Impact of ageing and pregnancy on the minute ventilation/carbon dioxide production response to exercise

Michele R. Schaeffer1,2, Jordan A. Guenette1,2,3 and Dennis Jensen4,5,6

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Edited by Pierantonio Laveneziana and Paolo Palange

1Centre for Heart Lung Innovation, Providence Health Care Research Institute, The University of British Columbia, St. Paul’s Hospital, Vancouver, Canada. 2Dept of Physical Therapy, The University of British Columbia, Vancouver, Canada. 3School of Kinesiology, The University of British Columbia, Vancouver, Canada. 4Dept of Kinesiology and Physical Education, McGill University, Montréal, Canada. 5Research Institute of the McGill University Health Centre, Translational Research in Respiratory Diseases Program, Montréal, Canada. 6Research Centre for Physical Activity and Health, Faculty of Education, McGill University, Montréal, Canada.

Corresponding author: Jordan A. Guenette (jordan.guenette@hli.ubc.ca)

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The minute ventilation/carbon dioxide production response to exercise is elevated with advancing age and in healthy pregnancy due to increased dead space and lowering of the arterial partial pressure of carbon dioxide equilibrium point, respectively. https://bit.ly/2GJXm0o

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Abstract
Ventilatory efficiency can be evaluated using the relationship between minute ventilation ($V'_E$) and the rate of CO₂ production ($V'_CO₂$). In accordance with the modified alveolar ventilation equation, this relationship is determined by changes in dead space volume ($V_D$) and/or the arterial CO₂ tension ($P_{aCO₂}$) equilibrium point. In this review, we summarise the physiological factors that may account for normative ageing and pregnancy induced increases in $V'_E/V'_CO₂$ during exercise. Evidence suggests that age-related increases in $V_D$ and pregnancy-related decreases in the $P_{aCO₂}$ equilibrium point are mechanistically linked to the increased $V'_E/V'_CO₂$ during exercise. Importantly, the resultant increase in $V'_E/V'_CO₂$ (ratio or slope), with normal ageing or pregnancy, remains below the critical threshold for prognostic indication in cardiopulmonary disease, is not associated with increased risk of adverse health outcomes, and does not affect the respiratory system’s ability to fulfil its primary role of eliminating CO₂ and maintaining arterial oxygen saturation during exercise.

Introduction
The ventilatory response to exercise is well coordinated and matched to the rate of CO₂ production ($V'_CO₂$). The strength of the relationship between minute ventilation ($V'_E$) and $V'_CO₂$ is marked by relative homeostasis of the arterial CO₂ tension ($P_{aCO₂}$) even in the context of the large increases in $V'_CO₂$ that occur during exercise [1]. Ventilatory efficiency can be evaluated using this relationship, whereby an increase in $V'_E/V'_CO₂$ has been suggested to indicate less efficiency [2].

As summarised by the modified alveolar ventilation equation: $V_E=(V_{CO₂}×863)/(P_{aCO₂}×(1−V_D/V_T))$ (figure 1), $V'_E/V'_CO₂$ is dependent on both the $P_{aCO₂}$ equilibrium point and the fraction of dead space, which is expressed as the ratio of dead space volume to tidal volume ($V_D/V_T$). According to established models of ventilatory control [3–5], resting steady-state $V'_E$ and $P_{aCO₂}$ are determined by chemoreflex (central and peripheral) and non-chemoreflex (“wakefulness”) drives to breathe and their intersection with the metabolic hyperbola (figure 2), which represents the curvilinear relation between $V'_E$ and $P_{aCO₂}$ at any given $V_{CO₂}$ and $V_D/V_T$. This point of intersection, often referred to as the respiratory control system’s $P_{aCO₂}$ equilibrium point, is inversely
related to the \( V'_E/V'_{CO2} \) response to exercise at a constant \( V'_D/V'_T \). For example, at a \( V'_D/V'_T \) of 0.20, a decrease in the respiratory control system’s \( PaCO_2 \) equilibrium point from 40 mmHg to 32 mmHg would increase \( V'_E \) from \(~40\) to \(~50\) L·min\(^{-1}\) at a \( V'_E/V'_{CO2} \) of 1.5 L·min\(^{-1}\), which corresponds to moderate intensity exercise (figure 1). Accordingly, a lowering of the \( PaCO_2 \) equilibrium point, such as occurs during pregnancy, results in a higher \( V'_E/V'_{CO2} \) (e.g. at any given \( V'_D/V'_T \), \( V'_E/V'_{CO2} \) will increase as \( PaCO_2 \) decreases), while an increase in relative \( V'_D/V'_T \), such as occurs with normative ageing, results in a higher \( V'_E/V'_{CO2} \) (e.g. at any given \( PaCO_2 \), \( V'_E/V'_{CO2} \) will increase as \( V'_D/V'_T \) increases).

