The impact of human pregnancy on perceptual responses to chemoreflex vs. exercise stimulation of ventilation: A retrospective analysis

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Abstract

We examined the impact of human pregnancy on breathlessness intensity at matched levels of ventilation (VE) during isoxic hyperoxic CO₂ rebreathing and incremental cycle exercise tests in 21 healthy women in the third trimester (TM 3) and again ~5 months post-partum (PP). Pregnancy had no significant (P>0.05) effect on the slope or threshold of the breathlessness intensity–VE relationship during both exercise and rebreathing. By contrast, the slope of the breathlessness intensity–VE relationship was significantly higher, while the threshold of this relationship was consistently lower during rebreathing vs. exercise (both P<0.05), regardless of pregnancy status (P>0.05). As a result, breathlessness intensity was markedly higher at any given VE (e.g., by ~4 Borg units at 40 L/min) during rebreathing vs. exercise, regardless of pregnancy status. Inter-subject variation in breathlessness intensity–VE slopes during exercise was not associated with inter-subject variation in breathlessness intensity–VE slopes during rebreathing or with increased central chemoreflex responsiveness during pregnancy (both P>0.05). In conclusion, the intensity of perceived breathlessness for a given VE depends, at least in part, on the nature and source of increased central respiratory motor command output, independent of pregnancy status; and pregnancy-induced increases in activity-related breathlessness cannot be easily explained by increased central chemoreflex responsiveness.

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1. Introduction

Breathlessness, the subjective experience of breathing discomfort, is a common complaint of as many as 75% of healthy pregnant women, particularly during physical activity (Milne et al., 1978; Moore et al., 1987). The mechanism(s) of gestational breathlessness, however, are only partially understood but alterations in respiratory mechanical/muscular function (Gilroy et al., 1988; Contreras et al., 1991; Garcia-Rio et al., 1997) and chemoreflex drives to breathe (Moore et al., 1987; Garcia-Rio et al., 1996) may be involved.

We recently reported that neither pregnancy nor advancing gestation altered the relationship between increasing breathlessness intensity ratings and increasing ventilation (VE) during incremental cycle exercise (Jensen et al., 2007, 2008b, 2009b). We concluded that (i) respiratory mechanical/muscular factors (which would increase breathlessness intensity at a given VE) are not a major source of breathlessness in pregnancy and (ii) gestational breathlessness reflects the awareness of increased VE and contractile respiratory muscle effort that accompanies the increased central motor command output to the respiratory muscles (as sensed by increased central corollary discharge to the somatosensory cortex). This latter interpretation, however, may be overly simplistic as it does not allow for the possibility that breathlessness intensity for a given VE and contractile respiratory muscle effort may vary depending on the nature and source (reflex/medullary or voluntary/motor cortical) of increased central respiratory motor command output and attendant corollary discharge. Indeed, there is evidence to suggest that the intensity of perceived breathlessness in humans is higher when a greater portion of a given VE is achieved reflexively vs. motor cortically. For example, humans exposed to a hypercapnic ventilatory stimulus at rest report greater breathlessness intensity at matched levels of VE compared with exercise or voluntary hyperventilation (Stark et al., 1981; Adams et al., 1985a,b; Chonan et al., 1990).

In light of these observations, the objectives of the present study were to (i) advance our understanding of the role of pregnancy-induced increases in central chemoreflex responsiveness in the genesis of gestational breathlessness and (ii) examine the effects of human pregnancy on breathlessness intensity at matched levels of VE during hyperoxic–hypercapnia compared with exercise (that is, during increased central chemoreflex vs. increased motor cortical stimulation of VE). We took advantage of an opportunity to address these pre-specified study objectives by conducting a detailed
retrospective analysis of selected data from a group of 27 healthy women who participated in a recently published study from our laboratory (Jensen et al., 2009b) and in whom measured perceptual responses to both incremental cycle exercise and Duffin's modified isoxic hyperoxic CO₂ rebreathing tests were available.

Data on perceptual responses to rebreathing in TM₃ and PP are presented here for the first time. Data concerning the impact of pregnancy on (i) perceptual responses to exercise and (ii) ventilatory responses to rebreathing, used in the new comparative analysis, are quantitatively and qualitatively similar to those published elsewhere (Jensen et al., 2009b). To minimize any duplication with our previous reports, we restricted ourselves to the use of data that are pertinent to the objectives of the current study.

