The increased ventilatory response to exercise in pregnancy reflects alterations in the respiratory control systems ventilatory recruitment threshold for CO₂

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Abstract

We tested the hypothesis that the magnitude of the pregnancy-induced increase in exercise hyperpnea is predictable based on the level at which PaCO₂ is regulated at rest. We performed a detailed retrospective analysis of previous data from 25 healthy young women who performed exercise and rebreathing tests in the third trimester (TM3; 36.5 ± 0.2 weeks gestation; mean ± SEM) and again 20.4 ± 1.7 weeks post-partum (PP). At rest, arterialized venous blood was obtained for the estimation of PaCO₂, [H⁺] and [HCO₃⁻]; and serum progesterone ([P₄]) and 17β-estradiol ([E₂]) concentrations. Duffin’s modified hyperoxic rebreathing procedure was used to evaluate changes in central ventilatory chemoreflex control characteristics at rest. Breath-by-breath ventilatory and gas exchange variables were measured at rest and during symptom-limited incremental cycle exercise tests. At rest in TM3 compared with PP: PaCO₂, [H⁺], [HCO₃⁻] and the central chemoreflex ventilatory recruitment threshold for P CO₂ (VRTCO₂) decreased, while ventilation (VE), [P₄], [E₂] and central chemoreflex sensitivity (VES) increased (all p < 0.001). The slope of the linear relation between VE and VCO₂ during exercise was significantly higher in TM3 vs. PP (31.2 ± 0.6 vs. 27.5 ± 0.5, p < 0.001). The magnitude of this change in the VE–VCO₂ slope correlated significantly with concurrent reductions in each of the VRTCO₂ (R² = 0.619, p < 0.001), PaCO₂ (R² = 0.203, p = 0.024) and [HCO₃⁻] (R² = 0.189, p = 0.030); and was independent (p > 0.05) of changes in [P₄], [E₂] and VES. In conclusion, the increased ventilatory response to exercise in pregnancy can be explained, in large part, by reductions in the respiratory control system’s resting P CO₂ equilibrium point as manifest primarily by reductions in the VRT CO₂.

1. Introduction

Human pregnancy is characterized by significant increases in minute ventilation (VE) with attendant reductions in arterial P CO₂ (PaCO₂ by 5–10 mmHg), plasma bicarbonate ([HCO₃⁻]) and arterial hydrogen ion concentrations ([H⁺]) both at rest and during standard submaximal exercise (Wolfe et al., 1998; Jensen et al., 2007). The physiological mechanisms of the increased ventilatory response to exercise in pregnancy, however, remain poorly understood, largely understudied and represent the primary focus of this study.

According to the “Oxford model” of ventilatory control (Lloyd and Cunningham, 1963; Cunningham et al., 1986), resting steady-state VE and PaCO₂ are determined by chemoreflex and ‘other’ non-chemoreflex drives to breathe and their interaction with the metabolic hyperbola (Fig. 1), which represents the relationship between VE and PaCO₂ at any given metabolic rate (VCO₂), as defined by the alveolar gas equation for CO₂: VE = (VCO₂ / PaCO₂) x (1 – VD/VT), where V̇O₂/V̇R represents dead space ventilation. Because PaCO₂ remains relatively unchanged from rest through moderate intensity exercise in healthy humans (Wasserman et al., 1973, 2005; Oren et al., 1981; Dempsey et al., 2006), including pregnant women (Pivarnik et al., 1992; Heenan and Wolfe, 2000, 2003; Charlesworth et al., 2006; Weissgerber et al., 2006), it can be considered an ‘equilibrium point’ with respect to ventilatory control. Thus, the alveolar gas equation predicts that, in the setting of an unchanged V̇O₂/V̇R, the ventilatory response to any given increment in V̇C O₂ during exercise will increase as the respiratory control system’s resting P CO₂ equilibrium point decreases. In other words, the ventilatory response to exercise would be greater when resting PaCO₂ is regulated at 30 mmHg vs. 40 mmHg.

