Ventilatory efficiency in athletes, asthma and obesity

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Number 5 in the Series "Ventilatory efficiency and its clinical prognostic value in cardiorespiratory disorders"
Edited by Pierantonio Laveneziana and Paolo Palange

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Shareable abstract (@ERSpublications)
The minute ventilation/CO_2 production ratio is useful when evaluating exercise responses. This review describes the physiology of the minute ventilation/CO_2 production ratio and the ratio response in endurance athletes, asthma and obesity. https://bit.ly/3mFdr81

Cite this article as: Collins SÉ, Phillips DB, Brotto AR, *et al*. Ventilatory efficiency in athletes, asthma and obesity. *Eur Respir Rev* 2021; 30: 200206 [DOI: 10.1183/16000617.0206-2020].

Received: 30 June 2020
Accepted: 16 Sept 2020

Abstract

During submaximal exercise, minute ventilation (V'_E) increases in proportion to metabolic rate (*i.e.* carbon dioxide production (V'_{CO_2})) to maintain arterial blood gas homeostasis. The ratio V'_E/V'_{CO_2}, commonly termed ventilatory efficiency, is a useful tool to evaluate exercise responses in healthy individuals and patients with chronic disease. Emerging research has shown abnormal ventilatory responses to exercise (either elevated or blunted V'_E/V'_{CO_2}) in some chronic respiratory and cardiovascular conditions. This review will briefly provide an overview of the physiology of ventilatory efficiency, before describing the ventilatory responses to exercise in healthy trained endurance athletes, patients with asthma, and patients with obesity. During submaximal exercise, the V'_E/V'_{CO_2} response is generally normal in endurance-trained individuals, patients with asthma and patients with obesity. However, in endurance-trained individuals, asthmatics who demonstrate exercise induced-bronchoconstriction, and morbidly obese individuals, the V'_E/V'_{CO_2} can be blunted at maximal exercise, likely because of mechanical ventilatory constraint.

Introduction

During submaximal exercise, minute ventilation (V'_E) increases in proportion to metabolic rate (*i.e.* oxygen consumption (V'_{O_2}); and carbon dioxide production (V'_{CO_2})) to maintain arterial blood gas and acid–base balance. The response of V'_E relative to V'_{CO_2} (V'_E/V'_{CO_2}) during exercise is said to reflect ventilatory efficiency [1]. Examining the V'_E/V'_{CO_2} relationship during exercise has become a common tool to evaluate exercise responses in patients with respiratory or cardiovascular abnormalities. Further, ventilatory inefficiency (*i.e.* high V'_E/V'_{CO_2}) can help to explain why some individuals with normal lung function present with abnormally high dyspnoea upon exertion [2]. While the V'_E relative to V'_{O_2} response has also demonstrated prognostic value in various disease states [3–5], the V'_E–V'_{CO_2} response has been shown to have superior prognostic value [3, 6]. Further, V'_E/V'_{CO_2} shows less variability than V'_E/V'_{O_2} during moderate intensity exercise, due to the tight control of ventilation relative to the arterial partial pressure of CO_2 [7–10], and therefore V'_E/V'_{CO_2} is typically the preferred variable to evaluate ventilation relative to metabolic demand. This review will briefly provide an overview of the physiology and clinical utility of V'_E/V'_{CO_2}, before describing the ventilatory responses to exercise in healthy trained endurance athletes, patients with asthma, and patients with obesity.

Pulmonary gas exchange and ventilatory efficiency

Alveolar ventilation (V'_A) is defined as the ventilation which takes part in gas exchange. The relationship between V'_A, V'_{CO_2}, and the alveolar partial pressure of CO_2 (P_{ACO_2}) can be described by the following equation [11]:

$$P_{ACO_2} = (V'_{CO_2}/V'_A) \times K \quad (1)$$

Both V'_A and P_{ACO_2} are reported under body temperature ambient pressure, saturated (BTPS) with water vapour. V'_{CO_2} is reported at 0°C, 760 mmHg, standard temperature and pressure dry (STPD). K is a conversion factor (normally=863 at sea level and at a normal body temperature of 37°C) used to convert V'_{CO_2}, from STPD to BTPS [11, 12]. Due to technical limitations, arterial P_{CO_2} (P_{aCO_2}) is often used as a surrogate for P_{ACO_2}. Importantly, all of the CO_2 in the expired gas originates from V'_A, and, assuming complete gas exchange (*i.e.* negligible ventilation-perfusion mismatch, diffusion limitation and/or shunt), alveolar and arterial P_{CO_2} are equal ($P_{ACO_2} \approx P_{aCO_2}$) [13]. While alveolar ventilation is generally well matched to perfusion in healthy individuals with normal lung function [6, 14–16], a portion of gas remains in conducting airways and does not participate in gas exchange and is termed anatomical dead space. Further, alveoli that are ventilated but not perfused represent alveolar dead space. The sum of alveolar and anatomical dead space makes up the total dead space ventilation (V'_D), while the total expired minute ventilation (V'_E) is a combination of V'_A and V'_D and is displayed as:

