Respiratory Physiology & Neurobiology 175 (2011) 55–61

Contents lists available at ScienceDirect

Respiratory Physiology & Neurobiology

journal homepage: www.elsevier.com/locate/resphysiol

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

Dennis Jensen*, Denis E. O'Donnell

Respiratory Investigation Unit, Department of Medicine, Queen's University c/o Kingston General Hospital, Kingston, Ontario, Canada

ARTICLE INFO

Article history:
Accepted 9 September 2010

Keywords:
Pregnancy
Breathlessness
Ventilation
Hypercapnia
Central chemoreflex

ABSTRACT

We examined the impact of human pregnancy on breathlessness intensity at matched levels of ventilation ($\dot{V}E$) during isoxic hyperoxic CO_2 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–$\dot{V}E$ relationship during both exercise and rebreathing. By contrast, the slope of the breathlessness intensity–$\dot{V}E$ 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 $\dot{V}E$ (e.g., by ~4 Borg units at 40 L/min) during rebreathing vs. exercise, regardless of pregnancy status. Inter-subject variation in breathlessness intensity–$\dot{V}E$ slopes during exercise was not associated with inter-subject variation in breathlessness intensity–$\dot{V}E$ 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 $\dot{V}E$ 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.

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 ($\dot{V}E$) 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 $\dot{V}E$) are not a major source of breathlessness in pregnancy and (ii) gestational breathlessness reflects the awareness of increased $\dot{V}E$ 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 $\dot{V}E$ 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 $\dot{V}E$ 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 $\dot{V}E$ 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 $\dot{V}E$ during hyperoxic–hypercapnia compared with exercise (that is, during increased central chemoreflex vs. increased motor cortical stimulation of $\dot{V}E$). We took advantage of an opportunity to address these pre-specified study objectives by conducting a detailed

* Corresponding author at: Respiratory Investigation Unit, Douglas 5, Room 8-536B, Kingston General Hospital, Kingston, Ontario, Canada K7L 2V7.
Tel.: +1 613 549 6666x4910; fax: +1 613 548 1307.
E-mail address: dennis.jensen@queensu.ca (D. Jensen).

1569-9048/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.resp.2010.09.007

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 CO_2 rebreathing tests were available.

Data on perceptual responses to rebreathing in TM_3 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, 2010b). 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 TM_3 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 P_{CO_2} (PET_{CO_2}) 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% 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. Following equilibration, subjects were instructed to relax and breathe as they felt the need.

During rebreathing, PET_{CO_2} increased progressively from hypo- to hypercapnia while isoxia was maintained at a hyperoxic end-tidal P_{O_2} (PET_{O_2}) of 150 mm Hg by providing a computer-controlled flow of 100% O_2 to the rebreathing bag. Rebreathing was terminated at the point of symptom-limitation or when PET_{CO_2} 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 (PET_{CO_2}, PET_{O_2}) and ventilatory parameters ($\dot{V}E$, tidal volume (VT), breathing frequency (fR)) 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 PET_{CO_2} at which $\dot{V}E$ increased with progressive increases in PET_{CO_2} was identified as the central chemoreflex ventilatory recruitment threshold ($VRTCO_2$). The slope of the ventilatory response above the $VRTCO_2$ was taken as an estimate of central chemoreflex sensitivity ($\dot{V}ET$).

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 ($\dot{V}E$, VT, fR, PET_{CO_2}) 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 out requires more effort"
6. "I feel a need for more air"
7. "I cannot get enough air in"
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 breath does not go all the way out"
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 $\dot{V}E$, VT, f_R and PET_{CO_2} 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 $\dot{V}E$ and PET_{CO_2} during rebreathing was plotted and examined for each subject at TM_3 and PP. The slope and extrapolated threshold of the breathlessness intensity–$\dot{V}E$ and breathlessness intensity–PET_{CO_2} relationship – above the $VRTCO_2$ – were calculated for each subject at TM_3 and PP by linear regression analysis using breathlessness intensity ratings $\geq$0.5 Borg units.

Breath-by-breath measurements of $\dot{V}E$, VT, f_R and PET_{CO_2} 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-