

Mechanical ventilatory constraints during incremental cycle exercise in human pregnancy: implications for respiratory sensation

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The aim of this study was to identify the physiological mechanisms of exertional respiratory discomfort (breathlessness) in pregnancy by comparing ventilatory (breathing pattern, airway function, operating lung volumes, oesophageal pressure (P_{oes})-derived indices of respiratory mechanics) and perceptual (breathlessness intensity) responses to incremental cycle exercise in 15 young, healthy women in the third trimester (TM₃; between 34 and 38 weeks gestation) and again 4–5 months postpartum (PP). During pregnancy, resting inspiratory capacity (IC) increased ($P < 0.01$) and end-expiratory lung volume decreased ($P < 0.001$), with no associated change in total lung capacity (TLC) or static respiratory muscle strength. This permitted greater tidal volume (V_T) expansion throughout exercise in TM₃, while preserving the relationship between contractile respiratory muscle effort (tidal P_{oes} swing expressed as a percentage of maximum inspiratory pressure (P_{Imax})) and thoracic volume displacement (V_T expressed as a percentage of vital capacity) and between breathlessness and ventilation (\dot{V}_E). At the highest equivalent work rate (HEWR = 128 ± 5 W) in TM₃ compared with PP: \dot{V}_E , tidal P_{oes}/P_{Imax} and breathlessness intensity ratings increased by 10.2 l min^{-1} ($P < 0.001$), $8.8\%P_{Imax}$ ($P < 0.05$) and 0.9 Borg units ($P < 0.05$), respectively. Pulmonary resistance was not increased at rest or during exercise at the HEWR in TM₃, despite marked increases in mean tidal inspiratory and expiratory flow rates, suggesting increased bronchodilatation. Dynamic mechanical constraints on V_T expansion ($P < 0.05$) with associated increased breathlessness intensity ratings ($P < 0.05$) were observed near peak exercise in TM₃ compared with PP. In conclusion: (1) pregnancy-induced increases in exertional breathlessness reflected the normal awareness of increased \dot{V}_E and contractile respiratory muscle effort; (2) mechanical adaptations of the respiratory system, including recruitment of resting IC and increased bronchodilatation, accommodated the increased V_T while preserving effort–displacement and breathlessness– \dot{V}_E relationships; and (3) dynamic mechanical ventilatory constraints contributed to respiratory discomfort near the limits of tolerance in late gestation.

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Perceived respiratory discomfort (breathlessness) is reported during activities of daily living by as many as 75% of healthy pregnant women (Milne *et al.* 1978; Moore *et al.* 1987). The aetiology of gestational breathlessness, however, remains poorly understood and it is often difficult to differentiate physiological from patho-physiological breathlessness in this population. Purported mechanisms of gestational breathlessness include: (1) the normal awareness of increased ventilation (\dot{V}_E) (Moore *et al.* 1987; Field *et al.* 1991; Garcia-Rio *et al.*

1996); (2) an exaggerated central perception of discomfort at any given \dot{V}_E (Gilbert *et al.* 1962; Gilbert & Auchincloss, 1966); (3) increased O₂ cost of breathing, secondary to progressive thoraco-abdominal distortion (Bader *et al.* 1959); or (4) any combination of the above.

A mechanistic study by Field *et al.* (1991) found that tidal volume (V_T), inspiratory oesophageal pressure (P_{oes}) swings and breathlessness intensity ratings were consistently higher during exercise in the third trimester (TM₃) compared with the postpartum (PP)

state, suggesting that pregnancy-induced increases in breathlessness reflect the normal awareness of increased \dot{V}_E and contractile inspiratory muscle effort. Thus, increased central respiratory motor output command and the attendant increase in central corollary discharge to the somatosensory cortex (Chen *et al.* 1991, 1992; Manning & Schwartzstein, 1995; O'Donnell *et al.* 2007) remains a plausible mechanistic explanation of gestational breathlessness. In the study of Field *et al.* (1991), however, comparisons were made at a standardized submaximal cycle work rate of only 48 W, corresponding to breathlessness intensity ratings of 'very slight' to 'slight' (i.e. 1–2 Borg units) in TM₃ and PP, respectively. The concern remains that the exercise-testing protocol was too conservative to unmask potential mechanical ventilatory constraints relevant to the origin of exertional respiratory discomfort in this population. The present study is the first to examine detailed sensory–mechanical relationships at the limits of tolerance in human pregnancy.