$$V'_E = V'_A + V'_D \quad (2)$$

V'_E can be measured noninvasively at the mouth with expired gas analysis, while V'_A and V'_D are more technically difficult to evaluate. If P_{aCO_2} is measured by arterial blood gas analysis, then V'_A can be determined using equation 1. Additionally, total physiologic dead space as a proportion of tidal volume (V_D/V_T) can be determined using Enghoff's modified Bohr equation [13, 17]:

$$V_D/V_T = (P_{aCO_2} - P_{ECO_2})/(P_{aCO_2}) \quad (3)$$

Where P_{ECO_2} is the mixed expired partial pressure of CO_2. The relationship between P_{aCO_2}, V'_E/V'_{CO_2} and V_D/V_T can be described by the modified alveolar ventilation equation:

$$V'_E/V'_{CO_2} = K/(P_{aCO_2} \times (1 - (V_D/V_T)) \quad (4)$$

K is the same conversion factor applied to equation 1, used to convert V'_{CO_2} from STPD to BTPS [11, 12].

During exercise, P_{aCO_2} is determined by equation 1. In practice, individuals often hyperventilate immediately prior to exercise and at low exercise intensities, and therefore P_{aCO_2} is often slightly reduced. Once breathing is stabilised, the increase in ventilation is appropriate for metabolic demand and P_{aCO_2} remains relatively constant (within 1–3 mmHg of resting values) at submaximal intensities in healthy individuals [7–10, 18]. To compensate for excessive metabolic acidosis during high intensity exercise, V'_A increases disproportionately to V'_{CO_2} (often termed the respiratory compensation point) [19]. The net effect is a drop in P_{aCO_2} below resting values, and an increase in V'_E/V'_{CO_2}. As such, P_{aCO_2} typically drops to 30–35 mmHg at maximal exercise, while a P_{aCO_2} between 35–38 mmHg at maximal exercise would be suggestive of a borderline effective alveolar hyperventilation, and a P_{aCO_2}>38 mmHg would be indicative of an inadequate compensatory hyperventilatory response to exercise [20].

In many respiratory and cardiovascular conditions, increased dead space and hyperventilation frequently co-exist. Without direct measurements of P_{aCO_2}, it can be difficult to quantify the contribution of each to V'_E/V'_{CO_2}. Often, the end-tidal partial pressure of CO_2 (P_{ETCO_2}) is used as a surrogate for P_{aCO_2}, as it can be easily acquired noninvasively using a breath-by-breath metabolic measurement system. However, multiple studies have shown inaccuracies between arterial blood-gas derived P_{aCO_2} and expired gas derived P_{ETCO_2} in patients with pulmonary gas-exchange abnormalities and increased alveolar dead space [21–24]. Therefore, care should be taken when using end-tidal values to infer P_{aCO_2} and calculate dead space ventilation.

In various chronic respiratory and cardiovascular conditions, V'_E/V'_{CO_2} is elevated at rest and throughout exercise compared to healthy individuals. The increased V'_E/V'_{CO_2} is secondary to alveolar hyperventilation (low P_{aCO_2}) and/or high dead space. The mechanisms for hyperventilation are multifactorial and complex,

however, increased afferent stimulation from chemoreceptors, ergoreceptors, baroreceptors and pulmonary c-fibres have been identified [25–30]. In some chronic conditions, V'_E/V'_{CO_2} is blunted during exercise, secondary to alveolar hypoventilation (increased P_{aCO_2}). Alveolar hypoventilation can be secondary to expiratory flow limitation (EFL) and severe ventilatory mechanical constraint [31, 32].

Shortly after the onset of exercise, V_D/V_T falls from values around 0.28–0.35 to approximately 0.20 in healthy individuals, and stays relatively constant during exercise [33–36]. If total dead space or V_D/V_T is abnormally elevated, the total ventilation must increase to maintain V'_A and P_{aCO_2}. Following equation 4, an elevated V_D/V_T (assuming a preserved P_{aCO_2}) would therefore increase V'_E/V'_{CO_2} [37]. The potential causes for increased dead space include: 1) a tachypnoeic breathing pattern (small tidal volume and rapid breathing frequency) [38, 39], 2) increased ventilation–perfusion mismatching, specifically areas of ventilation with no perfusion [40], 3) an increase in the mean ventilation-perfusion ratio (*i.e.* a rightward shift in the overall relationship) secondary to alveolar hyperventilation and/or impaired cardiac output [41, 42], and 4) intrapulmonary shunt, as P_{aCO_2} would increase relative to P_{ECO_2}; see equation 3 [40, 43].

