$, normally ~ 25 when reported in the same units, *e.g.* L·min⁻¹, mL·min⁻¹ *etc.*, with V'_E being reported as body temperature and pressure, saturated and V'_{CO_2} as standard temperature and pressure, dry), and c is the V'_E intercept (normally ~ 3 – 5 L·min⁻¹) when allowance is made for breathing apparatus (valve or facemask) dead space [17–19], *i.e.* by subtracting the product of apparatus V_D and breathing frequency from the measured V'_E . Without this correction, the V'_E intercept will be over-estimated, to a degree that naturally depends on the size of the apparatus V_D .

Encapsulated in m are the composite response profiles of P_{aCO_2} and V_D / V_T , while c is the value of V'_E at a hypothetical V'_{CO_2} of zero. And as the V'_A – V'_{CO_2} relationship is normally also linear but intersects the origin (*i.e.* no V'_A intercept) [20], the corresponding relationship between dead space ventilation (V'_D) and V'_{CO_2} has also to be linear, with a V'_D intercept equal to c .

For the rapidly changing work-rate protocols used in CPET, the range of V'_E – V'_{CO_2} linearity actually extends beyond LT. That is, the onset of respiratory compensation for the metabolic acidosis (the

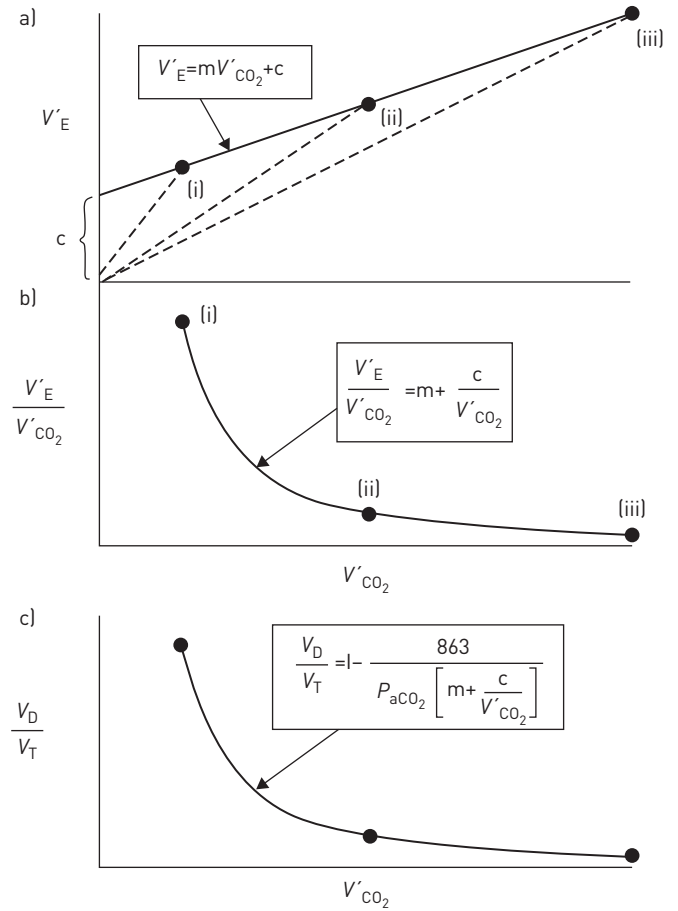


FIGURE 1 Schematic representation of a) ventilation (V'_E), b) ventilatory equivalent for CO₂ (V'_E/V'_{CO_2}) and c) physiological dead space fraction of the breath (V_D/V_T) as a function of CO₂ output (V'_{CO_2}) during rapid-incremental (or ramp) exercise for work rates where arterial CO₂ tension (P_{aCO_2}) is assumed to be stable. m : $V'_E-V'_{CO_2}$ slope; c : V'_E intercept. Modified with permission from a, b) [15] and c) [16].

