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The increased ventilatory response to exercise in pregnancy reflects alterations in the respiratory control systems ventilatory recruitment threshold for CO_2

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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 Pa_{CO_2} 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 (TM_3; 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 Pa_{CO_2}, $[H^+]$ and $[HCO_3^-]$; and serum progesterone ($[P_4]$) and 17β-estradiol ($[E_2]$) 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 TM_3 compared with PP: Pa_{CO_2}, $[H^+]$, $[HCO_3^-]$ and the central chemoreflex ventilatory recruitment threshold for P_{CO_2} (VRT_{CO_2}) decreased, while ventilation ($\dot{V}E$), $[P_4]$, $[E_2]$ and central chemoreflex sensitivity ($\dot{V}ES$) increased (all $p \leq 0.001$). The slope of the linear relation between $\dot{V}E$ and $\dot{V}_{CO_2}$ during exercise was significantly higher in TM_3 vs. PP (31.2 ± 0.6 vs. 27.5 ± 0.5, $p < 0.001$). The magnitude of this change in the $\dot{V}E$–$\dot{V}_{CO_2}$ slope correlated significantly with concurrent reductions in each of the VRT_{CO_2} ($R^2 = 0.619$, $p < 0.001$), Pa_{CO_2} ($R^2 = 0.203$, $p = 0.024$) and $[HCO_3^-]$ ($R^2 = 0.189$, $p = 0.030$); and was independent ($p > 0.05$) of changes in $[P_4]$, $[E_2]$ and $\dot{V}ES$. 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_{CO_2} equilibrium point as manifest primarily by reductions in the VRT_{CO_2}.

1. Introduction

Human pregnancy is characterized by significant increases in minute ventilation ($\dot{V}E$) with attendant reductions in arterial P_{CO_2} (Pa_{CO_2} by 5–10 mmHg), plasma bicarbonate ($[HCO_3^-]$) 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 $\dot{V}E$ and Pa_{CO_2} are determined by chemoreflex and '*other*' non-chemoreflex drives to breathe and their intersection with the metabolic hyperbola (Fig. 1), which represents the relationship between $\dot{V}E$ and Pa_{CO_2} at any given metabolic rate ($\dot{V}_{CO_2}$), as defined by the alveolar gas equation for CO_2: $\dot{V}E = (\dot{V}_{CO_2} \times 863)/(Pa_{CO_2} \times [1 - VD/VT])$, where V_D/V_T represents dead space ventilation. Because Pa_{CO_2} 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 V_D/V_T, the ventilatory response to any given increment in $\dot{V}_{CO_2}$ during exercise will increase as the respiratory control systems *resting* P_{CO_2} equilibrium point decreases. In other words, the ventilatory response to exercise would be greater when resting Pa_{CO_2} 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 Pa_{CO_2} 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 CO_2 at rest, significantly increased $\dot{V}E$ by ~10–30% at

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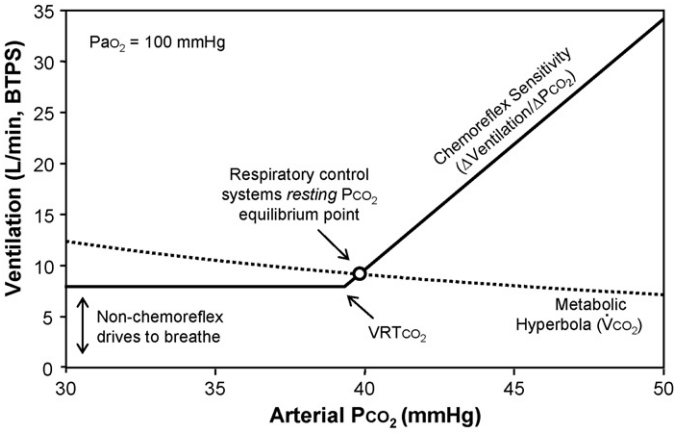

Fig. 1. Graphical representation of the determinants of the respiratory control systems *resting* P_{CO_2} equilibrium point. Briefly, resting steady-state minute ventilation and arterial P_{CO_2} depend on chemoreflex as well as '*other*' non-chemoreflex drives to breathe and their intersection with the metabolic hyperbola, which represents the relationship between ventilation and arterial P_{CO_2} at a constant metabolic rate of carbon dioxide production ($\dot{V}_{CO_2}$). Pa_{O_2}, partial pressure of oxygen in arterial blood; VRT_{CO_2}, ventilatory recruitment threshold for carbon dioxide; P_{CO_2}, partial pressure of carbon dioxide; Δ, change.

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 P_{CO_2} by ~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 ($\dot{V}_{CO_2}$ = 1–2 L/min) and heavy ($\dot{V}_{CO_2}$ = 2–3 L/min) intensity cycle exercise by ~15–20% and ~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* P_{CO_2} equilibrium point could be largely accounted for by reductions in the central chemoreflex ventilatory recruitment threshold for CO_2 (VRT_{CO_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* P_{CO_2} equilibrium point as manifest primarily by a decrease in the VRT_{CO_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 (TM_3) and again ~5 months post-partum (PP) as part of a recently published study from our laboratory designed to elucidate the physiological mechanism(s) of activity-related breathlessness in pregnancy (Jensen et al., 2009). To our knowledge, the present study is the first to examine the inter-relationships between the increased ventilatory response to (i) central chemoreflex stimulation by progressive hyperoxic–hypercapnia and (ii) symptom-limited incremental cycle exercise during pregnancy.

2. Methods

2.1. Subjects

Subjects included 25 healthy women, 20–40 years, parity ≤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 TM_3 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 TM_3 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 ≥12 h before TM_3 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 P_{CO_2} (Pa_{CO_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 hyperventilated room air for 5-min to reduce end-tidal P_{CO_2} (PET_{CO_2}) 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% O_2, 6% CO_2, N_2 balanced). Rebreathing began with 3–5 deep breaths causing rapid equilibration of the P_{CO_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 PET_{CO_2} and was a prerequisite for continuing the test. Following equilibra-