2. Methods

2.1. Subjects and experimental design

Subjects in this study, which addressed de novo objectives that were independent of our previous reports (Jensen et al., 2009b, 2010b), included 21 healthy women who completed both exercise and rebreathing tests to the point of symptom-limitation in the TM₃ condition: 19 of these 21 women were among the 25 subjects studied retrospectively in Jensen et al. (2010b), which in turn were among the 27 subjects studied prospectively in Jensen et al. (2009b). Detailed information on subject recruitment procedures, inclusion/exclusion criterion and the experimental study design have been published elsewhere (Jensen et al., 2009b). 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. Duffin's modified isoxic hyperoxic rebreathing procedure

Duffin's modified isoxic hyperoxic rebreathing procedure, apparatus, data acquisition and analysis software have been described in detail previously (Jensen et al., 2010a). Briefly, before rebreathing trials, subjects voluntarily hyperventilated room air for 5-min using a deep and deliberate breathing pattern to reduce end-tidal PₐCO₂ (PETCO₂) between 19 and 23 mm Hg. 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 PₐCO₂ in the rebreathing bag, lungs and arterial blood with that of the mixed-venous blood. Following equilibration, subjects were instructed to relax and breathe as they felt the need.

During rebreathing, PETCO₂ increased progressively from hypo- to hypercapnia while isoxia was maintained at a hyperoxic end-tidal PₐO₂ (PETO₂) of 150 mm Hg by providing a computer-controlled flow of 100% O₂ to the rebreathing bag. Rebreathing was terminated at the point of symptom-limitation or when PETCO₂ exceeded 60 mm Hg, whichever occurred first.

During rebreathing, subjects were comfortably seated, wore nose clips and breathed through a mouthpiece connected to a 3-way T-shaped wide-bore manual directional valve (Model 2100a; Hans Rudolph, Inc., Kansas City, MO) that permitted switching from room air to the rebreathing bag. Expired gases (PETCO₂) were collected on a breath-by-breath basis using a respiratory mass spectrometer (Perkin Elmer MGA 1100) and a low resistance bi-directional volume turbine (VMM-2A; Alpha Technologies, Laguna Niguel, CA), respectively.

The PETCO₂ at which VE increased with progressive increases in PETCO₂ was identified as the central chemoreflex ventilatory recruitment threshold (VRTCO₂). The slope of the ventilatory response above the VRTCO₂ was taken as an estimate of central chemoreflex sensitivity (VET).

2.3. 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., 2009b). Exercise tests consisted of a steady-state resting period of at least 6-min followed by 25 W increases in cycle work rate every 2-min to the point of symptom-limitation. Ventilatory parameters (VE, VT, fR, PETCO₂) were collected on a breath-by-breath basis at rest and during exercise.

2.4. Symptom evaluation

Breathlessness was defined to each subject as the “sensation of labored or difficult breathing.” Before rebreathing and exercise tests, subjects were familiarized with Borg’s 0–10 category ratio scale (Borg, 1982) and its endpoints were anchored such that “0” represented “no breathlessness” and “10” represented “the most severe breathlessness you have ever experienced or could ever imagine experiencing.” By pointing to the Borg scale, subjects rated the intensity of their perceived breathlessness at rest, within the last 10-s of each minute of rebreathing, within the last 30-s of each 2-min interval during exercise, and immediately at the end of rebreathing and exercise. Qualitative descriptors of perceived breathlessness at the end of each rebreathing and exercise test were collected by questionnaire to help identify what the women were experiencing and rating. Subjects were asked to identify as many or as few of the following descriptor phrases that applied to how their breathing felt at the very end of each test:

1. “I feel that I am suffocating”
2. “My breathing requires more work”
3. “Breathing in requires more effort”
4. “My breathing is heavy”
5. “Breathing in requires more effort”
6. “Breathing out requires more effort”
7. “I feel that my breathing is shallow”
8. “My breath does not go all the way in”
9. “I cannot take a deep breath in”
10. “I feel that my breathing is rapid”
11. “I feel that my breathing is shallow”
12. “My chest feels tight”
13. “I feel that I am breathing more air”
14. “My chest feels tight”

2.5. Analysis of rebreathing and exercise endpoints

Breath-by-breath measurements of VE, VT, fR and PETCO₂ were averaged in 20-s intervals during rebreathing. The averaged physiological data collected over (i) the last 20-s of each minute of rebreathing and (ii) the last 20-s of the rebreathing test were linked with the corresponding breathlessness intensity ratings. The relationship between increasing breathlessness intensity and each of increasing VE and PETCO₂ during rebreathing was plotted and examined for each subject at TM₃ and PP. The slope and extrapolated threshold of the breathlessness intensity–VE and breathlessness intensity–PETCO₂ relationship – above the VRTCO₂ – were calculated for each subject at TM₃ and PP by linear regression analysis using breathlessness intensity ratings ≥ 0.5 Borg units.