respiratory compensation point (RCP)) is delayed relative to the onset of the acidosis itself, *i.e.* at $\hat{L}\hat{T}$ (figure 2) [7, 8, 14, 21–24]. As a result, V'_E continues to remain coupled to V'_{CO_2} , providing a supra-threshold region of P_{aCO_2} stability (termed “isocapnic buffering”, in a physiological rather than a physicochemical sense) [25]. In contrast, for slow-incremental and steady-state exercise tests, $\hat{L}\hat{T}$ and the RCP are coincident. The slow response dynamics of the compensatory hyperventilation, in the context of rapid work-rate incrementation rates, has been suggested to reflect the carotid body chemoreceptors having an amplitude or time-related threshold for metabolic H⁺ detection [8], possibly expressed through slow intracellular expression of the metabolic acidosis and/or slow subsequent signal transduction at H⁺-sensitive type I TASK-1 potassium channels [26, 27]. The RCP is thus a manifestation of H⁺-related ventilatory control (and is therefore not a metabolic construct). For example, the RCP becomes closer to $\hat{L}\hat{T}$ when carotid chemoreflex drive is enhanced by the imposition of hypoxia [28–30] but farther from $\hat{L}\hat{T}$ when the work rate is incremented more rapidly [29–31].

The V'_E/V'_{CO_2} response

V'_E/V'_{CO_2} can be viewed as a variable “derived” from the $V'_E-V'_{CO_2}$ relationship; being numerically equal to the slope of a hypothetical line joining a given V'_E , V'_{CO_2} point to the origin (dashed lines in figure 1a). The linearity of the $V'_E-V'_{CO_2}$ relationship and its positive V'_E intercept (figure 1a; equation 5) requires V'_E/V'_{CO_2} to decline hyperbolically as work rate and therefore V'_{CO_2} increase (figure 1b). Over a considerable portion of the tolerable work-rate range, V'_E/V'_{CO_2} clearly exceeds the $V'_E-V'_{CO_2}$ slope (m), specifically by the variable factor c/V'_{CO_2} :

$$\frac{V'_E}{V'_{CO_2}} = m + c/V'_{CO_2} \tag{6}$$

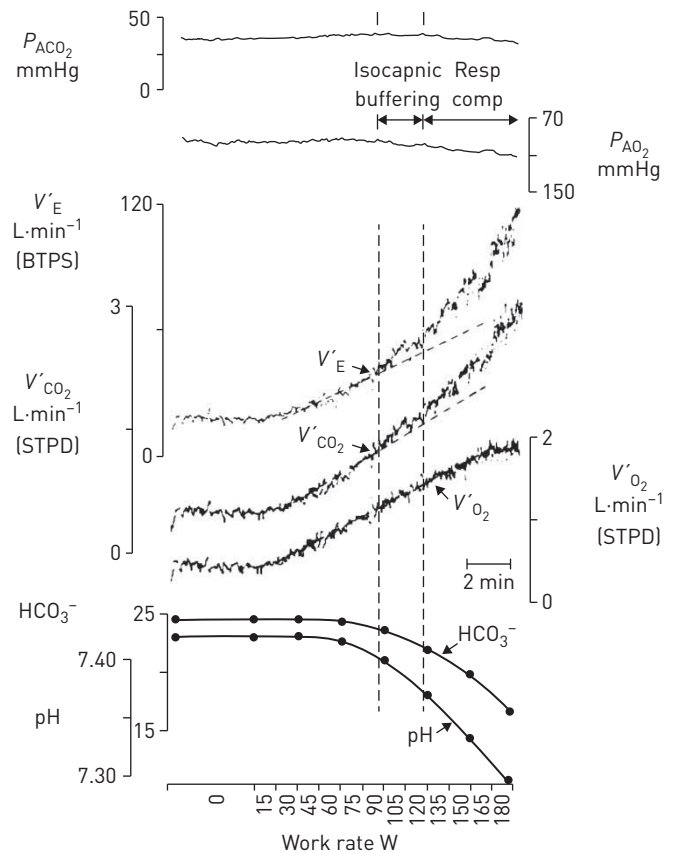


FIGURE 2 Alveolar end-tidal P_{CO_2} and P_{O_2} (P_{ACO_2} , P_{AO_2}), ventilation (V'_E), CO_2 output (V'_{CO_2}), O_2 uptake (V'_{O_2}), arterial $[HCO_3^-]$ and arterial pH as a function of work rate for a rapid-incremental cycle-ergometer exercise test. The lactate threshold occurs when arterial $[HCO_3^-]$ starts to buffer the metabolic acidosis, evidenced in the accelerating V'_{CO_2} response (left vertical dashed line). As V'_E continues to respond in proportion to V'_{CO_2} , it therefore increases out of proportion to V'_{O_2} , and P_{AO_2} therefore begins to rise. P_{ACO_2} remains stable until respiratory compensation for the metabolic acidosis develops (right vertical dashed line; isocapnic buffering). Beyond this point, V'_E increases at a greater rate than V'_{CO_2} , and P_{ACO_2} therefore starts to decrease (respiratory compensation). Reproduced with permission from [3].