The three most common ways of assessing exercise ventilatory efficiency are: 1) using the \( V'_E/V'_{CO2} \) slope (i.e. \( \Delta V'_E/\Delta V'_{CO2} \)) in the aerobic working range; 2) the value of \( V'_E/V'_{CO2} \) at the anaerobic threshold (\( V'_E/V'_{CO2,AT}) \); and/or 3) the \( V'_E/V'_{CO2} \) nadir, which represents the lowest \( V'_E/V'_{CO2} \) during exercise. While the \( V'_E/V'_{CO2} \) nadir has been shown to be the most reproducible index of exercise ventilatory efficiency, it is nearly identical to \( V'_E/V'_{CO2,AT} \) for a given age and sex, and both are slightly higher than the \( V'_E/V'_{CO2} \) slope [6]. A \( V'_E/V'_{CO2} \) slope during exercise between 21–31 [6] and a \( V'_E/V'_{CO2} \) (\( V'_E/V'_{CO2,AT} \) or nadir) <34 [7] are considered normal. Of note, use of the \( V'_E/V'_{CO2} \) slope alone should be made with caution as it does not provide information on the orientation of this relationship relative to the \( V'_E \) axis [8]. Proper evaluation using this approach should also include the \( V'_E \) intercept. An additional methodological consideration is the subtraction of instrument dead space (e.g. mouthpiece, adapters, flow transducer, etc.) multiplied by the breathing frequency from the measured \( V'_E \), which, when unaccounted for, has been shown to artificially inflate both the \( V'_E/V'_{CO2} \) slope and intercept [6].

The assessment of \( V'_E/V'_{CO2} \) during cardiopulmonary exercise testing can distinguish pathologies as well as elucidate mechanisms of exertional dyspnoea [9]. With less ventilatory efficiency, mechanical ventilatory constraints may be attained at a lower \( V'_E \), and neural respiratory neural drive may be increased, both of

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**FIGURE 1** Minute ventilation (\( V'_E \)) required for various rates of metabolic production of carbon dioxide production (\( V'_{CO2} \)) as modified by the carbon dioxide tension (\( PaCO_2 \)) in the arterial blood and the physiological dead space volume to tidal volume ratio (\( V'_D/V'_T \)). Adapted and modified from [82] with permission from the publisher.

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which can contribute to dyspnoea and exercise intolerance. For example, an elevated $V′_{E}/V′_{CO2}$ in the context of a preserved $P_{aCO2}$ equilibrium point suggests high dead space ventilation ($V′_{D}$) due to ventilation–perfusion mismatching. A low $P_{aCO2}$ equilibrium point could be attributed to chronic respiratory alkalosis. Importantly, a lower ventilatory efficiency has been identified as a predictor of mortality for patients with cardiopulmonary disease including, but not limited to, COPD, pulmonary hypertension and chronic heart failure [10–12].

Given this guiding framework, the purpose of this narrative review is to summarise the physiological factors that may account for a higher $V′_{E}/V′_{CO2}$ during exercise with advancing age and in healthy pregnancy, both of which are progressive life stages.

Normal ageing

The respiratory system reaches maturity around 20–25 years, after which there is a progressive decline in pulmonary function [13]. Despite this regression, the respiratory system is capable of maintaining adequate pulmonary gas exchange throughout the lifespan in the absence of cardiopulmonary disease [13–15]. Significant structural changes to the lungs, airways, chest wall and respiratory muscles result in a lower ventilatory capacity in healthy individuals above the age of 60 years when compared to individuals aged 20–30 years [13] as demonstrated by the size and shape of their maximum expiratory flow–volume curves (figure 3) [16]. Accordingly, older individuals have a reduced ability to accommodate increases in ventilatory demand during exercise relative to their younger counterparts, and are subject to greater mechanical ventilatory constraints and associated exertional symptoms (i.e. dyspnoea) [17]. A more detailed summary of the implications of these age-related structural and functional changes to the respiratory system on the ventilatory response to exercise have been presented elsewhere [13].