Analyzing the V'_E/V'_{CO_2} response to exercise

During cardiopulmonary exercise testing, the slope of the V'_E–V'_{CO_2} relationship can be determined using linear regression. Typically, the V'_E–V'_{CO_2} slope is calculated from the start of exercise up to the respiratory compensation point [6, 14, 16]. Minute ventilation rises disproportionally to V'_{CO_2} at near-maximal intensities, secondary to excessive metabolic acidosis and respiratory compensation [19], and therefore when data points past the respiratory compensation point are included, the V'_E–V'_{CO_2} slope can be inflated. In addition to the V'_E–V'_{CO_2} slope, the y-intercept (V'_E when V'_{CO_2}=0) of the regression equation can also be reported [44, 45]. The y-intercept is usually small (<3 L·min^{-1}) in healthy participants [6], and an elevated y-intercept may be suggestive of ventilatory inefficiency. Because of the typical hyperventilation at the start of exercise (see above), the V'_E/V'_{CO_2} ratio is elevated during light exercise and progressively decreases to its lowest point (nadir V'_E/V'_{CO_2}) in tandem with V_D/V_T, just prior to the respiratory compensation point [14, 16]. In most healthy individuals, the V'_E/V'_{CO_2} ratio at the nadir and anaerobic threshold are often similar [6], and the nadir V'_E/V'_{CO_2} ratio may be of more clinical utility, since the V'_E/V'_{CO_2} ratio at the anaerobic threshold may not always be identified in clinical populations [46]. Not surprisingly, in healthy individuals at maximal exercise, the V'_E/V'_{CO_2} ratio is higher than the nadir V'_E/V'_{CO_2} ratio, because of hyperventilation secondary to excessive metabolic acidosis (figure 1).

Sun *et al*. [6] have created prediction equations for the nadir V'_E/V'_{CO_2} ratio and V'_E–V'_{CO_2} slope based on participant age (in years), sex (nadir only) and height (in cm):

$$\text{Nadir } V'_E/V'_{CO_2} = 27.94 + 0.108\ (\text{age}) + 0.97\ (\text{if female}) - 0.0376\ (\text{height}) \quad (5)$$

$$V'_E - V'_{CO_2}\text{slope} = 34.38 + 0.082\ (\text{age}) - 0.0723\ (\text{height}) \quad (6)$$

As demonstrated in these equations, V'_E/V'_{CO_2} (slope and nadir) increases progressively with age, and the nadir V'_E/V'_{CO_2} is slightly higher in females than in males [6]. These equations can be helpful in determining the normal response to exercise, and therefore were used in figure 1 to demonstrate the normal nadir V'_E/V'_{CO_2} ratio and V'_E–V'_{CO_2} slope response to exercise. Within the manuscript text, these reference equations were also used to evaluate the response in endurance-trained athletes, as well as in participants with asthma or obesity when normative control groups were not presented for comparison.

Ventilatory efficiency in endurance trained athletes

Endurance trained athletes typically achieve a maximum rate of oxygen consumption (V'_{O_2max}) that is 50–100% greater than normally active young healthy individuals [47], and as such the requirement for CO_2 clearance can become challenging [48]. To enable CO_2 clearance at high absolute metabolic rates, endurance athletes must achieve higher ventilation rates than healthy individuals of moderate fitness. In endurance trained athletes during submaximal exercise, ventilation is sufficient to maintain P_{aCO_2} and acid–base balance. However, some endurance trained athletes may demonstrate a ventilatory limitation at maximal exercise intensities, which could lead to inadequate compensatory hyperventilation and blunt the V'_E/V'_{CO_2} response [49–53].

Ventilatory responses to submaximal exercise

As endurance-trained athletes have superior cardiovascular conditioning, they typically demonstrate lower V'_E at a given submaximal work rate when compared to untrained individuals due to less reliance on anaerobic metabolism [54, 55]. However, these between-group (trained *versus* untrained) differences