As c/V'_{CO_2} diminishes with increasing work rate (and V'_{CO_2}), V'_E/V'_{CO_2} will decline to achieve an asymptotic value at high levels of V'_{CO_2} that is equal to m (figure 1b) [15, 17, 32].

“It is important, therefore, that if the values of the ventilatory equivalent for CO_2 are to be used for characterising a subject’s ventilatory response to exercise they should be reported together with the values of V'_{CO_2} at which they were obtained. Or, better still, both the slope and intercept parameters of the $V'_E-V'_{CO_2}$ relationship should be defined” [15]. And it should also be noted that V'_E/V'_{CO_2} will equal m not only at very high V'_{CO_2} values, but also when the V'_E/V'_{CO_2} relationship extrapolates to the origin (*i.e.* when $c=0$) (equation 6) [18, 19].

Equation 1 indicates that maintained regulation of P_{aCO_2} requires the response profiles of V'_E/V'_{CO_2} and V_D/V_T to be qualitatively and quantitatively matched. That is, the normal hyperbolic decline of V'_E/V'_{CO_2} with increasing work rate (figure 1b) necessitates a similar profile of V_D/V_T decline (figure 1c) [10, 15, 29]:

$$V_D/V_T = 1 - (863/(P_{aCO_2} \cdot (m + c/V'_{CO_2}))) \tag{7}$$

Substituting V'_E/V'_{CO_2} for $m+c/V'_{CO_2}$ from equation 6 into equation 7, and re-arranging in terms of V'_E/V'_{CO_2} , yields:

$$V'_E/V'_{CO_2} = 863/(P_{aCO_2} \cdot (1 - V_D/V_T)) \quad (8)$$

A modest contribution to the declining V_D/V_T with increasing work rate derives from a more-even perfusion of the lungs (Q') that results in an improved V'_A/Q' distribution [33–36]. However, the predominant influence is the consequence of disproportionate increases in V_D and V_T ; the former being less than the latter. This reflects the compliance of the conducting airways being appreciably less than that of the alveoli.

As for the $V'_E-V'_{CO_2}$ relationship, the resulting V_D-V_T relationship is normally also linear with a positive V_D intercept [34] which confers hyperbolicity on the V_D/V_T decline. Were V_D/V_T not to decline hyperbolically, a necessary consequence would be the introduction of nonlinearities into the $V'_E-V'_{CO_2}$ relationship or P_{aCO_2} not being regulated, or both [15], unless, of course, the V'_E intercept were to be zero (equations 7 and 8). In this latter situation, therefore, V_D/V_T will not decline with increasing work rate and, if P_{aCO_2} remains regulated, neither will V'_E/V'_{CO_2} .

Exactly how such apparent matching between V'_E/V'_{CO_2} and V_D/V_T might be mediated has yet to be resolved, but “the system seems to “know” that when V_D/V_T is reduced (making V'_E more efficient with respect to V'_A) V'_E “needs” to increase less per unit V'_{CO_2} to effect its regulatory function, with the necessary logical assumption, of course, that there is such regulation. But unless one is badly confusing subsequence and consequence, it is hard to believe, in the light of the evidence cited above, that there is not.” [10].

Ventilatory efficiency indices

The $V'_E-V'_{CO_2}$ and V'_E/V'_{CO_2} response profiles provide indices of ventilatory efficiency [1–3] as, respectively, a) the slope of the linear region of the $V'_E-V'_{CO_2}$ relationship (*i.e.* normally up to the RCP) (figure 1a and b) either V'_E/V'_{CO_2} at $\hat{L}T$ ($V'_E/V'_{CO_2}\hat{L}T$) or its minimum value ($V'_E/V'_{CO_2}\min$) typically occurring soon thereafter $L\hat{T}$ but before the RCP (figure 1b), and have been shown to be essentially indistinguishable in healthy individuals [19]. When these several indices are increased relative to normal, ventilatory efficiency is assumed to have decreased (*i.e.* greater ventilatory inefficiency).