Very little is known about the role of altered dynamic ventilatory mechanics in the perception of exertional breathlessness in pregnancy (Bader *et al.* 1959; Field *et al.* 1991). Conventional wisdom suggests that pregnancy-induced changes in the shape and configuration of the abdomen, diaphragm and chest wall may alter the normal mechanical response of the respiratory system to exercise, thereby constraining V_T expansion especially when ventilatory requirements are high. Hypothetically, it is possible that an impaired ability to reduce end-expiratory lung volume during exercise in pregnancy (secondary to the mechanical effects of the gravid uterus) would compromise power-sharing between the inspiratory and expiratory muscles, and force dynamic end-inspiratory lung volume closer to total lung capacity. These restrictive changes in the setting of an increased central ventilatory drive (Jensen *et al.* 2007a, 2008) would be expected to uncouple the otherwise harmonious relationship between contractile respiratory muscle effort and thoracic volume displacement with attendant increases in perceived breathlessness. Accordingly, based on our previous work on the impact of mechanical restriction on exercise performance, we can predict that in the presence of significant restrictive ventilatory constraints, the ratio of contractile effort (tidal P_{oes} swing expressed as a percentage of maximal inspiratory pressure ($P_{I_{max}}$)) to volume displacement (V_T expressed as a percentage of vital capacity) will increase (O'Donnell *et al.* 1997, 2000, 2006). This increased effort–displacement ratio, an index of neuromechanical (un)coupling of the respiratory system, would in turn be associated with greater perceived respiratory discomfort at any given \dot{V}_E particularly during strenuous exercise in late gestation when the mechanical encumbrance of the gravid uterus is greatest. Contrary to our expectations, however, we recently found

that neither pregnancy nor advancing gestation altered breathlessness– \dot{V}_E relationships during incremental cycle exercise (Jensen *et al.* 2007b). These results strongly suggested the existence of specific respiratory mechanical adaptations that accommodate the increased central ventilatory drive (i.e. V_T expansion) of pregnancy while preserving neuromechanical coupling during exercise. The present study is the first to consider the potential relevance of resting inspiratory capacity recruitment and bronchodilatation (Rubin *et al.* 1956; Gee *et al.* 1967; Garrard *et al.* 1978; Gilroy *et al.* 1988; Berry *et al.* 1989; Contreras *et al.* 1991; Garcia-Rio *et al.* 1996, 1997) to respiratory sensation during exercise in pregnancy.

The aim of the present study therefore was to identify the physiological mechanisms of exertional breathlessness in pregnancy by comparing ventilatory (breathing pattern, airway function, operating lung volumes, P_{oes} -derived indices of respiratory mechanics) and perceptual (breathlessness intensity) responses to incremental cycle exercise in 15 young, healthy women in TM₃ (between 34 and 38 weeks gestation) and again 4–5 months PP. We hypothesized that: (1) breathlessness intensity would be consistently higher at any given work rate in TM₃ compared with PP, reflecting the normal awareness of increased \dot{V}_E and contractile respiratory muscle effort; (2) effort–displacement and breathlessness– \dot{V}_E relationships would be preserved throughout exercise in TM₃ compared with PP, indicating the existence of respiratory mechanical adaptations; and (3) mechanical ventilatory constraints would contribute importantly to perceived respiratory discomfort during exercise near the limits of tolerance in TM₃.