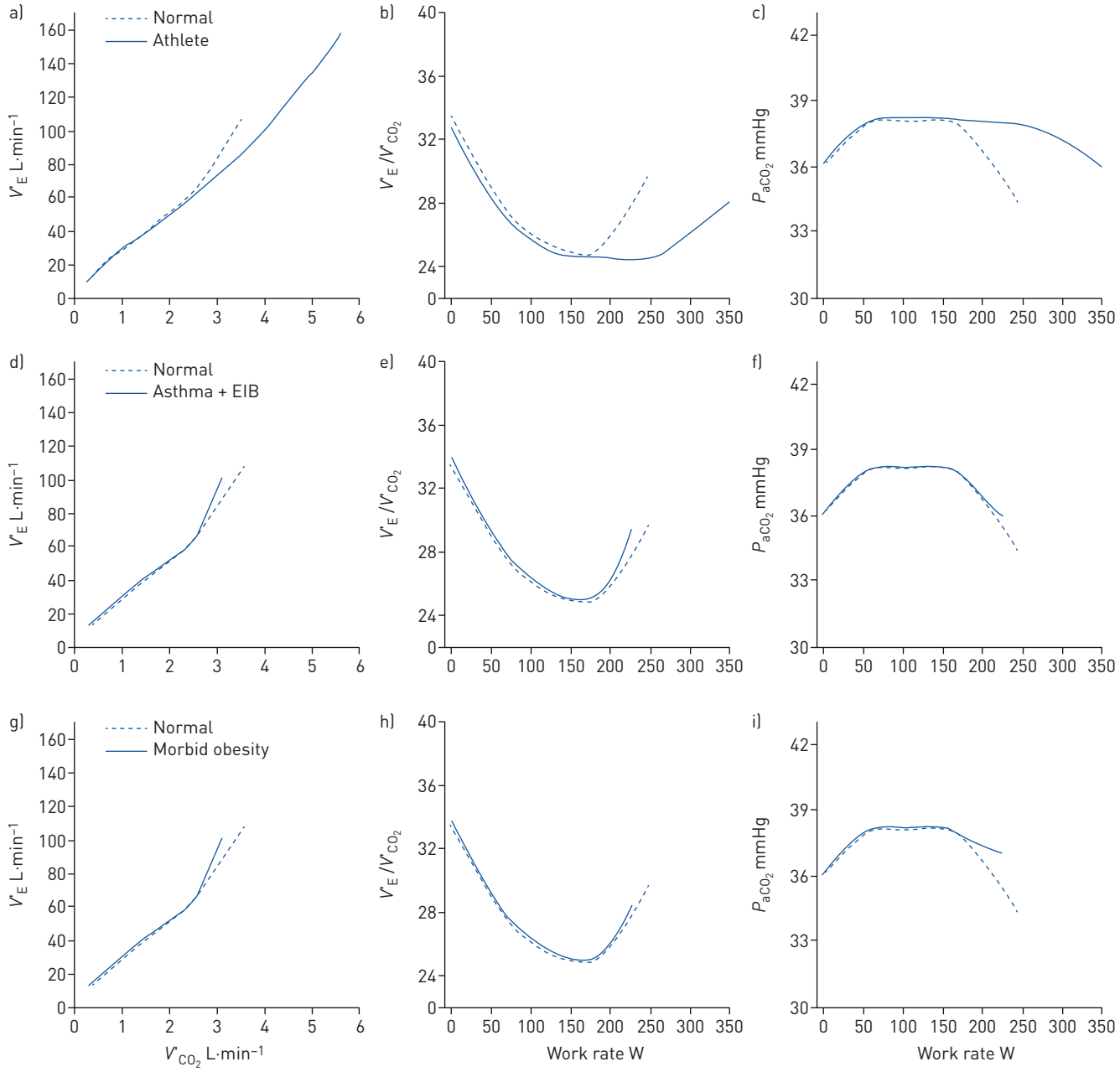

FIGURE 1 Representative ventilatory and gas exchange responses to incremental exercise in a–c) an endurance trained athlete, d–f) an asthmatic with exercise induced bronchoconstriction and g–i) an individual with morbid obesity, when compared to a healthy individual of average aerobic fitness. EIB: exercise-induced bronchoconstriction; V'_E: minute ventilation; V'_{CO_2}: carbon dioxide production; V'_E/V'_{CO_2}: ventilatory equivalent for carbon dioxide production; P_{aCO_2}: arterial partial pressure of carbon dioxide.

disappear when V'_E is normalised to metabolic rate (figure 1). Multiple studies have demonstrated no difference in V'_E/V'_{CO_2} in moderate-to-highly endurance trained male athletes (V'_{O_2max} 55–70 mL·kg^{-1}·min^{-1}) during submaximal exercise, when compared to individuals with normal to low aerobic fitness (V'_{O_2max} ~40 mL·kg^{-1}·min^{-1}) [56–59], or predicted values [6]. To our knowledge, there are no studies that compare V'_E/V'_{CO_2} slope, nadir and y-intercept values between trained and untrained individuals. Therefore, we analysed unpublished data from our laboratory, and found that the V'_E/V'_{CO_2} slope, nadir and y-intercept were similar between 16 endurance trained (V'_{O_2max} 67±7 mL·kg^{-1}·min^{-1}) and 16 untrained (V'_{O_2max} 43±4 mL·kg^{-1}·min^{-1}) age- and sex-matched healthy individuals (table 1). Although there are limited data directly comparing arterial blood gas derived parameters in trained *versus* untrained

TABLE 1 General ventilatory and pulmonary gas exchange responses to submaximal and maximal exercise in endurance trained athletes, asthmatics and obese when compared to normative values