Breath-by-breath measurements of VE, VT, fR and PETCO₂ were averaged in 30-s intervals at rest and during exercise. The averaged physiological data collected over (i) the first 30-s period of every second minute during exercise and (ii) the last 30-s of loaded pedaling were linked with the corresponding breathlessness inten-
### Table 1

Impact of human pregnancy on breathlessness intensity–ventilation relationship characteristics during incremental cycle exercise vs. modified isoxic hyperoxic rebreathing tests (refer also to Fig. 1a).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Exercise</th>
<th>Rebreathing</th>
<th>P value</th>
<th>Condition (EX vs. RBR)</th>
<th>Visit (TM3 vs. PP)</th>
<th>Condition × visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slope (Borg units/L/min)</td>
<td>0.13 ± 0.01</td>
<td>0.12 ± 0.01</td>
<td>0.17 ± 0.02</td>
<td>0.18 ± 0.02</td>
<td>0.002</td>
<td>0.842</td>
</tr>
<tr>
<td>Extrapolated threshold (L/min)</td>
<td>23.6 ± 1.6</td>
<td>19.3 ± 2.0</td>
<td>6.8 ± 3.8</td>
<td>6.4 ± 2.1</td>
<td>&lt;0.001</td>
<td>0.801</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. TM3, third trimester; PP, post-partum; EX, exercise; and RBR, rebreathing.

Breathlessness intensity ratings. The relationship between increasing breathlessness intensity ratings and increasing VE during exercise was plotted and examined for each subject at TM3 and PP. The slope and extrapolated threshold of the breathlessness intensity–VE relationship were calculated for each subject at TM3 and PP by linear regression analysis using breathlessness intensity ratings ≥0.5 Borg units.

2.6. **Statistical analysis**

Paired t-tests were used to examine the impact of human pregnancy on (i) selected rebreathing and incremental cycle exercise test parameters and (ii) the slope and extrapolated threshold of the breathlessness intensity–VE relationship during rebreathing (SigmaStat for Windows Version 3.10, Systat Software, Inc., San Jose, CA). A two-way repeated measures analysis of variance with Tukey’s HSD post hoc test was used to examine the effect of experimental visit (TM3 vs. PP), condition (exercise vs. rebreathing) and their interaction (visit × condition) on the slope and extrapolated threshold of the breathlessness intensity–VE relationship. Pearson product-moment correlation coefficients were calculated to examine associations between (i) pregnancy-induced changes (Δ) in breathlessness intensity–VE slopes during rebreathing vs. exercise and (ii) Δbreathlessness intensity–VE slopes during exercise vs. ΔVES. A *P* < 0.05 level of statistical significance was used for all analyses. Data are presented as mean ± SEM.

3. **Results**

Twenty-one healthy, young (29.9 ± 0.8 years at TM3), non-smoking, regularly active women participated in experimental testing at 36.5 ± 0.2 weeks gestation and again 20.8 ± 2.0 weeks...

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**Fig. 1.** Impact of healthy human pregnancy on perceptual (panels a and b) and breathing pattern responses (panels c and d) to incremental cycle exercise and Duffin’s modified isoxic hyperoxic rebreathing tests; that is, during increased motor cortical and central chemoreflex stimulation of ventilation. TM3, third trimester; PP, post-partum.
post-partum. Data on subject characteristics, baseline pulmonary function and blood biochemistry test parameters in TM3 and PP are quantitatively and qualitatively similar to those reported elsewhere (Jensen et al., 2009b, 2010b).

3.1. Perceptual and physiological responses to exercise and rebreathing

All 21 women completed exercise and rebreathing tests to the point of symptom-limitation at TM3. In the PP condition, all subjects exercised to the point of symptom-limitation, while 17 of the 21 rebreathing tests were stopped by the investigator prior to symptom-limitation due to attainment of a pre-determined PETCO2 end-point of ∼60 mm Hg. Therefore, comparisons of perceptual and physiological responses at the symptom-limited peak of exercise vs. rebreathing were limited to the TM3 condition only.