As $V'_E/V'_{CO_2}\min$ approximates the $V'_E-V'_{CO_2}$ slope at very high V'_{CO_2} values (figure 1a and b) [10, 15, 32], these two indices are essentially equal in fit individuals for whom $L\hat{T}$ and the RCP occur at relatively high absolute values of V'_{CO_2} [19, 37]. Interestingly, slightly higher values for ventilatory efficiency have been reported with ageing [19], and also in females compared to males [19, 37]. Ventilatory efficiency indices have been reported by some to be unaffected by exercise modality (*i.e.* cycle ergometer *versus* treadmill) [19], although others report slightly higher values for treadmill exercise in females [38] and in males [39]. Finally, there is some question as to whether test–retest reliability differs between ventilatory efficiency indices, being reported either to be greater for $V'_E/V'_{CO_2}\min$ than for the V'_E/V'_{CO_2} slope [19] or not to differ [37].

Interpretation of abnormally high values for ventilatory efficiency does require some care, however, recognising that this could reflect impairments in V_D/V_T or P_{aCO_2} regulation, or both. For example, higher-than-normal values of $V'_E-V'_{CO_2}$ slope and $V'_E/V'_{CO_2}\min$ could reflect a low P_{aCO_2} (reflective of a high ventilatory control “gain”, as with hyperventilatory conditions such as arterial hypoxaemia, metabolic acidemia and increased central neural respiratory drive), a high V_D/V_T (reflective of increased V'_A/Q' mismatch, as in the healthy elderly and lung and cardiovascular disease patients) or both. In addition, a high $V'_E/V'_{CO_2}\min$ might be expected in individuals having a low respiratory quotient (*i.e.* with a lower-than-normal CO_2 production at a given work rate) and, as discussed later, in those having significantly compromised exercise tolerance.

Complicating issues

$V'_E-V'_{CO_2}$ slope estimation

From a physiological perspective, it is important that the $V'_E-V'_{CO_2}$ slope estimate is constrained to the linear region of the relationship, *i.e.* not beyond the RCP where respiratory compensation for the metabolic acidosis introduces nonlinearity. Thus, while a $V'_E-V'_{CO_2}$ slope estimate obtained from the entire work-rate range (*e.g.* [40–42]) tends to be favoured for cardiological cohorts because of demonstrably better prognostication (*e.g.* [43–46]), the departure from $V'_E-V'_{CO_2}$ linearity will result in the $V'_E-V'_{CO_2}$ slope being over-estimated and the V'_E intercept being under-estimated, with implications for ventilatory efficiency judgements [47].

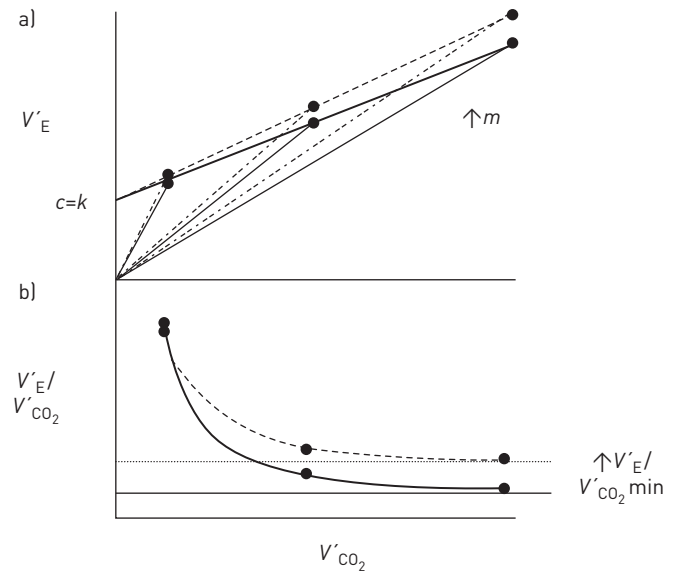


FIGURE 3 Schematic representation of a) the effects of a hypothetical intervention that increased the V'_E - V'_{CO_2} slope (m) with no change in the V'_E intercept (c) on ventilation (V'_E) and b) ventilatory equivalent for CO_2 (V'_E/V'_{CO_2}) as a function of CO_2 output (V'_{CO_2}) during rapid-incremental (or ramp) exercise for work rates where arterial CO_2 tension (P_{aCO_2}) is assumed to be stable. Solid profiles: pre-intervention; dashed profiles, post-intervention.