Indeed, Oren et al. (1981, 1991) previously showed that induction of a chronic partially compensated metabolic acidosis, which decreased resting PaCO₂ by ~7.5 mmHg, secondary to a parallel leftward shift (i.e., reduced threshold with no change in the slope or sensitivity) of the central ventilatory chemoreflex response curve to exogenous CO₂ at rest, significantly increased VE by ~10–30% at
any given submaximal $\dot{V}CO_2$ during both incremental and constant-load cycle exercise in healthy men. Similarly, both Skatrud et al. (1978) and Robertson et al. (1982) found that administration of the synthetic progestin, medroxyprogesterone acetate, to healthy men significantly (i) decreased arterial, end-tidal and cerebrospinal fluid $PCO_2$ by $\sim 5–6$ mmHg at rest, despite no change in resting measures of central or peripheral chemoreflex sensitivity; and (ii) increased the ventilatory response to mild ($V_{PCO_2} = 1–2$ L/min) and heavy ($V_{PCO_2} = 2–3$ L/min) intensity cycle exercise by $\sim 15–20\%$ and $\sim 25\%$, respectively.

We recently demonstrated that the hyperventilation and attendant hypocapnia/alkalosis of human pregnancy at rest results from a complex interaction between alterations in acid–base balance and other factors that directly affect $\dot{V}E$, including increased non-chemoreflex and central chemoreflex drives to breathe (Jensen et al., 2008a). More specifically, we provided evidence to suggest that pregnancy-induced reductions in the respiratory control systems resting $PCO_2$ equilibrium point could be largely accounted for by reductions in the central chemoreflex ventilatory recruitment threshold for CO2 ($VRTCO_2$; refer to Fig. 4 in Jensen et al., 2008a), which in turn reflected the effects of long-term compensatory acid–base adjustments (i.e., reduced $[HCO_3^-]$) on the relationship between the measured, $P_{CO_2}$, and actual, $[H^+]$, stimulus to the respiratory chemoreceptors.

The purpose of the current study, therefore, was to extend our previous work by testing the hypothesis that the magnitude of the increased ventilatory response to exercise in pregnancy can be explained, at least in part, by a reduction in the respiratory control systems resting $PCO_2$ equilibrium point as manifest primarily by a decrease in the $VRTCO_2$. To this end, we performed a comprehensive retrospective analysis of data from a group of 25 healthy women who underwent both exercise and rebreathing tests in the third trimester (TM3) and again 4–5 months PP. Visit 1 included blood taking and Duffin’s modified hyperoxic rebreathing test. Visit 2 included pulmonary function tests and a symptom-limited incremental cycle exercise test. Subjects abstained from exercise, caffeine, heavy meals and alcohol for $\geq 12$ h before TM3 and PP tests, which were conducted at the same time of day for each subject. Neither menstrual cycle phase (Slatkovska et al., 2006) nor oral contraceptive use (Nettlefold et al., 2007) affects the ventilatory response to hypercapnia in healthy young women. Therefore, no attempt was made to control for menstrual cycle status, lactation and/or oral contraceptive use in PP.

2. Methods

2.1. Subjects

Subjects included 25 healthy women, 20–40 years, parity $\leq 2$ and experiencing uncomplicated singleton pregnancies. These women had no history of smoking or cardiovascular, respiratory, neuromuscular, musculoskeletal, metabolic and/or haematological disease; and were not taking medications (other than prenatal vitamins) that could affect the ventilatory and/or perceptual response to hyperoxic–hypercapnia. Subjects were recruited via posted announcements, newspaper advertisements and contact with local health care providers. Prior to participation, subjects completed the Physical Activity Readiness Medical Examination for Pregnancy (http://www.csep.ca) and obtained medical clearance from their primary caregiver. Approximately 1–2 weeks prior to TM3 tests, subjects underwent a fetal ultrasound and biophysical profile examination to ensure appropriate fetal growth, behaviour and amniotic fluid volume. The study protocol and consent form were approved by the Queen’s University and Affiliated Teaching Hospitals Health Sciences Human Research Ethics Board in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