Variable	Elite endurance trained athlete		Asthmatic	Obese	
	Male	Female		BMI 30–40 kg·m^{-2}	BMI>40 kg·m^{-2}
Submaximal exercise					
V'_E/V'_{CO_2} nadir	↔	↔	N/A	N/A	N/A
V'_E/V'_{CO_2} y-intercept	↔	↔	N/A	N/A	N/A
V'_E-to-V'_{CO_2} slope	↔	↔	N/A	↔	↔
V_D/V_T	↔	↔	↔	↔	↔
P_{aCO_2}	↔	↔	↔	↔	↔
Maximal exercise					
V'_E/V'_{CO_2} peak	↓	↓	↔ or ↓	↔	↓
V_D/V_T	↔	↔	↔	↔	↔
P_{aCO_2}	↑	↑	↔ or ↑	↔	↑

V'_E/V'_{CO_2}: minute ventilation relative to carbon dioxide production; V_D/V_T: total physiologic dead space as a proportion of tidal volume; P_{aCO_2}: arterial partial pressure of CO_2; N/A: not available. The arrows represent the direction of change compared to age and height matched normative values [6, 20, 33–36]. ↔: no difference; ↓: decrease; ↑: increase.

individuals, previous studies in elite endurance trained athletes with arterial blood sampling have shown that submaximal P_{aCO_2} and V_D/V_T values are similar to values observed in moderately trained healthy individuals [55, 60, 61], and are within normal ranges (table 1) [20, 33–36]. When combined, it is evident that the ventilatory response to submaximal exercise and therefore ventilatory efficiency is not altered by aerobic fitness in young, healthy individuals. Should an abnormal (lower or higher) V'_E/V'_{CO_2} response to submaximal exercise develop, further clinical investigation would be warranted (see the "Pulmonary gas exchange and ventilatory efficiency" section for explanation of potential mechanism(s)).

Ventilatory responses at maximal exercise

At high metabolic rates, elite endurance trained athletes may exhibit a blunted V'_E/V'_{CO_2} ratio at maximal exercise intensities [51, 53, 62–65]. Although data are limited, arterial blood gas-derived V_D/V_T values at maximal exercise are generally within normal ranges in endurance trained athletes [53, 64, 66], when compared to normative data (table 1) [33–36]. Some endurance trained athletes demonstrate an inadequate compensatory hyperventilatory response at maximal exercise, as P_{aCO_2} fails to drop <35 mmHg (figure 1) [50, 51, 53]. Importantly, the higher P_{aCO_2} typically observed in some endurance trained athletes is not necessarily the result of alveolar hypoventilation *per se*, but rather an inadequate compensatory hyperventilatory response to excessive metabolic acidosis (table 1) [20, 53].

Several mechanisms for inadequate compensatory hyperventilation in endurance trained individuals are possible. First, respiratory muscle fatigue: multiple studies have shown evidence of respiratory muscle fatigue during heavy exercise in healthy individuals [67–69]. However, experimental data linking respiratory muscle fatigue to inadequate hyperventilation are lacking. Second, altered chemoreflex function: previous work has examined central (V'_E response to hypercapnia) and peripheral (V'_E response to hypoxia) chemoreceptor function in athletes [53, 61, 63, 70–73]. However, findings are inconsistent, and it is therefore difficult to conclude that a blunted chemoreflex is predictive of an inadequate hyperventilatory response to exercise [20]. Third, mechanical ventilatory constraint: multiple studies have shown evidence of EFL and dynamic mechanical ventilatory constraint at near maximal ventilatory rates in young, trained healthy males and females [53, 62, 74]. Importantly, previous work has shown that when nitrogen is replaced by helium in the inspired gas (*i.e.* a less dense gas promoting greater airflow), endurance trained athletes achieve a higher V'_E and V'_E/V'_{CO_2}, and lower P_{aCO_2} at maximal exercise [64, 75, 76]. These experimental studies support the hypothesis that mechanical ventilatory constraint is a primary cause of inadequate hyperventilation in endurance trained athletes.

Because V'_E/V'_{CO_2} may be blunted in exceptional athletes at maximal exercise, it may be difficult to distinguish physiological from pathological responses. However, elevated V'_E/V'_{CO_2} responses to either submaximal or maximal exercise would be considered abnormal [6], and in such cases, potential cardiovascular or pulmonary abnormalities should be investigated.

In summary, the blunted hyperventilatory response to maximal exercise often observed in highly trained endurance athletes is most likely secondary to mechanical ventilatory constraint, although the potential contributions of respiratory muscle fatigue, and central and peripheral chemoreflexes cannot be excluded.