Methods

Subjects

Subjects included 15 healthy women, 20–40 years, parity ≤ 2 , who were experiencing uncomplicated singleton pregnancies; had no history of smoking or cardiovascular, respiratory, neuromuscular, musculoskeletal, metabolic or haematological (i.e. [haemoglobin] ≥ 10 g dl⁻¹) disease; and were not taking medications (other than prenatal vitamins) that could affect the ventilatory or perceptual response to exercise. Subjects were recruited via posted announcements, newspaper advertisements and contact with local obstetricians, midwives and health care providers. Prior to participation, subjects completed the Physical Activity Readiness Medical Examination for Pregnancy (available at <http://www.csep.ca>) and obtained medical clearance from their primary care giver. 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. As an incentive for study

participation, subjects were given the opportunity to take part in a closely monitored prenatal muscle conditioning programme designed specifically to maintain (not improve) general muscular fitness, promote proper posture, and prevent urinary incontinence and diastasis recti, without causing improvement in the aerobic energy system. Fourteen women participated in 1.3 ± 0.1 classes week⁻¹ (mean \pm S.E.M.) for an average of 19.1 ± 1.1 weeks prior to TM₃ testing; these classes were not continued in the postnatal period. 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.

Experimental design

This was a controlled, longitudinal study in which experimental tests were conducted at 36.6 ± 0.3 weeks gestation (i.e. when the mechanical encumbrance of the gravid uterus is greatest) and again 17.9 ± 0.9 weeks postpartum (i.e. long enough after delivery to ensure a complete return to the non-pregnant control state). The majority of available research suggests that menstrual cycle phase and oral contraceptive use has little or no effect on ventilatory control at rest and during exercise in healthy young women (Redman *et al.* 2003; Itoh *et al.* 2007; Nettlefold *et al.* 2007; Smekal *et al.* 2007). Therefore, no attempt was made to control for menstrual cycle status, lactation and/or oral contraceptive use in PP. Experimental visits included: evaluation of anthropometry (i.e. body height and mass) and persistent activity-related breathlessness using the modified baseline dyspnoea index (BDI) scale (Stoller *et al.* 1986); pulmonary function tests; and an incremental cycle exercise test. The BDI is a validated, reliable multidimensional discriminative instrument (Mahler *et al.* 1984): a focal score of '0' indicates severe impairment and breathlessness at rest, while a score of '12' indicates breathlessness only with intense physical activity. Subjects abstained completely from exercise, caffeine, heavy meals and alcohol for at least 12 h before TM₃ and PP tests, which were conducted at the same time of day for each subject. Blood for the estimation of arterial P_{CO_2} (P_{aCO_2}), $[\text{H}^+]$ and $[\text{HCO}_3^-]$; and serum progesterone ($[\text{P}_4]$) and 17β -oestradiol ($[\text{E}_2]$) concentrations was collected from each subject on a separate day within the same week, as previously described (Jensen *et al.* 2008).

Pulmonary function testing

Pulmonary function measurements, including routine spirometry, constant volume body plethysmography, single breath diffusing capacity for carbon monoxide

(D_{LCO}), and maximum inspiratory (MIP) and expiratory (MEP) mouth pressures measured at functional residual capacity (FRC) (i.e. MIP was not corrected for the change in FRC during pregnancy) and total lung capacity (TLC), respectively, were collected according to recommended techniques (ATS/ERS, 2002; MacIntyre *et al.* 2005; Miller *et al.* 2005a,b; Wanger *et al.* 2005) using automated equipment (Vmax 229d with Autobox 6200 DL; SensorMedics, Yorba Linda, CA, USA) and expressed in absolute terms. Static lung recoil pressure (P_{st}) as well as both static (C_{st}) and dynamic (C_{dyn}) lung compliance was measured in a subgroup of seven volunteers using automated equipment (Vmax 229d with Autobox 6200 DL) according to recommended techniques (Gibson & Pride, 1976).