2.2. Experimental design

This was a controlled, longitudinal study in which subjects completed two experimental visits (conducted $<5$ days apart) in the TM3 and again 4–5 months PP. Visit 1 included blood taking and Duffin’s modified hyperoxic rebreathing test. Visit 2 included pulmonary function tests and a symptom-limited incremental cycle exercise test. Subjects abstained from exercise, caffeine, heavy meals and alcohol for $\geq 12$ h before TM3 and PP tests, which were conducted at the same time of day for each subject. Neither menstrual cycle phase (Slatkovska et al., 2006) nor oral contraceptive use (Nettlefold et al., 2007) affects the ventilatory response to hypercapnia in healthy young women. Therefore, no attempt was made to control for menstrual cycle status, lactation and/or oral contraceptive use in PP.

2.3. Blood biochemistry

Arterialized venous blood was collected and analyzed in accordance with previously published methods (Jensen et al., 2008a) for the estimation of resting arterial $PCO_2$ ($P_{ACO_2}$), hydrogen ion ($[H^+]$) and bicarbonate ($[HCO_3^-]$) concentrations, as well as for serum progesterone ($[P_4]$) and 17β-estradiol ($[E_2]$) concentrations.

2.4. Duffin’s modified hyperoxic rebreathing procedure

Duffin’s modified hyperoxic rebreathing procedure (Duffin et al., 2000) was used to evaluate the effects of human pregnancy on central chemoreflex and non-chemoreflex ventilatory control characteristics. The modified rebreathing procedure, apparatus, data acquisition and analysis software have been described in detail elsewhere (Jensen et al., 2008a).

Briefly, before rebreathing trials, subjects voluntarily hyper-ventilated room air for 5 min to reduce end-tidal $P_{CO_2}$ (PETCO2) between 19 and 23 mmHg. Following hyperventilation, subjects were switched from breathing room air to a 15 L rebreathing bag containing 10 L of a hyperoxic–hypercapnic gas mixture (24% O2, 6% CO2, N2 balanced). Rebreathing began with 3–5 deep breaths causing rapid equilibration of the $PCO_2$ in the rebreathing bag, lungs and arterial blood with that of the mixed-venous blood. Equilibration was verified by the observance of a plateau in PETCO2 and was a prerequisite for continuing the test. Following equilibra-
ventilation, PaCO2, arterialized venous PCO2; [H+], arterialized venous hydrogen ion concentration; [HCO3−], plasma bicarbonate concentration; VRT CO2, ventilatory recruitment threshold for CO2; ˙VES, chemoreflex sensitivity.

Modified hyperoxic rebreathing responses

<table>
<thead>
<tr>
<th>Blood biochemistry</th>
<th>TM3 (36.5 ± 0.2 weeks)</th>
<th>PP (20.4 ± 1.7 weeks)</th>
<th>Δ (TM3 – PP)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaCO2 (mmHg)</td>
<td>32.0 ± 0.4</td>
<td>40.3 ± 0.5</td>
<td>–8.3 ± 0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>[H+] (mequiv/L)</td>
<td>36.2 ± 0.2</td>
<td>38.5 ± 0.3</td>
<td>–2.3 ± 0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>[HCO3−] (mequiv/L)</td>
<td>21.4 ± 0.2</td>
<td>25.2 ± 0.3</td>
<td>–3.8 ± 0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Progesterone (nmol/L)</td>
<td>916 ± 89</td>
<td>915 ± 89</td>
<td>1.2 ± 0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>17β-Estradiol (pmol/L)</td>
<td>103,496 ± 28,468</td>
<td>103,353 ± 28,468</td>
<td>143 ± 42</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. PP, post-partum; TM3, third trimester; Δ, pregnancy-induced change; V0, metabolic rate of oxygen consumption; Tvent, ventilatory threshold; VE, minute ventilation; PaCO2, arterialized venous PCO2; [H+], arterIALIZED venous hydrogen ion concentration; [HCO3−], plasma bicarbonate concentration; VEB, sub-VRTCO2 ventilation, estimating non-chemoreflex drives to breathe; VRTCO2, ventilatory recruitment threshold for CO2; VES, chemoreflex sensitivity.