Ventilatory efficiency is lower for any given work-rate during exercise [18, 19], and also when assessed as the $V′_{E}/V′_{CO2}$ slope [6, 8, 20–25], the $V′_{E}/V′_{CO2,AT}$ [6, 19, 23, 26] or the $V′_{E}/V′_{CO2}$ nadir [6] in healthy older compared to younger individuals. These observations are independent of cardiorespiratory fitness [27] and unrelated to oxygen saturation or metabolic acidosis [20, 21]. Lower ventilatory efficiency in
healthy older compared to younger individuals in the context of an isocapnic response to exercise supports the idea that the higher $V'_E/V'_CO2$ associated with normal ageing is a compensatory response to an increase in $V_D$ and not a lowering of the $P_{aCO2}$ equilibrium point [15, 20, 21, 28]. This is further supported by a widening of the difference in measured $P_{aCO2}$ and end-tidal CO2 tension ($P_{ETCO2}$) in healthy older individuals compared to their younger counterparts [29].

There is a greater non-uniformity of $V'_A$ relative to perfusion ($V'_A/Q'$) in healthy older compared to younger individuals [30–34]. The resultant increase in physiological dead space is likely the most significant contributor to the higher $V'_E/V'_CO2$ response to exercise observed in the former. However, the precise mechanism(s) responsible for the progressive rise in $V'_A/Q'$ inequality with age remains equivocal. Age-related loss in elastic recoil of the lungs causes the sigmoidal pressure-volume relationship of the lungs to shift to the right (i.e. increased lung compliance) [35], which can lead to dynamic narrowing or closure of the airways at lower lung volumes, reduced maximal expiratory flows and alveolar gas trapping [13]. Nonetheless, evidence does not support a role of decreased closing volume in the aged-related increase in $V'_A/Q'$ inequality [33]. The increase in diameter of the larger airways with normal ageing causes an ~55% greater anatomical dead space, assuming a dead space volume of 150 mL in a healthy younger individual [34]. However, even though the $V_D/V_T$ has been shown to be elevated in older individuals (~30 years old) compared with younger individuals (~60 years old) by 15–20%, abnormally high $V_D/V_T$ values are not observed [13]. The age-related increase in anatomical dead space is therefore unlikely to contribute meaningfully to the lower exercise ventilatory efficiency (higher $V'_E/V'_CO2$ response) in healthy older individuals compared with younger individuals [32]. Other potential contributors to an increased physiological dead space include the age-related losses in alveolar-capillary surface area [34] as well as pulmonary capillary blood volume [36]. In addition to an increased physiological dead space, we cannot discount potential age-related differences in neural, mechanical, or humoral stimuli in increasing $V'_E/V'_CO2$, which are known to stimulate $V'_E$ during exercise [20]. For example, there is evidence for factors linked to alterations in central motor-neuron drive [37, 38], regulation of muscle contraction as a result of fibre type shifts [39], and higher blood lactate concentrations [19] with advancing age. Importantly, despite the potential for greater ventilatory mechanical constraints and inefficiencies in gas exchange observed in healthy older individuals compared with younger individuals, the respiratory system nevertheless fulfills its primary role of eliminating CO2 and maintaining arterial oxygen saturation. Accordingly, the normal age-related decline in exercise ventilatory efficiency is generally not a primary cause of exercise limitation in older healthy individuals and is of little clinical significance [40].

The normal decline in exercise ventilatory efficiency with advancing age is more prominent in men than women [20, 24]. For example, Poulin et al. [20] showed that the slope of the $V'_E/V'_CO2$ response to exercise rises at a rate of 1.23% versus 0.93% per year in healthy men and women, respectively. Whether

![FIGURE 3](https://doi.org/10.1183/16000617.0225-2020)