Cardiopulmonary exercise testing

Evidence-based guidelines for exercise during pregnancy (Davies *et al.* 2003) recommend that women participate in weight-supported exercise (e.g. stationary cycling) and avoid activities that increase the risk of loss of balance and fetal trauma (e.g. treadmill running). Therefore, incremental exercise tests were conducted on an electronically braked cycle ergometer (Ergometrics 800S; SensorMedics) by use of a cardiopulmonary exercise testing system (Vmax229d; SensorMedics). Prior to TM₃ tests, the bicycle seat height was adjusted so that the subject's legs were almost completely extended when the pedals were at the lowest point; the seat was adjusted to the same height at PP. 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. Pedalling cadence was maintained between 60 and 70 r.p.m. Subjects were verbally encouraged to cycle to the point of symptom-limitation.

Measurements were collected at rest and during exercise while subjects breathed through a mouthpiece and a low-resistance flow transducer with nasal passages occluded by a noseclip. Measurements included: standard cardiorespiratory and breathing pattern parameters (\dot{V}_{E} , oxygen uptake (\dot{V}_{O_2}), carbon dioxide production (\dot{V}_{CO_2}), end-tidal P_{O_2} and P_{CO_2} ($P_{\text{ET,CO}_2}$), tidal volume (V_{T}), breathing frequency (f_{R}), inspiratory (T_{I}) and expiratory time (T_{E}), inspiratory duty cycle ($T_{\text{I}}/T_{\text{TOT}}$), and mean tidal inspiratory ($V_{\text{T}}/T_{\text{I}}$) and expiratory ($V_{\text{T}}/T_{\text{E}}$) flow) were collected on a breath-by-breath basis and compared with predicted normal values based on age and height (Jones, 1997); oxygen saturation by finger pulse oximetry; heart rate (HR) by 12-lead ECG; blood pressure by auscultation of the brachial artery using a sphygmomanometer with an arm cuff; intensity of perceived breathing and leg discomfort;

dynamic operating lung volumes; and oesophageal pressure-derived indices of respiratory mechanics.

Symptom evaluation

Respiratory discomfort (breathlessness) was defined as the 'sensation of laboured or difficult breathing' and leg discomfort as 'the level of leg discomfort experienced during pedalling.' Before exercise testing, subjects were familiarized with Borg's 0–10 category ratio scale (Borg, 1982) and its endpoints were anchored such that '0' represented 'no respiratory (leg) discomfort' and '10' was 'the most severe respiratory (leg) discomfort you have ever experienced or could ever imagine experiencing.' By pointing to the Borg scale, subjects rated their intensity of perceived breathlessness and leg discomfort at rest, within the last 30 s of each 2 min interval during exercise, and at the symptom-limited peak of exercise. Symptom ratings preceded IC manoeuvres by at least 5 breaths to avoid interference with pre-IC breathing patterns, and to avoid the possible influence that the performance of an IC manoeuvre might have on perceived breathlessness. Upon exercise cessation, subjects were asked to verbalize their main reason for stopping exercise (i.e. respiratory discomfort, leg discomfort, combination of respiratory and leg discomfort or other) and this reason was documented. Finally, qualitative descriptors of respiratory discomfort at the symptom-limited peak of cycle exercise were collected by questionnaire (O'Donnell *et al.* 2000).