Equality between $V'_E/V'_{CO_2 \text{ min}}$ and V'_E - V'_{CO_2} slope

This equality reflects $V'_E/V'_{CO_2 \text{ min}}$ approximating the V'_E - V'_{CO_2} slope at high V'_{CO_2} values (figure 1a and b) [10, 15, 32]. However, when circumstances change, maintained equality depends critically on the behaviour of the V'_E intercept. For example, were the V'_E - V'_{CO_2} slope to be caused to increase but with no change in the V'_E intercept, this would result in predictable increases in V'_E/V'_{CO_2} (equation 6) such that the V'_E/V'_{CO_2} response profile would be shifted upwards with a new increased $V'_E/V'_{CO_2 \text{ min}}$ equal to the new increased V'_E - V'_{CO_2} slope (figure 3). In contrast, were the V'_E intercept to increase but with no change in the V'_E - V'_{CO_2} slope, the V'_E/V'_{CO_2} -response profile would be shifted upwards with a new increased $V'_E/V'_{CO_2 \text{ min}}$ that would exceed the unchanged V'_E - V'_{CO_2} slope (figure 4).

However, when exercise tolerance is severely compromised, the normal equality between $V'_E/V'_{CO_2 \text{ min}}$ and the V'_E - V'_{CO_2} slope may not obtain. Thus, in poorly fit individuals and in significantly limited patients, the RCP may be sufficiently low as to occur on the still-falling V'_E/V'_{CO_2} trajectory [18, 48]. In such a situation, as $V'_E/V'_{CO_2 \text{ min}}$ will exceed the V'_E - V'_{CO_2} slope, the latter would therefore be the only physiologically meaningful index of ventilatory efficiency. This scenario also has implications for RCP estimation. That is, respiratory compensation could be achieved with V'_E/V'_{CO_2} still declining, but at a lesser rate than isocapnia would require, *i.e.* decreasing less than V_D/V_T [29, 30].

The V'_E intercept

The potential value of incorporating the V'_E intercept, conjointly with the V'_E - V'_{CO_2} slope, into clinical analyses of exercise intolerance in the context of co-morbidities and prognostication is becoming recognised [18, 49–52]. The physiological basis of the V'_E intercept can only be conjectured on, however. Simply put, it expresses a notional V_D at a hypothetical V'_{CO_2} of zero, and therefore is unlikely to represent any *actual* V_D [15, 17] *c.f.* [51, 53]. In a geometrical sense, the position of the V'_E - V'_{CO_2} relationship could be considered to be dictated by the resting V'_E , V'_{CO_2} “operator”, such that the V'_E intercept is merely a “passive” consequence of the underlying exercise ventilatory control process. Alternatively, the V'_E intercept could reflect some mechanistic interplay between V_D/V_T and P_{aCO_2} in setting the required exercise V'_E [10, 54]. This clearly demands resolution.

P_{aCO_2} in rapid-incremental exercise

The implicit assumption of a stable P_{aCO_2} over a wide range of work rates, accomplished through the proportional hyperbolic behaviours of V'_E/V'_{CO_2} and V_D/V_T is open to some question for rapid-incremental exercise. That is, while V'_E evidences a close dynamic coupling to V'_{CO_2} , its slightly longer time constant

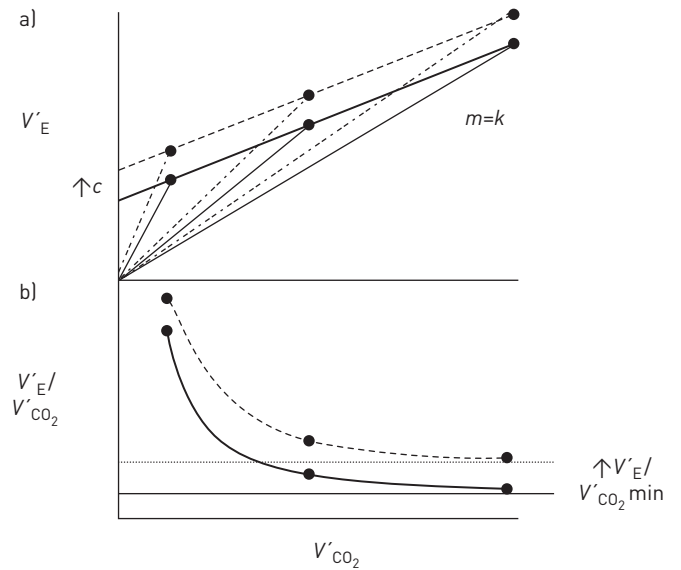


FIGURE 4 Schematic representation of a) the effects of a hypothetical intervention that increased the V'_E -intercept (c) with no change in the V'_E - V'_{CO_2} slope (m) on ventilation (V'_E) and b) ventilatory equivalent for CO₂ (V'_E/V'_{CO_2}) as a function of CO₂ output (V'_{CO_2}) during rapid-incremental or ramp exercise for work rates where arterial CO₂ tension (P_{aCO_2}) is assumed to be stable. Solid profiles: pre-intervention; dashed profiles, post-intervention.