FIGURE 3 Changes in the maximal expiratory flow–volume curve with normal ageing. Curves from an older (dashed line) and a younger individual (solid line), expressed as a percentage of vital capacity. TLC: total lung capacity; RV: residual volume. Reproduced from [14] with permission from the publisher.
this sex difference relates to a relatively larger increase in $V'_D$ or a lower $P_{aCO_2}$ equilibrium point in men compared with women has not been determined [24]. Interestingly, despite a slower decline with age, women tend to have a slightly higher $V'_E/V'_CO_2$ at rest compared to age-matched men [6, 23, 26, 41]. This higher $V'_E/V'_CO_2$ in women was shown to be significantly associated with a lower $P_{ETCO_2}$ rather than a more tachypnoeic breathing pattern [41]. Therefore, a relatively greater $V'_D$ in healthy women compared to men is an unlikely explanation. An alternative explanation is that leg strength is inversely related to $V'_E/V'_CO_2$ in healthy older women but not in men during exercise, independent of age and cardiorespiratory fitness [41]. Gonzalez et al. [41] therefore speculated that the lower muscular strength in women could result in a greater metabolic stress with attendant increased activation of group III and IV sensory afferents, which could stimulate a disproportionate increase in $V'_E$ relative to $V'_CO_2,$ as has been shown in people with heart failure [42–44] or chronic obstructive pulmonary disease [45]. Additionally, $V'_E/V'_CO_2$ is elevated in the presence of respiratory flow limitation (EFL) at higher levels of $V'_E$ during exercise [46], which reflects greater mechanical ventilatory constraints. Older individuals are more likely to develop EFL compared with younger individuals due to the loss of ventilatory capacity with normal ageing, and older women are more likely to develop EFL compared with older men due to relatively smaller lungs and disproportionately narrower airways [17]. Further research on the mechanisms of sex differences in ventilatory efficiency is warranted.

### Healthy pregnancy

Human pregnancy is characterised by a series of well-orchestrated progressive adaptations to several integrated physiological systems (i.e. respiratory, cardiovascular, metabolic, renal and thermoregulatory) that are initiated and maintained by gestational hormones, which are almost fully established by the end of the first trimester and are critical to fetal growth and development [47]. The respiratory effects of human pregnancy are well documented [48–51], and include adaptations in static and dynamic pulmonary mechanics as well as increases in the drive to breathe both at rest and during exercise. In this section of our review, we focus specifically on the physiological determinants of the exaggerated $V'_E/V'_CO_2$ response to exercise in healthy human pregnancy uncomplicated by co-existing pathology (e.g. pulmonary hypertension, pre-eclampsia).

Compared with the non-pregnant control condition, both $V'_E$ and $V'_{A}$ are higher by 3–5 L·min⁻¹ at rest during pregnancy [52–68]. Pregnancy-induced increases in $V'_E$ and $V'_{A}$ are proportionally greater than concomitant increases in $V'_CO_2$ [61, 65]. As a result, resting measures of $P_{aCO_2}$ and cerebrospinal fluid $P_{CO_2}$ ($P_{CSF-CO_2}$) are reduced by 6–10 mmHg: from ~38–40 mmHg to ~30–34 mmHg for $P_{aCO_2}$, and from ~41–47 mmHg to ~37–42 mmHg for $P_{CSF-CO_2}$ [52, 54–57, 59, 62, 65, 68–71]. This maternal hyperventilation and attendant respiratory alkalosis are only partially compensated for by the kidneys via lowering of plasma and cerebrospinal fluid (CSF) bicarbonate concentrations such that arterial and CSF hydrogen ion concentrations are reduced by 2–5 nEq·L⁻¹ at rest [52, 54–57, 59, 60, 65, 68, 70, 71]. According to more contemporary quantitative acid–base theory [72], pregnancy-induced reductions in arterial and CSF hydrogen ion concentrations reflect the alkalising effect of reductions in $P_{aCO_2}$ and $P_{CSF-CO_2}$, which are partially offset by the acidifying effect of reductions in plasma and CSF strong ion difference [54, 55, 57, 60, 69, 73], where the strong ion difference represents the concentration difference of strongly dissociated positive (e.g. sodium, potassium, calcium and magnesium) and negative ions (e.g. chloride and lactate) in solution.

A detailed description of the complex physiological mechanisms underlying maternal hyperventilation is beyond the scope of this review and has been presented elsewhere [47, 49, 73]. Briefly, evidence suggests that the hyperventilation and attendant hypocapnia/alkalosis of human pregnancy results from a complex interaction between alterations in acid–base balance (arterial and CSF) and several other factors that affect the control of breathing, including increased circulating levels of female sex steroid hormones (i.e. progesterone and oestrogen), decreased plasma osmolality, augmented circulating levels of angiotensin II and arginine vasopressin, increased non-chemoreflex (wakefulness) drives to breathe, increased central and peripheral chemoreflex sensitivity, increased $V'_CO_2,$ and decreased cerebral blood flow [52, 54, 55, 57, 60, 69, 74–78].