Operating lung volumes

Changes in end-expiratory lung volume (EELV) were estimated from IC measurements collected at rest, at the end of each 2 min interval during exercise and at end-exercise. Assuming that TLC does not change during exercise (Stubbing *et al.* 1980), changes in IC and inspiratory reserve volume (IRV) reflect changes in dynamic EELV ($EELV = TLC - IC$) and end-inspiratory lung volume ($EILV = TLC - IRV$), respectively. This has been found to be a reliable method of tracking acute changes in operating lung volumes (Yan *et al.* 1997; O'Donnell *et al.* 1998). Confirmation of satisfactory technique and reproducibility of IC manoeuvres for each subject was established during an initial practice session at rest by evaluating the consistency of volume and peak inspiratory P_{oes} measurements, as described in detail previously (O'Donnell *et al.* 1997, 2001). Subjects were given a few breaths' warning before an IC manoeuvre, a prompt for the manoeuvre (i.e. 'at the end of the next normal breath out, take a big, deep breath all the way IN') and then strong verbal encouragement to make a maximal inspiratory effort (i.e. 'IN... IN... IN...'). To verify that TLC was attained with each IC manoeuvre during exercise we confirmed that peak inspiratory P_{oes}

values matched those obtained at rest. When subjects indicated the desire to stop exercise, an end-exercise IC manoeuvre was performed within 15 s; or if an acceptable IC had been performed within the preceding 30 s and the breathing pattern had not restabilized, then the value from that IC was used as the end-exercise value. The resting IC was recorded as the mean of the two best reproducible efforts.

Oesophageal pressure-derived respiratory mechanics: measurement and analysis

Oesophageal pressure-derived measures of respiratory mechanics were collected on a breath-by-breath basis using an integrated data-acquisition setup. Briefly, an adult balloon-tipped oesophageal catheter (Ackrad Laboratories, Cranford, NJ, USA) containing 0.5 ml of air was positioned according to an accepted technique (Baydur *et al.* 1982). We have previously determined (authors' unpublished observations) that 0.5 ml of air represents the minimal balloon volume for zero pressure using our testing setup and this particular oesophageal catheter. The placement and position (i.e. right/left nostril, distance from the nare) of the catheter was identical at TM_3 and PP for each subject. Oesophageal pressure was sampled continuously at a rate of 100 Hz using a differential pressure transducer (MP45; Validyne Engineering, Northridge, CA, USA), a signal conditioner (Carrier amplifier; Gould Electronics, Chandler, AZ, USA) and computer data-acquisition software (Advanced CODAS; Dataq Instruments, Akron, OH, USA). The continuous flow signal from the Vmax229d system was simultaneously input into this system for further analysis. Maximum inspiratory sniff manoeuvres against an occluded airway at EELV were performed at rest and within 30 s of exercise cessation to obtain maximal values for inspiratory P_{oes} ($P_{I_{max}}$). In our experience, performance of $P_{I_{max}}$ manoeuvres during exercise is not practical because it disrupts the pattern of breathing, thereby increasing breathlessness intensity ratings. Therefore, values for $P_{I_{max}}$ at each submaximal work rate during exercise were calculated at iso-time (i.e. at the concurrent exercise time corresponding to minutes 2, 4, 6, etc.) by linear interpolation between simultaneous $P_{I_{max}}$ and exercise time measurements taken at rest and at end-exercise. All tidal P_{oes} swing measurements were subsequently compared with iso-time values of $P_{I_{max}}$.

Campbell diagrams were constructed to calculate: expiratory (W_{Eres}) and inspiratory (W_{Ires}) flow resistive work of breathing; inspiratory elastic work of breathing (W_{Iel}); and total inspiratory ($WOB = W_{Iel} + W_{Ires}$) and resistive ($W_{RES} = W_{Eres} + W_{Ires}$) work of breathing (Otis, 1964). We assumed that pregnancy had no effect on static (or dynamic) chest wall compliance (C_w), which we estimated as 4% predicted vital capacity (VC; cmH_2O^{-1})