Table 1

Subject characteristics, blood biochemistry and modified rebreathing parameters.

<table>
<thead>
<tr>
<th>Subject characteristics</th>
<th>TM3 (36.5 ± 0.2 weeks)</th>
<th>PP (20.4 ± 1.7 weeks)</th>
<th>Δ (TM3 – PP)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.6 ± 0.8</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163.3 ± 1.4</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Body mass (kg)</td>
<td>77.2 ± 2.3</td>
<td>66.2 ± 2.3</td>
<td>11.0 ± 0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.5 ± 0.6</td>
<td>24.7 ± 0.7</td>
<td>4.2 ± 0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak V02 [L/min] (% predicted)</td>
<td>1.97 ± 0.07 (108 ± 3)</td>
<td>1.96 ± 0.08 (107 ± 4)</td>
<td>0.01 ± 0.04 (1 ± 2)</td>
<td>0.716</td>
</tr>
<tr>
<td>Peak cycle work rate (W) [% predicted]</td>
<td>141 ± 5 (98 ± 3)</td>
<td>147 ± 5 (103 ± 3)</td>
<td>–6 ± 3 (–4 ± 2)</td>
<td>0.031</td>
</tr>
<tr>
<td>Duration of loaded pedalling (min)</td>
<td>10.9 ± 0.4</td>
<td>11.4 ± 0.4</td>
<td>–0.5 ± 0.2</td>
<td>0.020</td>
</tr>
<tr>
<td>V02 at Tvent (L/min)</td>
<td>1.07 ± 0.03</td>
<td>0.99 ± 0.03</td>
<td>0.08 ± 0.03</td>
<td>0.005</td>
</tr>
</tbody>
</table>

During rebreathing, PETCO2 increased progressively from hypo- to hypercapnia while isoaix was maintained at a hyperoxic end- tidal PO2 (PETO2) of 150 mmHg by providing a computer-controlled flow of 100% O2 to the rebreathing bag. Rebreathing was terminated when VE exceeded 100 L/min; PETCO2 exceeded 60 mmHg; and/or subject discomfort. Fetal heart rate was monitored and recorded electronically before, during and immediately after TM3 experiments as previously described (Fraser et al., 2008).

During rebreathing, subjects were comfortably seated, wore nose clips and breathed through a mouthpiece connected to a 3-way manual directional valve (Model 2100a; Hans Rudolph, Inc., Kansas City, MO) that permitted switching from room air to the rebreathing bag. PETCO2 and PETCO2 were measured continuously at the mouth using a respiratory mass spectrometer (Perkin Elmer MGA 1100). VE was measured using a low resistance bi-directional volume turbine (VMM-2A; Alpha Technologies, Laguna Niguel, CA) and expressed in units adjusted to BTPS. The rebreathing system was calibrated with precision analyzed gases of known concentrations and a 3 L volume syringe prior to each test.

Analysis and interpretation of the ventilatory response to Duffin’s modified rebreathing procedure has been described in detail elsewhere (Duffin et al., 2000; Jensen et al., 2008a). Briefly, the PETCO2, at which VE increased with progressive increases in PETCO2 during rebreathing was identified as the VRTCO2. The ventilatory response below and above the VRT CO2 was taken as an estimate of non-chemoreflex drives to breathe (VEB) and chemoreflex sensitivity (VES), respectively. We assumed that the VRTCO2 and VES parameters originated from the central chemoreflex alone since hyperoxia effectively silences the peripheral chemoreflex response to CO2 in most humans (Cunningham, 1987).