As shown in Table 1 and Fig. 1a, pregnancy had no significant effect on either the slope or extrapolated threshold of the relationship between increasing breathlessness intensity and increasing VE during both exercise and rebreathing. By contrast, the slope of the breathlessness intensity–VE relationship was significantly higher, while the extrapolated threshold of this relationship was consistently lower during rebreathing vs. exercise, independent of pregnancy status (Fig. 1a, Table 1). As a result, breathlessness intensity ratings were markedly higher at any given VE during rebreathing vs. exercise, regardless of pregnancy status: breathlessness intensity increased from ∼2 Borg units (“slight”) to ∼6 Borg units (“severe” to “very severe”) at an iso-VE of 40 L/min during rebreathing vs. exercise (Fig. 1a).

The slope of the relationship between breathlessness intensity and VT expansion (standardized for VE) was similar in TM3 vs. PP (Fig. 1d). As illustrated in Fig. 1a, the c and d, breathlessness intensity ratings were significantly higher (by 1.7 Borg units or ∼27%, \( P < 0.001 \)) at the symptom-limited peak of rebreathing vs. exercise in the TM3 condition, even though VE was ∼18 L/min (or ∼25%) lower in the former (\( P < 0.001 \)), secondary to a reduced \( fR \) (\( P < 0.001 \)) with no difference in VT (\( P > 0.05 \)).

Pregnancy had little/no effect on VT–VE (Fig. 1c) and \( fR \)–VE (Fig. 1d) relationships within either of the experimental test conditions; however, VT and \( fR \) were consistently higher and lower, respectively, at equivalent levels of VE during rebreathing vs. exercise.

The VRTCO2 increased by 7.3 ± 1.0 mm Hg (40.6 ± 0.6 vs. 47.9 ± 0.8 mm Hg), while VE decreased by 2.55 ± 0.49 L/min/mm Hg (5.20 ± 0.55 vs. 2.66 ± 0.24 L/min/mm Hg) from TM3 to PP (both \( P < 0.0001 \)).

No statistically significant association was observed between (i) \( \Delta \) breathlessness intensity–VE slopes during exercise vs. rebreathing (\( R^2 = 0.01, P = 0.71 \)) and (ii) \( \Delta \) breathlessness intensity–VE slopes during exercise vs. \( \Delta VES (R^2 = 0.05, P = 0.34) \).

Fig. 2 shows that the slope (0.58 ± 0.05 vs. 0.39 ± 0.03 Borg units/mm Hg) and extrapolated threshold (35.5 ± 1.3 vs. 43.4 ± 1.0 mm Hg) of the breathlessness intensity–PETCO2 relationship during rebreathing was significantly higher and lower in TM3 vs. PP, respectively (both \( P < 0.001 \)).

3.2. Qualitative descriptors of perceived breathlessness

Women were more likely to self-select descriptor phrases alluding to the sense of not getting enough air into their lungs (e.g., “I feel that I am suffocating” and “I cannot get enough air in”) at the symptom-limited peak of rebreathing vs. exercise in the TM3 condition (Table 2).

4. Discussion

The primary findings of this study include: (i) breathlessness intensity–VE relationships were preserved in TM3 vs. PP during modified isoxic hyperoxic CO2 rebreathing tests; (ii) breathlessness intensity ratings were markedly increased at matched levels of VE during rebreathing (increased central chemoreflex stimulation) compared with exercise (increased motor cortical activation) regardless of pregnancy status; (iii) inter-subject variation in breathlessness intensity–VE slopes during exercise was not associated with inter-subject variation in breathlessness intensity–VE slopes during rebreathing or with altered measures of central chemoreflex responsiveness during pregnancy; and (iv) breathlessness intensity ratings were significantly higher at any given hypercapnic PETCO2 during rebreathing in TM3 vs. PP.

4.1. Role of respiratory mechanical/muscular factors in gestational breathlessness

Here we show, for the first time, that pregnancy had no significant effect on breathlessness intensity–VE slopes during pro-
gressive increases in central chemoreflex stimulation (Table 1, Fig. 1a). This finding further supports our contention (e.g., Jensen et al., 2009a) that respiratory mechanical/muscular factors are not a major source of breathlessness in pregnancy.