(Agostoni & Mead, 1964). The C_w curve was anchored using the predicted normal FRC (Crapo *et al.* 1982), i.e. resting relaxation volume of the respiratory system for each subject in PP and TM₃. We must point out, however, that if our assumption is wrong and C_w decreased from PP to TM₃ (Marx *et al.* 1970), then TM₃ values for W_{rel} and thus WOB at any given work rate and \dot{V}_E would tend to be overestimated. Work of breathing measurements were multiplied by f_R and expressed as joules min^{-1} . The tension–time index of the inspiratory muscles was calculated as the product of mean inspiratory $P_{\text{oes}}/P_{\text{Imax}}$ and T_I/T_{TOT} (Baydur *et al.* 1982). Pulmonary resistance was calculated as the average of 5 breaths at rest, at the highest-equivalent work rate and at end-exercise for each subject in PP and TM₃ using the iso-volume method (Tobin, 1998). The ratio of contractile respiratory muscle effort (tidal $P_{\text{oes}}/P_{\text{Imax}}$) to thoracic volume displacement (V_T/VC) was calculated for each subject and used as an index of neuromechanical (un)coupling of the respiratory system (O'Donnell *et al.* 1997, 2000, 2006).

Analysis of exercise endpoints

All breath-by-breath measurements were averaged in 30 s intervals at rest and during exercise. Volume (integrated flow) and P_{oes} signals were also averaged in 30 s intervals for reconstruction of P_{oes} –volume loops. Cardiorespiratory and P_{oes} -derived measurements collected over the first 30 s period of every second minute during exercise were linked with symptom ratings and IC measurements collected in the latter 30 s of the respective minute so as to avoid contamination of averaged breath-by-breath data by irregular breaths surrounding IC manoeuvres.

Five main time points were used for the evaluation of exercise parameters: (1) pre-exercise rest; (2) the ventilatory threshold (Tvent); (3) the highest equivalent work rate (HEWR); (4) the V_T/\dot{V}_E inflection; and (5) peak 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 and P_{oes} -derived measurements were averaged over the last 30 s of this period; and IC measurements for this period were collected during breathing on the same circuit immediately after completion of the quiet breathing period. Tvent was detected and verified individually using the V-slope and dual criterion methods (Beaver *et al.* 1986; Wasserman *et al.* 2005). HEWR was defined as the highest equivalent cycle work rate achieved during each of the symptom-limited incremental cycle exercise tests performed by a given subject (i.e. iso-work for each subject). The relationship between V_T and \dot{V}_E (Hey *et al.* 1966) was examined and a point of inflection (i.e. V_T/\dot{V}_E inflection) was determined for each subject at TM₃ and PP. Finally, *peak* exercise was defined as the last 30 s

of loaded pedalling: cardiorespiratory and P_{oes} -derived measurements were averaged over this time period; and IC measurements and Borg ratings of breathlessness and leg discomfort were collected immediately at the end of this period. Peak work rate was defined as the highest cycle work rate that the subject was able to maintain for at least 30 s; endurance time was defined as the duration of loaded pedalling. Ventilation was compared with the maximal ventilatory capacity (MVC), which was estimated by multiplying the measured FEV₁ by 35 (Gandevia & Hugh-Jones, 1957). Mean arterial blood pressure was estimated as the diastolic pressure plus one-third of the pulse pressure.

Statistical analysis

A one-way repeated measures analysis of variance (ANOVA) was used to examine the effects of human pregnancy on measured variables at each measurement time (SigmaStat for Windows Version 3.10, Systat Software, Inc., San Jose, CA, USA). Pregnancy- and exercise-induced changes in P_{Imax} and in peak inspiratory P_{oes} recorded during sequential IC manoeuvres were compared using a two-way repeated measures ANOVA with Tukey's (HSD) *post hoc* test, respectively. Reasons for stopping exercise and qualitative descriptors of breathlessness at end-exercise were analysed using Fisher's exact test.

The effects of pregnancy on cardiorespiratory, perceptual and respiratory mechanical responses during exercise near the limits of tolerance were examined by comparing (1) measurements at the V_T/\dot{V}_E inflection and at peak exercise both within and between conditions using a two-way repeated measures ANOVA with Tukey's (HSD) *post hoc* test and (2) the change in parameter values from the V_T/\dot{V}_E inflection to end-exercise between PP and TM₃ using a one-way repeated measures ANOVA. A $P < 0.05$ level of significance was used for all analyses. Results are reported as means \pm S.E.M.