We recently reported between-day intraclass correlation coefficients of 0.867, 0.823 and 0.782 for hyperoxic VEB, VRTCO2 and VES, respectively, indicating excellent test-retest reliability of Duffin’s modified hyperoxic rebreathing procedure in healthy humans (Jensen et al., 2010).

2.5. Cardiopulmonary exercise testing

Incremental exercise tests were conducted on an electronically braked cycle ergometer (Ergometrics 800S; SensorMedics, Yorba Linda, CA) by use of a cardiopulmonary exercise testing system (Vmax229d; SensorMedics) in accordance with previously published methods (Jensen et al., 2008b). Exercise tests consisted of a steady-state resting period of at least 6-min followed by 25 watt increases in cycle work rate every 2-min to the point of symptom-limitation. Standard cardiorespiratory and breathing pattern parameters (e.g., VE, oxygen uptake (V02), carbon dioxide production (VCO2), PETCO2, PETO2) were collected on a breath-by-breath basis at rest and during exercise as previously described (Jensen et al., 2008b).

2.6. Analysis of exercise endpoints

All breath-by-breath measurements were averaged in 30-s intervals at rest and during exercise. Pre-exercise rest was defined as the steady-state period after at least 3 min of breathing on the mouthpiece while seated on the cycle ergometer at rest before exercise was initiated: cardiorespiratory measurements were averaged over the last 30-s of this period. The ventilatory threshold (Tvent) was identified and verified individually using the V-slope and dual criterion methods (Beaver et al., 1986; Wasserman et al., 2005). Peak exercise was defined as the last 30-s of loaded pedalling: cardiorespiratory measurements were averaged over this time period. Peak work rate was defined as the highest cycle work rate that the subject was able to maintain for at least 30-s; exercise endurance time was defined as the duration of loaded pedalling.

Logering et al. (1995) observed a linear relationship between VE and VCO2 during incremental cycle exercise below the respiratory compensation point at both TM3 and PP in a group of 33 healthy women with similar physical characteristics as those studied here. In the current study, a respiratory compensation point was identified in a minority of women at TM3 (8/25) and PP (11/25); 7 of these at both measurement times. For simplicity, therefore, we modeled the slope of the relation between VE and VCO2 using the 30-s averaged data from rest through to end-exercise for each subject.

2.7. Statistical analysis

The effects of human pregnancy on measured parameters were examined using paired t-tests (SigmaStat for Windows Version
from TM3 to PP, respectively.

3. Results

Twenty-five healthy, young, non-smoking, regularly active women with normal baseline pulmonary function as determined by routine spirometry (FEV1 = 99 ± 2% predicted; FEV1/FVC = 101 ± 2% predicted) participated in experimental testing at 36.5 ± 0.2 weeks gestation and again 20.4 ± 1.7 weeks post-partum (Table 1). Sixteen women were nulliparous, seven were primiparous and two were para 2. Body mass, body mass index, serum [P4] and [E2] decreased, while resting PacO2, [H+] and [HCO3−] increased from TM3 to PP (Table 1). Mean serum [P4] and [E2] values at PP were not significantly different (p > 0.05) than those previously reported from our laboratory in a group of 14 healthy eumenorrheic women in the follicular phase of their menstrual cycle (Slatkovska et al., 2006), suggesting that women had returned to their non-pregnant control state.

3.1. Rebreathing responses

Mean pregnancy-induced changes in the ventilatory response to Duffin’s modified hyperoxic rebreathing test are presented in Table 1, with a typical response from a representative subject illustrated in Fig. 2. The VRTCO2 increased by 7.0 ± 0.8 mmHg, while VEB and VES decreased by 2.0 ± 0.9 L/min and 2.42 ± 0.41 L/min/mmHg from TM3 to PP, respectively.