4.2. Chemoreflex- vs. exercise-stimulation of ventilation: implications for respiratory sensation

The origin(s) of increased respiratory motor command output and thus VE during exercise are complex and multifactorial (for example, refer to: Bell, 2006; Haouzi, 2006; Waldrop and Iwamoto, 2006), but increased motor cortical activation is believed to be largely involved (Duffin, 1994; Mateika and Duffin, 1995; Kaufman and Forster, 1996). In contrast, it is generally accepted that the increased respiratory motor command output and VE that accompanies breathing a hyperoxic–hypercapnic inspirate at rest primarily reflects central chemoreflex–mediated increases in brainstem respiratory control center activation (Duffin, 1990; Duffin and Mahamed, 2003).

We reasoned that if pregnancy-induced increases in the intensity of activity-related breathlessness reflect the awareness of increased VE and contractile respiratory muscle effort (e.g., Field et al., 1991; Jensen et al., 2008b) regardless of the source of increased central motor command output and corollary discharge, then breathlessness intensity–VE relationships would be superimposed across all four experimental conditions in this study. However, this was not borne out: breathlessness intensity ratings were substantially greater across the entire range of VE encountered (e.g., by ~4 Borg units at 40 L/min) during rebreathing vs. exercise tests, independent of pregnancy status (Fig. 1a). We also demonstrated that pregnant women self-selected descriptor phrases alluding to an increased sense of not getting enough air into their lungs (Table 2) more frequently at the symptom-limited peak of rebreathing vs. exercise, even though VE was ~18 L/min less in the former (Fig. 1a). These findings are in keeping with those of previous investigators (Stark et al., 1981; Adams et al., 1985a,b; Chonan et al., 1990; Demediuk et al., 1992) and provide evidence that pregnancy-induced increases in activity-related breathlessness cannot be easily explained by the awareness of increased VE and contractile respiratory muscle effort per se.

Brain imaging studies have shown that exercise stimulation of VE is associated with increased motor cortical activity (Fink et al., 1995; Thornton et al., 2001), whereas chemoreflex stimulation of VE by hypercapnia has no effect on motor cortical activity but is associated with activation of the limbic/paralimbic system (Corfield et al., 1995; Banzett et al., 2000; Evans et al., 2002; McKay et al., 2010). We speculate that these neurophysiological differences, combined with a more rapid time course of ventilatory stimulation and a greater degree of unfamiliarity associated with rebreathing vs. exercise (either one or both factors may also increase limbic/paralimbic system activity) may help to explain why the intensity and quality of perceived breathlessness differed in the former vs. the latter experimental condition of this study.

It may be argued that differences in breathlessness intensity–VE slopes observed during rebreathing vs. exercise (Fig. 1a) reflect, at least in part, the relatively deeper and slower breathing pattern (and, by extension, altered vagoafferent feedback from the lungs, airways and respiratory musculature) at a given VE during increased central chemostimulation (Fig. 1c and d). However, this seems unlikely considering that the slope of the relationship between breathlessness intensity and VT expansion (standardized for VE) was similar during rebreathing compared with exercise, regardless of pregnancy status (Fig. 1b).

4.3. Role of increased central chemoreflex drives to breathe to gestational breathlessness

The collective results of this study provide evidence that increases in central chemoreflex responsiveness do not contribute importantly to activity-related breathlessness in pregnancy. In this regard, no association was observed between the magnitude of inter-subject variation in (i) breathlessness intensity–VE slopes during rebreathing and exercise and (ii) breathlessness intensity–VE slopes during exercise and central chemoreflex sensitivity. Moreover, at the symptom-limited peak of exercise in the TM3 condition of the current study, women had mean PETCO2 values and breathlessness intensity ratings of 33.5 mm Hg (data not shown) and 6.3 Borg units (Fig. 1a), respectively. As illustrated in Fig. 2, these same PETCO2 values encountered during isoxic hyperoxic rebreathing tests were associated with no respiratory sensation. In light of these observations, we contend that pregnancy-induced increases in activity-related breathlessness reflect, at least in part, the awareness of increased motor cortical stimulation of respiratory motor command output as sensed by increased central corollary discharge.

4.4. Role of the respiratory chemoreflex in respiratory sensation

The role of the respiratory chemoreceptors in the genesis of breathlessness remains unclear (Buchanan and Richerson, 2009). Several investigators (e.g., Banzett and Lansing, 1996; Eldridge and Chen, 1996) have postulated that increased chemoreceptor stimulation may directly modulate breathlessness by increasing brainstem respiratory control center activity, which is conveyed to the somatosensory cortex by way of increased central corollary discharge. Our results are consistent with this hypothesis.