Jensen et al. [74] were the first to show that pregnancy-induced changes in arterial and CSF acid–base balance lowered the central chemoreflex’s ventilatory recruitment threshold for CO₂ (VRTCO₂), which subsequently decreased the respiratory control system’s resting $P_{aCO_2}$ equilibrium point from ~40 mmHg whilst non-pregnant to ~32 mmHg in the third pregnancy trimester (figure 4). In moving forward, the influence of these changes in the VRTCO₂ and $P_{aCO_2}$ equilibrium point on the $V'_E/V'_CO_2$ response to maternal exercise will be discussed.
There is universal agreement that the $V_E/V_{CO_2}$ response to both weight-bearing (e.g., treadmill walking) and weight-supported exercise (e.g. cycling) is elevated by as much as ~30% in the pregnant compared to non-pregnant state (figure 5) [52–59, 61, 62, 65–67, 69, 79] and largely unaffected by aerobic conditioning [64, 66, 79]. Typical values of the $V_E/V_{CO_2}$ slope during exercise in late pregnancy range from ~31–34 compared to postpartum values of ~26–28 (figure 5) [52, 63], while typical $V_E/V_{CO_2}$ values during exercise in late pregnancy compared to the non-pregnant control state range from: ~32–36 compared to ~27–30 at the ventilatory/anaerobic threshold [53, 63]; ~28–41 versus ~24–39 at any standardised submaximal exercise intensity (figure 5) [54–59, 62, 65, 67, 69]; and ~32–39 versus ~26–34 at peak exercise (figure 5) [53, 56, 58, 59, 61, 63]. As a consequence of the exaggerated $V_E/V_{CO_2}$ response to exercise, both $P_{ACO_2}$ and $P_{ETCO_2}$ are ~4–8 mmHg lower during maternal exercise [52, 54–57, 60, 62, 69, 79]. However, neither pregnancy nor advancing gestation has an effect on the exercise-induced change in $P_{ACO_2}$ or $P_{ETCO_2}$ from rest [52, 55, 57, 69]. The collective results of controlled longitudinal studies suggest that pregnancy-induced increases in the $V_E/V_{CO_2}$ response to exercise are evident by 7 weeks gestation and almost fully established by the end of the first trimester, with only modest progressive increases occurring thereafter in parallel with modest progressive decreases in the $P_{ACO_2}$ equilibrium point and its major physiological determinants [54, 58, 61, 63, 66, 67, 79].

Mechanistically, the exaggerated $V_E/V_{CO_2}$ response to exercise during pregnancy cannot be explained, in whole or in part, by concurrent pregnancy-induced increases in $V_D$ [65]. For example, PIVARNIK et al. [65] calculated $V_D$ from direct measures of $P_{ACO_2}$ obtained via radial artery cannulation at rest and during both constant-load cycling (at 50 and 75 Watts) and treadmill walking exercise (4.0 km·h⁻¹ at 2.5% and 12% grade) in seven healthy normal primigravid women studied late in the third trimester and again ~3 months postpartum. In that study, $V_E$, $V_A$ and $V_E/V_{CO_2}$ were significantly increased at rest (by ~4 L·min⁻¹, ~3 L·min⁻¹ and ~6 units, respectively) and during exercise (by ~8–13 L·min⁻¹, ~8–10 L·min⁻¹ and ~3–8 units, respectively) in late pregnancy compared to postpartum, despite no statistically significant effect of pregnancy status or exercise condition on $V_D$. The notion that the exaggerated $V_E/V_{CO_2}$ response to exercise during pregnancy is not mechanistically linked to increased $V_D$ is further supported, albeit

![Figure 4: Physiological determinants of the pregnancy-induced decrease in the respiratory control systems’ resting arterial carbon dioxide tension ($P_{ACO_2}$) equilibrium point, where open circles and closed stars represent predicted and measured equilibrium point values, respectively. (i.e. intersection between minute ventilation–$P_{ACO_2}$ response curve and the metabolic hyperbola). Briefly, pregnancy-induced reductions in the respiratory control systems’ resting $P_{ACO_2}$ equilibrium point are due primarily to reductions in the central chemoreflex ventilatory recruitment threshold for CO₂ that occurs in conjunction with pregnancy-induced changes in arterial and cerebrospinal fluid acid-base balance. TM₃: third pregnancy trimester; PP: postpartum; $P_{ao_2}$: arterial oxygen tension. Reproduced from [74] with permission from the publisher.](image-url)
indirectly, by an apparent lack of effect of pregnancy and advancing gestation on pulmonary diffusing
capacity for carbon monoxide [56, 77, 80, 81].