3.2. Physiological responses to exercise

Peak work rate and the duration of loaded pedalling were modestly, but significantly reduced in TM3 vs. PP; nevertheless, VO2 at Tvent was consistently higher, while VO2 at end-exercise was not significantly different in TM3 compared with PP (Table 1). Ventilatory and gas exchange responses at rest and during exercise are presented in Fig. 3. The slope of the relation between VE and VCO2 during exercise was significantly higher in TM3 vs. PP (31.2 ± 0.6 vs. 27.5 ± 0.5, p < 0.00001). Throughout exercise in TM3 compared with PP, VE increased as a result of an increase in tidal volume with no change in breathing frequency; the ventilatory equivalents for O2 (VE/VO2) and CO2 (VE/VCO2) increased, while PETCO2 decreased and PETO2 increased, with little/no associated change in estimated Vd/Vt and arterial blood O2 saturation as measured by finger pulse oximeter (data not shown).

3.3. Correlates of change

As illustrated in Fig. 4, the magnitude of the pregnancy-induced increase in the VE–VCO2 slope during exercise correlated significantly with concurrent reductions in PacO2, VRTCO2, and [HCO3−]; and were largely independent of changes in VEB, VES, [P4] and [E2] (R2 = 0.009, p = 0.652). Furthermore, pregnancy-induced reductions in the VRTCO2 correlated significantly with the fall in [HCO3−] (R2 = 0.212, p = 0.021).

4. Discussion

The main findings of this study support the following conclusions: (1) the hyperventilatory response to maternal exercise could not be easily explained by alterations in metabolic rate, dead space ventilation and/or central chemoreflex sensitivity; and (2) the increased ventilatory response to exercise in late pregnancy was associated with reductions in the respiratory chemoreflex control systems ventilatory recruitment threshold for CO2, which serves to decrease the regulated level of PacO2 at rest and during exercise.

In accordance with the results of many previous studies (Pivarnik et al., 1991, 1992; Wolfe et al., 1994; Lotgering et al., 1995, 1998; Ohtake and Wolfe, 1998; Heenan and Wolfe, 2000, 2003; Charlesworth et al., 2006; Weissgerber et al., 2006; Davenport et al., 2009), VE was consistently increased (with attendant reductions in PETCO2) both at rest (by 2.22 ± 0.41 L/min) and during exercise (by 9.32 ± 1.60 L/min at the highest equivalent work rate of 122 ± 4 W) in TM3 compared with PP (Fig. 3), despite little/no change in VCO2 (Fig. 3) and/or aerobic working capacity (Table 1). As a result, the slope of the relation between VE and VCO2 – an index of ventilatory drive – during exercise was significantly increased by ~13.5% during pregnancy (Fig. 3). Furthermore, resting measures of PacO2, [HCO3−] and [H+] increased (Table 1), while central chemoreflex and non-chemoreflex drives to breathe decreased from TM3 to PP (Table 1; Fig. 2). Collectively, these findings confirm the presence of maternal alveolar hyperventilation and a partially compensated respiratory alkalosis.

The alveolar gas equation for CO2, VE = (VCO2 × 863)/(Paco2 × [1 − Vd/Vt]), permits examination into the factors responsible for a given change in resting and/or exercise VE, including VCO2, PacO2 and Vd/Vt. The present study results do not support a role for increased VCO2 and/or Vd/Vt in the hyperventilatory response to maternal exercise: VE/VCO2 relationships were significantly increased, while PETCO2 and estimated Vd/Vt were significantly reduced and remained relatively unchanged, respectively, throughout exercise in TM3 compared with PP (Fig. 3). By exclusion, pregnancy-induced reductions in PacO2 and its physiological determinants must be contributory.

The alveolar gas equation for CO2 (above) predicts an inverse relationship between resting PacO2 and the ventilatory response to exercise; that is, as the regulated level of PacO2 decreases the ventilatory response to exercise increases. As previously discussed, resting steady-state VE and PacO2 depend on chemoreflex and non-chemoreflex drives to breathe and their intersection with the metabolic hyperbola (Fig. 1). Thus, any change in the respiratory control systems resting PCO2 equilibrium point may be accounted