Sex differences in ventilatory efficiency in endurance trained athletes

It has been well documented that young healthy females have an elevated ventilatory response to submaximal exercise (V'_E/V'_{CO_2} nadir, slope and y-intercept) when compared to males [6, 77–80], secondary to increased dead space and alveolar hyperventilation [80–82]. Previous studies have shown that the increased dead space (V_D/V_T) in females is due to a more rapid and shallow breathing pattern. This breathing response adopted by females has been attributed to a compensatory strategy to minimise the total work of breathing because of smaller lungs [74, 82–84]. It is unclear whether ventilatory responses to submaximal exercise are different in endurance trained female athletes as compared to non endurance-trained females. Elite endurance trained male and female athletes have similar V'_E/V'_{CO_2} ratios at maximal exercise [49, 62]. Like males, some endurance trained female athletes experience EFL and mechanical ventilatory constraint at heavy exercise intensities, which can result in an inadequate hyperventilatory response (*i.e.* P_{aCO_2} >35 mmHg) and a blunted V'_E/V'_{CO_2} ratio at maximal exercise [49, 74, 82]. Similar to males, helium inhalation significantly increases the hyperventilatory response (higher V'_E and lower P_{aCO_2}) to maximal exercise in females [74]. In summary, these findings suggest that females generally have an elevated V'_E/V'_{CO_2} response to submaximal exercise when compared to males, although it is unclear if differences exist between trained and untrained females.

Ventilatory efficiency in patients with asthma

Asthma is a heterogenous disease characterised by symptoms such as wheezing, coughing, chest tightness and shortness of breath [85], with patients presenting with various degrees of bronchoconstriction, EFL, dynamic hyperinflation and respiratory muscle weakness [86]; all of which can contribute to heightened dyspnoea and exercise intolerance. Some studies have examined people with controlled to partly controlled asthma, who may or may not demonstrate exercise-induced bronchoconstriction (EIB; defined as a ⩾10% fall in forced expiratory volume in 1 s (FEV_1) from baseline following exercise [87]). International guidelines define well controlled asthma as: 1) no or minimal daytime asthma symptoms, 2) no night waking due to asthma symptoms, 3) no activity limitation (including exercise), and 4) no or minimal need for rescue medications [85]. It is common for patients with asthma to experience EIB, with EIB being especially prevalent in uncontrolled asthma [85]. Due to the heterogeneity of asthma, diagnosis can be challenging, especially when symptomatology and objective measures of lung function do not align [85, 88, 89]. This review will focus on studies evaluating patients with clinical symptoms and physiological confirmation of asthma with and without EIB [85].

Ventilatory responses to submaximal exercise

During submaximal exercise, patients with asthma breathe at a higher operating lung volume and adopt a rapid and shallow breathing pattern [90]. Despite the tachypnoeic breathing pattern, it appears that patients with asthma have a similar V'_E/V'_{CO_2} compared to healthy controls during submaximal exercise (figure 1) [90–95]. Further, V'_E/V'_{CO_2} in asthmatics is unaffected following an inhaled short-acting β_2-agonist [90]. To our knowledge, there are no studies that report y-intercept, slope or nadir V'_E/V'_{CO_2} in asthmatics. Importantly, arterial blood gas derived P_{aCO_2} and V_D/V_T during submaximal exercise in asthmatics are similar to healthy controls and normative values (table 1) [20, 33–36, 96–98]. When combined, it is evident that patients with controlled or partly controlled asthma (with and without EIB) have a normal ventilatory response during submaximal exercise. Therefore, deviation (reduction or increase) in submaximal V'_E/V'_{CO_2} responses from normal predicted values [6] would warrant further clinical investigation, and may be indicative of comorbid cardiovascular and/or pulmonary vascular abnormalities.

Ventilatory responses at maximal exercise

Several studies report V'_E/V'_{CO_2} at peak exercise in asthmatics. Many studies have reported a normal V'_E/V'_{CO_2} response (table 1) [90, 92, 93], while others demonstrated a blunted V'_E/V'_{CO_2} at peak exercise in asthmatics [98, 99]. Examining the patient characteristics appears to provide information as to why some asthmatics show a blunted V'_E/V'_{CO_2} response to maximal exercise, while others do not. In looking at the studies showing similar V'_E/V'_{CO_2} responses to controls, most of the asthmatics in these studies did not demonstrate EIB [90, 92]. In contrast, in the studies demonstrating a blunted V'_E/V'_{CO_2} response at peak exercise, most of the patients demonstrated EIB [98], or were categorised by the presence of EIB [99]. Indeed, Haverkamp *et al*. [99] compared asthmatics with and without EIB, and showed an appropriate hyperventilatory response (*i.e.* P_{aCO_2}<35 mmHg at peak) to high intensity constant load exercise in asthmatics without EIB, and an inappropriate hyperventilatory response to exercise in patients with EIB

(*i.e.* P_{aCO_2}>35 mmHg at peak). Combined, these findings suggest that a blunted V'_E/V'_{CO_2} response to exercise in asthma may be observed in those who demonstrate EIB (table 1 and figure 1).