Results

Fifteen young, healthy, non-smoking, regularly active women with mild-to-moderate pregnancy-induced persistent activity-related breathlessness completed the study (Table 1). Nine women were nulliparous and six were primiparous. As expected, body mass and body mass index increased; $[P_4]$ and $[E_2]$ increased; and resting P_{aCO_2} , $[H^+]$ and $[HCO_3^-]$ decreased from PP to TM₃. Serum $[P_4]$ and $[E_2]$ values at PP were not significantly different ($P > 0.05$) than those previously reported from our laboratory in a group of 14 healthy eumenorrhoeic women in the follicular phase of their menstrual cycle (Slatkovska *et al.* 2006), suggesting that women had returned to their non-pregnant control state.

Table 1. Subject characteristics and resting pulmonary function

	PP	TM ₃	Δ(TM ₃ – PP)	P value
Age (years)	30.6 ± 1.0	—	—	—
Height (cm)	166.4 ± 1.9	—	—	—
Body mass (kg)	69.6 ± 3.1	80.9 ± 3.0	11.3 ± 0.8	<0.001
Body mass index (kg m ⁻²)	25.0 ± 0.8	29.1 ± 0.7	4.1 ± 0.3	<0.001
Baseline dyspnoea index (focal score)	11.9 ± 0.1	8.6 ± 0.4	-3.3 ± 0.4	<0.001
Blood biochemistry				
<i>P</i> _{aCO₂} (mmHg)	39.5 ± 0.6	31.6 ± 0.4	-7.9 ± 0.7	<0.001
[H ⁺] (nequiv l ⁻¹)	38.7 ± 0.4	35.8 ± 0.2	-2.9 ± 0.4	<0.001
[HCO ₃ ⁻] (mequiv l ⁻¹)	24.6 ± 0.3	21.3 ± 0.3	-3.3 ± 0.4	<0.001
Progesterone (nmol l ⁻¹)	1.1 ± 0.2	877 ± 73	876 ± 73	<0.001
17β-Oestradiol (pmol l ⁻¹)	106 ± 17	123 397 ± 47 068	123 291 ± 47 071	0.020
Pulmonary function				
FEV ₁ (l)	3.14 ± 0.09	3.28 ± 0.09	0.14 ± 0.04	0.002
FEV ₁ /FVC (%)	79.7 ± 2.1	80.2 ± 1.5	0.6 ± 0.9	0.527
FVC (l)	3.98 ± 0.15	4.11 ± 0.15	0.13 ± 0.03	0.001
PEF (l s ⁻¹)	6.82 ± 0.23	6.80 ± 0.28	-0.02 ± 0.14	0.898
FEF _{25%-75%} (l s ⁻¹)	3.07 ± 0.20	3.26 ± 0.16	0.19 ± 0.09	0.061
IC (l)	2.92 ± 0.11	2.65 ± 0.11	0.28 ± 0.08	0.003
FRC (l)	2.36 ± 0.14	2.71 ± 0.14	-0.36 ± 0.06	<0.001
sRaw (cmH ₂ O s ⁻¹)	6.59 ± 0.60	6.08 ± 0.54	-0.52 ± 0.27	0.072
<i>D</i> _{LCO} (ml min ⁻¹ mmHg ⁻¹)	21.3 ± 0.9	20.6 ± 0.8	-0.7 ± 0.4	0.136
MIP (cmH ₂ O)	76 ± 4	76 ± 5	0.1 ± 2.1	0.975
MEP (cmH ₂ O)	113 ± 6	104 ± 6	-9 ± 5	0.102
<i>C</i> _{st} (cmH ₂ O l ⁻¹)	0.25 ± 0.03	0.30 ± 0.06	0.04 ± 0.07	0.561
<i>C</i> _{dyn} (cmH ₂ O l ⁻¹)	0.17 ± 0.02	0.21 ± 0.04	0.04 ± 0.04	0.360
<i>P</i> _{st} (cmH ₂ O)	30.6 ± 4.5	31.0 ± 2.3	0.4 ± 2.4	0.864