![Fig. 2](https://www.example.com/fig2.png) Effect of human pregnancy on the ventilatory response to Duffin’s modified hyperoxic rebreathing procedure in a representative subject. Note the pregnancy-induced decrease of the ventilatory recruitment threshold for carbon dioxide as well as the increased ventilatory response below and above this threshold. TM3, third trimester; PP, post-partum; PETCO2, end-tidal partial pressure of carbon dioxide.
Fig. 3. Effects of human pregnancy on ventilatory, breathing pattern, metabolic and pulmonary gas exchange responses to symptom-limited incremental cycle exercise. Data points are mean ± SEM values at rest, at standardized submaximal cycle work rates and at peak exercise. TM3, third trimester; PP, post-partum; VE, minute ventilation; VCO₂, metabolic rate of carbon dioxide production; VE/VCO₂, ventilatory equivalent for carbon dioxide; PETCO₂, end-tidal partial pressure of carbon dioxide; VO₂, metabolic rate of oxygen consumption; VE/VO₂, ventilatory equivalent for oxygen; PETO₂, end-tidal partial pressure of oxygen; Vd/Vt, dead space ventilation. * p<0.05 TM3 versus PP.
Fig. 4. Physiological correlates of the pregnancy-induced change (Δ) in the slope of VE-VCO2 relationship during exercise. VE, minute ventilation; VCO2, metabolic rate of carbon dioxide production; VEB, sub-VRTCO2 ventilation, estimating non-chemoreflex drives to breathe; VRTCO2, ventilatory recruitment threshold for CO2; VES, chemoreflex sensitivity; PAO2, arterialized venous PO2; [HCO3−], plasma bicarbonate concentration; [P4], serum progesterone concentration.

for by a change in any one or combination of VEB, VES, VRTCO2, and VCO2. In reality, however, even large increases in VES, such as those observed during pregnancy in this study (Table 1; Fig. 2), will have only minor effects on resting PAO2 (and thus exercise VE) due to the close proximity of the metabolic hyperbola to the VRTCO2 (Fig. 1). This likely accounts for the lack of correlation between resting measures of chemoreflex sensitivity (VES) and the ventilatory response to exercise observed in this study (Fig. 4) as well as many previously published studies (Skatrud et al., 1978; Bradley et al., 1980; Oren et al., 1981; Mahler et al., 1982; Robertson et al., 1982; Heigenhauser et al., 1983; Menitove et al., 1984; Katayama et al., 2002; Foster et al., 2006; Sheel et al., 2006).

In contrast to the sensitivity parameter, however, even small decreases in the VRTCO2 will result in disproportionately large reductions in resting PAO2 (with attendant increases in exercise VE), because the metabolic hyperbola is fairly flat at the point of intersection between it and the VE-PAO2 response curve (Fig. 1). The VRTCO2 measured directly using Duffin’s modified rebreathing technique provides a robust physiological estimate of the respiratory chemoreflex control systems ventilatory recruitment threshold for CO2. Measurement of this parameter is almost completely independent of both VEB and VES, and has recently been shown to be highly reproducible: mean within-subject, between-day coefficients of variation were <4% and between-day interclass correlation coefficients were >0.80 (Jensen et al., 2010).

In this study, resting PAO2 and the VRTCO2 were consistently and similarly reduced by ~8.5 and ~7 mmHg in TM3 compared with PP, respectively (Table 1; Fig. 2). We recently demonstrated that the alveolar hyperventilation of human pregnancy and the attendant respiratory alkalosis can be explained, in large part, by reductions in the VRTCO2, which in turn fundamentally reflects the impact of long-term compensatory acid–base adjustments (e.g., reduced [HCO3−]) on the relationship between the measured, PCO2, and actual, [H+], stimulus to the respiratory chemoreceptors (Jensen et al., 2008a).