of response [7–9] predicts a modest but systematic increase in P_{aCO_2} [25, 55, 56]. This predictably impacts on ventilatory efficiency estimates, as illustrated by inserting the group-mean gas-exchange responses for ramp exercise reported by SUN *et al.* [56] into equation 7, with reasonable assumptions being made for the concomitant V_D/V_T responses [33–36]. When the measured P_{aCO_2} values (*i.e.* increasing from 40.8 mmHg at rest to 44.6 mmHg just prior to the RCP) were used, the V'_E - V'_{CO_2} slope and V'_E intercept were estimated to be 20.0 and 3.92 L·min⁻¹, respectively (figure 5, dashed line). This contrasts with slope and intercept values of 22.4 and 2.70 L·min⁻¹ if P_{aCO_2} were constrained to remain at the resting value of 40.8 mmHg (normocapnia) up to the RCP (figure 5, solid line). Likewise, the normocapnic V'_E/V'_{CO_2}

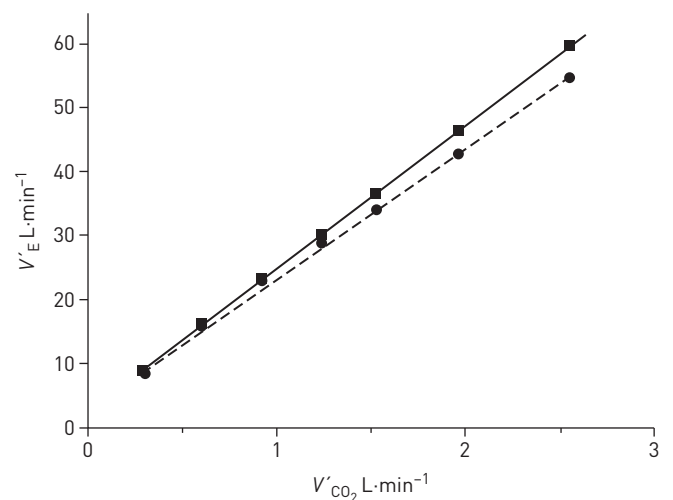


FIGURE 5 The V'_E - V'_{CO_2} relationship for ramp exercise in which arterial CO₂ tension (P_{aCO_2}) has been demonstrated to increase progressively up to the lactate threshold [25, 56, 57] (dashed line), compared with that obtaining with P_{aCO_2} constrained not to increase (solid line). Note the decreased slope in the former condition. Data taken from [56].

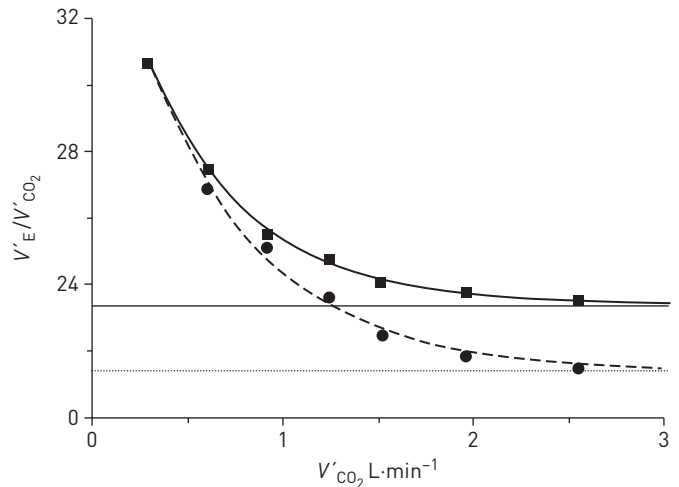


FIGURE 6 The corresponding V'_E/V'_{CO_2} relationships related to figure 5. Note the depressed V'_E/V'_{CO_2} profile consequent to the progressive P_{aCO_2} increase (circles, dashed curve), compared with that obtaining with arterial CO_2 tension (P_{aCO_2}) constrained not to increase (squares, solid curve). As a result, $V'_E/V'_{CO_2\min}$ was decreased in the former condition.

response profile was shifted upwards (figure 6, solid curve) relative to the actual V'_E/V'_{CO_2} profile (figure 6, dashed curve), with $V'_E/V'_{CO_2\min}$ being 23.5 compared with 21.5. While these differences are numerically modest, this raises the issue of ventilatory inefficiency being underestimated for the standard CPET ramp exercise testing paradigm, if P_{aCO_2} regulation is assumed.