A number of mechanisms for inadequate hyperventilation in asthmatics are possible including; respiratory muscle fatigue [86, 100, 101], decreased central and/or peripheral chemosensitivity [102–104], and EFL and respiratory mechanical constraint [98, 99, 105]. However, it is likely that respiratory mechanical constraint is the primary cause of inadequate hyperventilation, as previous work has nicely demonstrated that when airflow obstruction is reduced with inhaled corticosteroid therapy, V'_E/V'_{CO_2} at maximal exercise is increased, P_{aCO_2} reduced, and exercise tolerance improved in asthmatics [106]. Therefore, V'_E/V'_{CO_2} may be useful in monitoring therapy effectiveness in asthmatics. However, there is currently no indication on how V'_E/V'_{CO_2} pre-treatment may predict post-treatment outcomes.

Importantly, asthma has been shown to be associated with increased cardiovascular morbidity and mortality [107]. Therefore, careful interpretation of the V'_E/V'_{CO_2} response to exercise is encouraged in patients with asthma. While an elevated V'_E/V'_{CO_2} response to submaximal and/or maximal exercise could be due to a dysfunctional breathing pattern (*e.g.* hyperventilation syndrome [95]), it may be secondary to comorbid cardiovascular and/or pulmonary vascular abnormalities, and additional follow-up should be considered when a high V'_E/V'_{CO_2} response is observed in asthma.

When combined, it is evident that V'_E/V'_{CO_2} is similar during submaximal exercise in asthmatics as compared to non-asthmatics. However, V'_E/V'_{CO_2} at maximal exercise can be blunted in asthmatics, which is likely explained by mechanical ventilatory constraint secondary to EIB.

Ventilatory efficiency in patients with obesity

Based on BMI, individuals with obesity are often classified as mild/class I (30–34.99 $kg \cdot m^{-2}$), moderate/class II (35–39.99 $kg \cdot m^{-2}$) and morbid/class III (>40 $kg \cdot m^{-2}$) obesity. Exercise limitation is common in patients with obesity and the underlying mechanisms are complex and multifactorial, however, it is widely believed that respiratory abnormalities and elevated dyspnoea are important contributors.

Ventilatory responses to submaximal exercise

It is well established that ventilation is higher at rest and at any given work rate during incremental exercise in adults with obesity (even mild obesity) when compared to non-obese [108–112]. The increased ventilation in obesity reflects the higher metabolic cost (*i.e.* V'_{O_2} and V'_{CO_2}) of external work, which is primarily due to the increased energy requirement of lifting heavier limbs during weight-supported exercise (*i.e.* cycling) and, to a greater extent, weight-bearing exercise (*i.e.* walking) [108, 109, 111, 113, 114]. Additionally, the increased work and oxygen cost of breathing have been identified as potential contributors to the increased metabolic demand at rest and during exercise in obesity [109, 115–117]. Although sub-maximal exercise ventilation is consistently elevated at a given work rate in females and males with obesity compared to non-obese, the between-group differences in ventilation disappear when normalised to metabolic rate (*i.e.* V'_E/V'_{CO_2} *versus* work rate) (figure 1) [108, 118, 119].

Due to the extra mass loading on the thorax (direct result of extra adipose tissue), patients with obesity have reduced chest wall compliance and breathe at lower lung volumes [108, 120–123]. Further, individuals with obesity generally adopt a rapid and shallow breathing pattern to minimise the work of breathing, especially at higher ventilatory rates [108]. Despite the rapid and shallow breathing pattern, both arterial P_{CO_2} (or P_{ETCO_2}) and V_D/V_T are generally within normal ranges during submaximal exercise [23, 108, 113, 119, 124]. Further, multiple studies have reported a normal V'_E–V'_{CO_2} slope, even in morbid obesity, when compared to either non-obese control groups or normative values (table 1 and figure 1) [6, 108, 125–127]. However, one small study [128] in morbidly obese females (n=14, BMI: 49±7 $kg \cdot m^{-2}$) demonstrated a blunted V'_E–V'_{CO_2} slope, compared to non-obese controls, which suggests individuals nearing the super-obesity category (BMI>50 $kg \cdot m^{-2}$) may be prone to mechanical ventilatory constraints at submaximal exercise intensities. In general, deviation in submaximal V'_E/V'_{CO_2} responses from normal predicted values [6] may warrant further clinical investigation in patients with obesity. Specifically, should a patient show a higher than predicted V'_E/V'_{CO_2} response to submaximal exercise, cardiovascular and/or pulmonary abnormalities should be considered.

Ventilatory responses at maximal exercise

Although the V'_E/V'_{CO_2} response during submaximal exercise is relatively preserved in individuals with obesity, the ventilatory response during heavy to maximal exercise is more complex, and greater variability is often observed between different classifications of obesity. To our knowledge, there is no previous work

using arterial blood gas derived P_{aCO_2} during exercise in mild-moderate obesity. A few small studies reporting P_{ETCO_2} data would suggest that respiratory mechanical abnormalities do not impair people with mild-moderate obesity, as they generally show a normal hyperventilatory response at maximal exercise [108, 112].