It follows that the increased ventilatory response to exercise in TM3 compared with PP (Fig. 3) is at least partly due to reductions in resting PAO2 (Table 1) as manifest primarily by decreases in the VRTCO2 (Table 1; Fig. 2), secondary to the effects of a reduced [HCO3−] (Table 1) on PCO2-[H+] relationships in chemosensitive
areas of the brain. Significant correlations between (i) the magnitude of the pregnancy-induced increase in the $\text{VE} - \text{VCO}_2$ slope during exercise with concurrent reductions in the $\text{VRTCO}_2$, $\text{PaCO}_2$, and $[\text{HCO}_3^-]$ (Fig. 4) and (ii) the magnitude of the increase in the $\text{VRTCO}_2$ from TM$_3$ to PP with concomitant increases in $[\text{HCO}_3^-]$ support this contention.

These observations extend our previous work (Jensen et al., 2008a) and suggest, for the first time, that the magnitude of the increased ventilatory response to exercise in pregnancy is predictable based on the fall in the VRTCO$_2$, that occurs in conjunction with a chronic partially compensated respiratory alkalosis. This theory is bolstered by the results of Oren et al. (1981, 1991) who demonstrated that induction of a chronic partially compensated metabolic acidosis, which reduced resting $\text{PaCO}_2$ by ~7.5 mmHg, secondary to a reduction in the threshold with no associated change in the sensitivity of the central chemoreflex response to $\text{CO}_2$ at rest, significantly increased (vs. control) the ventilatory response to both incremental and constant-load cycle exercise in healthy men.

4.1. Limitations

As reviewed in detail elsewhere (Mateika and Duffin, 1995; Kaufman and Forster, 1996; Haouzi et al., 2004; Bell, 2006; Haouzi, 2006), the physiological mechanisms of exercise hyperpnea are complex and multifactorial. Thus, we cannot rule out the possibility that alterations in (i) feedforward (cortical or behavioural) drives to breathe; (ii) sensory feedback information from respiratory mechano- and metaboreceptors in the lungs, airways and respiratory musculature, secondary to progressive thoraco-abdominal distortion and/or increased tidal volume expansion; (iii) central integration of feedback information from respiratory and peripheral locomotor muscle mechano- and metaboreceptors; (iv) thermoregulation; and/or (v) the magnitude of the exercise-induced change in central and/or peripheral chemoreflex control characteristics contributed, at least in part, to the exaggerated ventilatory response to exercise during pregnancy. Furthermore, alterations in lifestyle (e.g., diet, habitual physical activity levels, sleep schedule) not strictly controlled for between TM$_3$ and PP tests may have contributed to our results. Our data do not permit examination into the relative importance of these factors. Although increases in the ventilatory response to exercise in pregnancy appear to reflect reductions in the VRTCO$_2$, we make this claim cautiously as it is based on correlative rather than causative evidence.

4.2. Summary

The results of this study support our contention that the increased ventilatory response to exercise in pregnancy can be at least partly explained by a reduction in the respiratory control systems resting $\text{PaCO}_2$ equilibrium point as manifest primarily by a decrease in the VRTCO$_2$. The implication of these novel results is that variability in the ventilatory response to exercise and the attendant perceived breathlessness among healthy pregnant women can be predicted by the inter-individual variation in the VRTCO$_2$ measured directly using Duffin’s modified rebreathing procedure.

Acknowledgements

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References

Duffin, J., 2006. Reflexes controlling circulatory, ventilatory and respiratory musculature, secondary to progressive thoraco-abdominal distortion and/or increased tidal volume expansion; (iii) central integration of feedback information from respiratory and peripheral locomotor muscle mechano- and metaboreceptors; (iv) thermoregulation; and/or (v) the magnitude of the exercise-induced change in central and/or peripheral chemoreflex control characteristics contributed, at least in part, to the exaggerated ventilatory response to exercise during pregnancy. Furthermore, alterations in lifestyle (e.g., diet, habitual physical activity levels, sleep schedule) not strictly controlled for between TM$_3$ and PP tests may have contributed to our results. Our data do not permit examination into the relative importance of these factors. Although increases in the ventilatory response to exercise in pregnancy appear to reflect reductions in the VRTCO$_2$, we make this claim cautiously as it is based on correlative rather than causative evidence.

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