In the setting of an unchanged $V'_{D}$ during maternal exercise, the modified alveolar ventilation equation
predicts that pregnancy-induced changes in the respiratory control systems' $P_{aCO_2}$ equilibrium point (and
its physiological determinants) are most likely responsible for the increased $V'E/V'CO_2$ response to exercise
during pregnancy. Indeed, a study of 25 healthy women found that the magnitude of the
pregnancy-induced increase in the $V'E/V'CO_2$ response to exercise was inversely related to the magnitude of
fall in the VRTCO₂ and, by extension, the respiratory control systems' $P_{aCO_2}$ equilibrium point [52] (figure 5).

By all accounts, an exaggerated $V'E/V'CO_2$ response to exercise is a normal physiological adaptation that
accompanies healthy human pregnancy and that is of little clinical significance. However, to our
knowledge, no study has examined the impact of comorbid conditions on the $V'E/V'CO_2$ response to
maternal exercise and whether pathophysiological increases in the $V'E/V'CO_2$ response to exercise above and
beyond those expected in a normal pregnancy predict adverse maternal and/or fetal health outcomes. It is
certainly reasonable to assume that any comorbid condition that has an adverse effect on cardiac,
pulmonary and/or circulatory function (e.g. pulmonary arterial hypertension, heart failure, cystic fibrosis,
interstitial lung disease, chronic kidney disease) would be associated with an abnormally high $V'E/V'CO_2$
response to maternal exercise. Further research is needed in this regard. Moreover, we are unaware of

FIGURE 5 Effect of pregnancy on the ventilatory equivalent for carbon dioxide ($V'/V'CO_2$) response to symptom-limited incremental cycle exercise
testing and physiological correlates of change in the exaggerated $V'/V'CO_2$ response. Data points are mean±SEM at rest, at standardised submaximal
power outputs during exercise, and at peak exercise. PP: postpartum; TM3: third pregnancy trimester; $V'$: minute ventilation; $V'CO_2$: carbon dioxide
production; $\triangle$: pregnancy-induced change (TM3 minus PP); VRTCO₂: ventilatory recruitment threshold for CO₂; $P_{aCO_2}$: arterial carbon dioxide tension.
*: $p<0.05$ versus PP. Adapted and modified from [52] with permission from the publisher.
studies that have examined the potential use of cardiopulmonary exercise testing with measurement of $V'_E/V'_{CO2}$ for early detection and diagnosis of potentially adverse pregnancy-induced adaptations in cardiac, pulmonary and/or circulatory function. Again, it is reasonable to hypothesise that a $V'_E/V'_{CO2}$ response to exercise above and beyond that expected for an otherwise healthy pregnant woman might help identify the existence of pregnancy related cardiopulmonary complication(s), especially those that might increase $V'_E/V'_{CO2}$ by increasing $V_D/V_T$ (e.g. abnormally high pulmonary vascular resistance due to pulmonary hypertension, abnormally low cardiac output due left ventricular dysfunction) in the setting of a $P_{aCO2}$ that is within the normal expected range.

Conclusion

The ventilatory equivalent for CO2 ($V'_E/V'_{CO2}$) is an index of ventilatory efficiency that is determined by changes in $V_D$ and/or $P_{aCO2}$. While the $V'_E/V'_{CO2}$ response to exercise is higher with normal ageing and during healthy pregnancy, these are anticipated consequences of age-related increases in $V_D$ and pregnancy-related decreases in the $P_{aCO2}$ equilibrium point. Importantly, the resultant increase in $V'_E/V'_{CO2}$ during exercise is not in the pathological range (i.e. identified as being associated with increased risk of adverse health outcomes, including premature death), and on average, is well below the critical threshold identified for prognostic indication in cardiopulmonary disease.