Interestingly, in patients with morbid obesity, a divergent ventilatory response at maximal exercise has been identified (table 1 and figure 1). Using arterial blood gas sampling, multiple studies have shown inadequate compensatory hyperventilation (*i.e.* P_{aCO_2} between 35–38 mmHg) or an absence of compensatory hyperventilation (P_{aCO_2}>38 mmHg) at maximal exercise in males and females with morbid obesity [23, 111, 128–130]. The underlying mechanism(s) for the inadequate and/or absent hyperventilatory response in patients with morbid obesity is not fully understood. However, it is suggested the large amount of fat mass surrounding the chest-wall and diaphragm in patients with morbid obesity results in severe EFL and mechanical ventilatory constraint at high ventilatory rates [108]. The net effect is: 1) an inability to increase alveolar ventilation sufficiently to compensate for the increased metabolic acidosis at heavy exercise and, 2) premature exercise termination. This conclusion is supported by multiple studies demonstrating an increase in peak V'_E/V'_{CO_2} and reduced P_{aCO_2} and/or P_{ETCO_2} following bariatric surgery in patients with morbid obesity [124, 130]. As such, the change in V'_E/V'_{CO_2} observed at peak exercise may be a useful clinical tool when evaluating responses following interventions such as bariatric surgery.

Due to the increasing prevalence of obesity, and the multi-comorbid nature of the disease [131], the authors stress the importance of careful interpretation of ventilatory responses to submaximal exercise in these patients. Furthermore, because other known drivers of ventilation (*e.g.* elevated physiological dead space, arterial O_2 desaturation, altered baseline P_{aCO_2}, earlier metabolic acidosis) do not appear to be altered in patients with obesity [108, 111, 118, 119, 129, 132, 133], the presence of an elevated V'_E/V'_{CO_2} response to submaximal exercise is unlikely to be secondary to obesity itself, and may suggest comorbid cardiovascular and/or pulmonary abnormalities.

When combined, the obesity-related research indicates that V'_E/V'_{CO_2} during submaximal exercise is normal across all classifications of obesity, while V'_E/V'_{CO_2} at maximal exercise appears blunted in patients with morbid obesity secondary to mechanical ventilatory constraint.

Prognostic utility of V'_E/V'_{CO_2}

Although there is evidence that an elevated V'_E/V'_{CO_2} response to exercise is prognostic of mortality in conditions such as chronic heart failure, chronic obstructive pulmonary disease, and pulmonary hypertension [26, 134, 135], it is currently unknown if V'_E/V'_{CO_2} can be used as a prognostic tool in athletes, asthma or obesity. Further, there is little research demonstrating the prognostic value of a low or blunted V'_E/V'_{CO_2} response to exercise. However, the V'_E/V'_{CO_2} response to exercise can be a valuable tool and may help identify abnormal ventilatory responses to exercise or signal the presence of underlying cardiovascular and/or pulmonary disease.

Conclusion

V'_E/V'_{CO_2} can provide important information to evaluate the ventilatory response to exercise and help to determine underlying mechanism(s) of exercise intolerance. The purpose of this review article was to describe the ventilatory responses to exercise in healthy trained endurance athletes, patients with asthma, and patients with obesity. In summary, moderately trained athletes, asthmatics, and individuals with obesity have normal V'_E/V'_{CO_2} responses to submaximal exercise. Despite representing distinct health and disease states, highly endurance trained athletes, asthmatics with EIB, and individuals with morbid obesity can display inadequate hyperventilatory responses (*i.e.* blunted V'_E/V'_{CO_2}) at maximal exercise secondary to mechanical constraints on ventilation.

Provenance: Commissioned article, peer reviewed.

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. **No. 4:** Ward SA. Ventilation/carbon dioxide output relationships during exercise in health. *Eur Respir Rev* 2021; 30: 200160.

Author Contributions: All authors (S.É. Collins, D.B. Phillips, A.R. Brotto, Z.H. Rampuri and M.K. Stickland) contributed to manuscript writing and approved the final version of the manuscript.

Conflict of interest: None declared.

Support statement: Funding was provided from the Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada and the Lung Association of Alberta and Northwest Territories (M.K. Stickland). S.É. Collins was supported by a Canadian Respiratory Research Network Doctoral Studentship. D.B. Phillips was supported by a postdoctoral fellowship from the Natural Sciences and Engineering Research Council of Canada. Z.H. Rampuri was supported by an Alexander Graham Bell Canada Graduate Scholarship (Masters) from the Natural Sciences and Engineering Research Council of Canada. Funding information for this article has been deposited with the Crossref Funder Registry.

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