We have provided evidence (Jensen et al., 2008a) that the chronic alveolar hyperventilation and attendant respiratory alkalosis of pregnancy initiates compensatory reductions in the strong ion difference concentration, which partially restores arterial and central (or brain tissue) [H+], thereby altering the relationship between the measured, PETCO2, and actual, central [H+] stimulus to the central chemoreceptors. Consequently, central [H+] and presumably therefore central chemoreceptor activity, brainstem respiratory control center activity and central corollary discharge are significantly increased at any given PETCO2 during rebreathing in TM3 vs. PP. This, in turn, decreases the threshold (VRCO2) and increases the sensitivity (VES) of the central ventilatory chemoreflex response to PETCO2, even though the threshold and sensitivity in terms of central [H+] likely do not change. The corollary of this is that central [H+] and presumably therefore central chemoreceptor activity, brainstem respiratory control center activity and central corollary discharge are not significantly different at any given VE during rebreathing in TM3 vs. PP, despite pregnancy-induced alterations in the VRCO2 and VES.

It follows that (i) breathlessness intensity–VE relationships were not significantly different during rebreathing in TM3 vs. PP (Fig. 1a) and (ii) pregnancy-induced increases in breathlessness intensity for a given hypercapnic stimulus (by ~5 Borg units at a PETCO2 of 50 mm Hg as illustrated in Fig. 2) reflects, at least in part, the impact of long-term compensatory acid–base adjustments on Pco2–[H+] relationships in chemosensitive areas of the brain, independent of concomitant changes in VE–PETCO2 relationships. This theory is bolstered by the results of Bloch-Salisbury et al. (1996), who showed that acid–base manipulations in the opposite direction of pregnancy (i.e., partially-compensated respiratory acidosis) had opposite effects on breathlessness (‘air hunger’) intensity during increased chemostimulation (i.e., rightward shift of the ‘air hunger’–PCO2 response curve) in a group of mechanically venti-
latory subjects; that is, in the presumed absence of any change in VE and contractile respiratory muscle effort.

4.5. Critique of methods

We made no attempt to control for menstrual cycle phase, lactation and/or oral contraceptive use in the PP condition. Nevertheless, the majority of available research suggests that neither menstrual cycle phase nor oral contraceptive use significantly alters the ventilatory response to hypercapnia and/or exercise in healthy women (Beidleman et al., 1999; Casazza et al., 2002; Redman et al., 2003; Slatkovska et al., 2006; Nettlefold et al., 2007; Itoh et al., 2007). Furthermore, mean serum progesterone and 17β-estradiol concentrations in the PP condition of this study (data not shown) 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). It could be argued that alterations in lifestyle (e.g., diet, habitual physical activity levels and sleep–wake schedules) not strictly controlled for between TM3 and PP tests may have contributed to our results; unfortunately, our data do not permit examination into the relative importance of these factors. We further acknowledge that the 5 min of voluntary hyperventilation (and attendant hypocapnia/alkalosis) performed immediately before rebreathing trials is a potentially confounding intervention that may have contributed to the observed differences in respiratory sensation during rebreathing vs. exercise. Finally, the results of the retrospective analyses performed here do not clarify to what extent pregnancy and advancing gestation per se has on the quality and unpleasantness of perceived breathlessness at matched levels of VE during central chemoreflex vs. exercise ventilatory stimulation.

4.6. Summary

In conclusion: (i) the intensity of perceived breathlessness for a given change in ventilation and, by extension, contractile respiratory muscle effort depends, at least in part, on the nature and source of increased central respiratory motor command output and presumably therefore central corollary discharge, independent of pregnancy status; (ii) pregnancy-induced increases in activity-related breathlessness cannot be easily explained by respiratory mechanical/muscular factors or increased central chemoreflex responsiveness, but likely reflect the awareness of increased motor cortical stimulation of respiratory motor command output as sensed by increased central corollary discharge to the somatosensory cortex; (iii) pregnancy-induced alterations in breathlessness intensity–PETCO₂ relationships during rebreathing fundamentally reflect the impact of compensatory acid–base adjustments on PCO₂–[H⁺] relationships in chemosensitive areas of the brain; and (iv) the provocation of breathlessness at rest by increased chemostimulation provides little/no mechanistic insight into the underlying mechanism(s) of exertional breathlessness in healthy human pregnancy.

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