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References

1 Cooper DM, Kaplan MR, Baumgarten L, et al. Coupling of ventilation and CO2 production during exercise in children. *Pediatr Res* 1987; 21: 568–572.
2 Forster HV, Pan LG. Breathing during exercise: demands, regulation, limitations. *Adv Exp Med Biol* 1988; 227: 257–276.
3 Duffin J. The chemoreflex control of breathing and its measurement. *Can J Anaesth* 1990; 37: 933–942.
4 Duffin J. Role of acid-base balance in the chemoreflex control of breathing. *J Appl Physiol* 2005; 99: 2255–2265.
5 Duffin J, Mohan RM, Vasiliou P, et al. A model of the chemoreflex control of breathing in humans: model parameters measurement. *Respir Physiol* 2000; 120: 13–26.
6 Sun XG, Hansen JE, Garatachea N, et al. Ventilatory efficiency during exercise in healthy subjects. *Am J Respir Crit Care Med* 2002; 166: 1443–1448.
7 ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Crit Care* 2003; 167: 211–277.
8 McConnell AK, Davies CT. A comparison of the ventilatory responses to exercise of elderly and younger humans. *J Gerontol* 1992; 47: B137–B141.
9 Stickland MK, Butcher SJ, Marciniuk DD, et al. Assessing exercise limitation using cardiopulmonary exercise testing. *Pulm Med* 2012; 2012: 824901.
10 Neder JA, Alharbi A, Berton DC, et al. Exercise ventilatory inefficiency adds to lung function in predicting mortality in COPD. *COPD* 2016; 13: 416–424.
11 Wensel R, Francis DP, Meyer FJ, et al. Incremental prognostic value of cardiopulmonary exercise testing and resting haemodynamics in pulmonary arterial hypertension. *Int J Cardiol* 2013; 167: 1193–1198.
12 Chua TP, Ponikowski P, Harrington D, et al. Clinical correlates and prognostic significance of the ventilatory response to exercise in chronic heart failure. *J Am Coll Cardiol* 1997; 29: 1585–1590.
45 Gagnon P, Bussieres JS, Ribeiro F, et al. Influences of spinal anesthesia on exercise tolerance in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2012; 186: 606–615.

46 Deruelle F, Nourry C, Mucci P, et al. Difference in breathing strategies during exercise between trained elderly men and women. Scand J Med Sci Sports 2008; 18: 213–220.

47 Weissgerber TL, Wolfe LA. Physiological adaptation in early human pregnancy: adaptation to balance maternal-fetal demands. Appl Physiol Nutr Metab 2006; 31: 1–11.

48 Hegewald MJ, Crapo RO. Respiratory physiology in pregnancy. Clin Chest Med 2011; 32: 1–13.

49 Jensen D, Webb KA, O’Donnell DE. Chemical and mechanical adaptations of the respiratory system at rest and during exercise in human pregnancy. Appl Physiol Nutr Metab 2007; 32: 1239–1250.

50 Jensen D, Ofir D, O’Donnell DE. Effects of pregnancy, obesity and aging on the intensity of perceived breathlessness during exercise in healthy humans. Respir Physiol Neurobiol 2009; 167: 87–100.

51 Jensen D, O’Donnell DE. Pregnancy/Obesity. In: Mahler DA, O’Donnell DE, eds. Dyspnea: Mechanisms, Measurement, and Management. Boca Raton, FL, CRC Press, 2014; pp. 39–54.

52 Jensen D, Webb KA, O’Donnell DE. The increased ventilatory response to exercise in pregnancy reflects alterations in the respiratory control systems ventilatory threshold for CO₂. Respir Physiol Neurobiol 2010; 171: 75–82.

53 Davenport MH, Steinback CD, Mottola MF. Impact of pregnancy and obesity on cardiorespiratory responses during weight-bearing exercise. Respir Physiol Neurobiol 2009; 167: 341–347.

54 Weissgerber TL, Wolfe LA, Hopkins WG, et al. Serial respiratory adaptations and an alternate hypothesis of respiratory control in human pregnancy. Respir Physiol Neurobiol 2006; 153: 39–53.

55 Heenan AP, Wolfe LA. Plasma acid-base regulation above and below ventilatory threshold in late gestation. J Appl Physiol 2000; 88: 149–157.

56 Jensen D, Webb KA, Davies GA, et al. Mechanical ventilatory constraints during incremental cycle exercise in human pregnancy: implications for respiratory sensation. J Physiol 2008; 586: 4735–4750.

57 Charlesworth SA, Wolfe LA, Davies GA. Physicochemical analysis of acid-base responses to prolonged moderate exercise in late gestation. Appl Physiol Nutr Metab 2006; 31: 744–752.

58 Jensen D, Webb KA, Wolfe LA, et al. Effects of human pregnancy and advancing gestation on respiratory discomfort during exercise. Respir Physiol Neurobiol 2007; 156: 85–93.

59 Jensen D, Webb KA, Davies GA, et al. Mechanisms of activity-related breathlessness in healthy human pregnancy. Eur J Appl Physiol 2009; 106: 253–265.