Interestingly, the profile of increasing P_{aCO_2} with ramp exercise only occurs up to $\hat{L}T$. Beyond $\hat{L}T$, P_{aCO_2} stabilises up to the RCP (*i.e.* isocapnic buffering) [25, 56]. Paraphrasing Whipp and colleagues “Consequently, P_{aCO_2} becomes constant at [$\hat{L}T$] because of a particular ventilatory response; it does not remain constant because of the lack of one” and “isocapnic buffering during rapid-incremental exercise actually reflects a ventilatory response to the metabolic acidosis which levels a systematically-rising phase of P_{ETCO_2} [end-tidal CO_2 tension] and P_{aCO_2} ” [25]. While isocapnic buffering does not represent respiratory compensation in the conventional sense (*i.e.* a V'_E response sufficient to elicit a decrease in P_{aCO_2}), one could reasonably argue that the lack of a continuing increase P_{aCO_2} in beyond $\hat{L}T$ (*i.e.* a lower-than-expected P_{aCO_2}) does not rule it out.

Conclusions

What, therefore, does (and does not) a decrease in ventilatory efficiency connote? One is reminded of Moritz Schlick’s statement in 1936 that “The meaning of a proposition is the method of its verification” and which he appropriately attributed to Ludwig Wittgenstein [57]. Generically speaking, ventilatory efficiency is simply the V'_E “tasked with” clearing metabolically-produced CO_2 during exercise, being expressed mathematically as either the $V'_E-V'_{CO_2}$ slope or the value of V'_E/V'_{CO_2} at $\hat{L}T$ or just prior to the RCP. However, interpretation of ventilatory efficiency should be undertaken with caution, as high values of $V'_E-V'_{CO_2}$ slope and $V'_E/V'_{CO_2\min}$ could reflect a low P_{aCO_2} , a high V_D/V_T or both; rigorous discrimination therefore requiring simultaneous P_{aCO_2} monitoring.

A clear distinction should be drawn between ventilatory efficiency and pulmonary CO_2 exchange efficiency; the latter being conventionally quantified as $(1-V_D/V_T)$ [1–3]. Thus, a decrease in $(1-V_D/V_T)$ reflects a reduction in gas-exchange efficiency, consequent to V_A/Q' mismatching and/or a right-to-left shunt. In such a situation, if V'_E is constrained or limited from increasing, P_{aCO_2} will rise (as with severely impaired respiratory mechanics). However, in individuals with normal pulmonary function, a high V_D/V_T can simply result from a tachypnoeic pattern of breathing.

In conclusion, if P_{aCO_2} is regulated, a high $V'_E-V'_{CO_2}$ slope is a useful but not rigorous index of a high V_D/V_T , unless account is taken of the V'_E intercept as is illustrated in figure 4. In contrast, a high $V'_E/V'_{CO_2\min}$ does provide a rigorous index of a high V_D/V_T (equation 8). For this reason, V'_E/V'_{CO_2} is better viewed as the primary CO_2 -linked ventilatory control variable than is the $V'_E-V'_{CO_2}$ slope [10]. And, of course, ventilatory

efficiency is necessarily defined over a constrained work-rate range, and thus does not address “efficiency” at high and potentially limiting work rates.

Previous articles in this series: No. 1: Laveneziana P, Di Paolo M, Palange P. The clinical value of cardiopulmonary exercise testing in the modern era. *Eur Respir Rev* 2021; 30: 200187. No. 2: Agnostoni P, Sciomer S, Palermo P, *et al.* Minute ventilation/carbon dioxide production in chronic heart failure. *Eur Respir Rev* 2021; 30: 200141. No. 3: Watson M, Ionescu MF, Sylvester K, *et al.* Minute ventilation/carbon dioxide production in patients with dysfunctional breathing. *Eur Respir Rev* 2021; 30: 200182.

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