60 Kemp JG, Greer FA, Wolfe LA. Acid-base regulation after maximal exercise testing in late gestation. J Appl Physiol 1997; 83: 644–651.

61 Lotgering FK, van Doorn MB, Struijk PC, et al. Maximal aerobic exercise in pregnant women: heart rate, O₂ consumption, CO₂ production, and ventilation. J Appl Physiol 1991; 70: 1016–1023.

62 Heenan AP, Wolfe LA, Davies GA. Maximal exercise testing in late gestation: maternal responses. Obstet Gynecol 2001; 97: 127–134.

63 Lotgering FK, Struijk PC, van Doorn MB, et al. Anaerobic threshold and respiratory compensation in pregnant women. J Appl Physiol 1995; 78: 1772–1777.

64 McAuley SE, Jensen D, McGrath MJ, et al. Effects of human pregnancy and aerobic conditioning on alveolar gas exchange during exercise. Can J Physiol Pharmacol 2005; 83: 625–633.

65 Pivarnik JM, Lee W, Spillman T, et al. Maternal respiration and blood gases during aerobic exercise performed at moderate altitude. Med Sci Sports Exerc 1992; 24: 868–872.

66 Wolfe LA, Walker RM, Bonen A, et al. Effects of pregnancy and chronic exercise on respiratory responses to graded exercise. J Appl Physiol 1994; 76: 1928–1936.

67 Pivarnik JM, Ayres NA, Mauer MB, et al. Effects of maternal aerobic fitness on cardiorespiratory responses to exercise. Med Sci Sports Exerc 1993; 25: 993–998.

68 Templeton A, Kelman GR. Maternal blood-gases (P₂O₅–P₂O₅), physiological shunt and VD/VT in normal pregnancy. Br J Anaesth 1976; 48: 1001–1004.

69 Heenan AP, Wolfe LA. Plasma osmolality and the strong ion difference predict respiratory adaptations in pregnant and nonpregnant women. Can J Physiol Pharmacol 2003; 81: 839–847.

70 Hirabayashi Y, Shimizu R, Saitoh K, et al. Acid-base state of cerebrospinal fluid during pregnancy and its effect on spread of spinal anaesthesia. Br J Anaesth 1996; 77: 352–355.

71 Machida H. Influence of progesterone on arterial blood and CSF acid-base balance in women. J Appl Physiol Respir Environ Exerc Physiol 1981; 51: 1433–1436.

72 Stewart PA. Modern quantitative acid-base chemistry. Can J Physiol Pharmacol 1983; 61: 1444–1461.

73 Wolfe LA, Kemp JG, Heenan AP, et al. Acid-base regulation and control of ventilation in human pregnancy. Can J Physiol Pharmacol 1998; 76: 815–827.

74 Jensen D, Duffin J, Lam YM, et al. Physiological mechanisms of hyperventilation during human pregnancy. Respir Physiol Neurobiol 2008; 161: 76–86.

75 Moore LG, Brodeur P, Chumbe O, et al. Maternal hypoxic ventilatory response, ventilation, and infant birth weight at 4,300 m. J Appl Physiol 1986; 60: 1401–1406.
Moore LG, McCullough RE, Weil JV. Increased HVR in pregnancy: relationship to hormonal and metabolic changes. J Appl Physiol 1987; 62: 158–163.

Garcia-Rio F, Pino JM, Gomez L, et al. Regulation of breathing and perception of dyspnea in healthy pregnant women. Chest 1996; 110: 446–453.

Jensen D, Wolfe LA, Slatkovska L, et al. Effects of human pregnancy on the ventilatory chemoreflex response to carbon dioxide. Am J Physiol Regul Integr Comp Physiol 2005; 288: R1369–R1375.

Ohtake PJ, Wolfe LA. Physical conditioning attenuates respiratory responses to steady-state exercise in late gestation. Med Sci Sports Exerc 1998; 30: 17–27.

McAuliffe F, Kametas N, Rafferty GF, et al. Pulmonary diffusing capacity in pregnancy at sea level and at high altitude. Respir Physiol Neurobiol 2003; 134: 85–92.

McAuliffe F, Kametas N, Costello J, et al. Respiratory function in singleton and twin pregnancy. BJOG 2002; 109: 765–769.

Wasserman K, Whipp BJ. Exercise physiology in health and disease. Am Rev Respir Dis 1975; 112: 219–249.