Values are means ± S.E.M. PP, postpartum; TM₃, third trimester; Δ, pregnancy-induced change; *P*_{aCO₂}, arterialized venous partial pressure of CO₂; [H⁺], arterialized venous hydrogen ion concentration; [HCO₃⁻], plasma bicarbonate concentration; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow; FEF_{25%-75%}, forced expiratory flow from 25% to 75% of the FVC manoeuvre; IC, inspiratory capacity; FRC, functional residual capacity; sRaw, specific airway resistance; *D*_{LCO}, single breath diffusing capacity for carbon monoxide; MIP and MEP, maximal inspiratory and expiratory pressure, respectively; *C*_{st} and *C*_{dyn}, static and dynamic lung compliance, respectively (*n* = 7); *P*_{st}, static lung recoil pressure (*n* = 7).

Resting pulmonary function

Pregnancy-induced changes in resting pulmonary function are shown in Table 1 and Fig. 1. In TM₃ compared with PP: FEV₁ and FVC increased, with no associated change in the FEV₁/FVC ratio; specific airway resistance (sRaw) decreased by ~9% (*P* = 0.072); IC increased; FRC, residual volume (RV) and expiratory reserve volume (ERV) decreased; and peak expiratory flow, TLC, slow vital capacity, *D*_{LCO}, MIP, MEP, *C*_{st} and *C*_{dyn} did not change. The fact that TLC did not change with pregnancy is further supported by the observation that *P*_{st} was similar in TM₃ and PP (Table 1).

Physiological responses to symptom-limited cycle exercise

Ventilatory and metabolic responses to exercise are shown in Fig. 2. At rest and throughout exercise in TM₃ compared

with PP: \dot{V}_E increased significantly as a result of an increase in V_T with no change in f_R ; and P_{ETCO_2} decreased significantly (Fig. 2). As expected, HR increased at rest (by 12 ± 3 beats min⁻¹, *P* < 0001) and reached a peak value that was 6 ± 1 beats min⁻¹ lower (*P* < 0.001) in TM₃ compared with PP (Table 2). Measurements at peak exercise and at the HEWR are provided in Table 2. Peak work rate, \dot{V}_{O_2} and \dot{V}_E were similar, although the duration of loaded pedalling decreased by 0.6 ± 0.3 min (*P* = 0.046) in TM₃ compared with PP. At the HEWR during exercise in TM₃ compared with PP (Table 2): \dot{V}_{O_2} increased; \dot{V}_E and V_T increased by 10.2 l min⁻¹ (20%) and 0.35 l (19%), respectively, with no associated change in f_R or breath timing (T_I , T_E , T_I/T_{TOT}). The \dot{V}_{O_2} at Tvent was not different despite a greater \dot{V}_E in TM₃ compared with PP: \dot{V}_{O_2} averaged 1.10 ± 0.03 and 1.05 ± 0.04 l min⁻¹ in TM₃ and PP, respectively; and \dot{V}_E at Tvent averaged 32.4 ± 1.3 versus 27.1 ± 1.1 l min⁻¹ in TM₃ versus PP, respectively (*P* = 0.005).

Respiratory mechanical responses to symptom-limited cycle exercise

The assumption that TLC did not change during exercise was supported by the fact that peak inspiratory P_{oes} values did not change during sequential IC manoeuvres from rest (TM₃, -26 ± 2 cmH₂O; PP, -25 ± 2 cmH₂O) and throughout exercise (e.g. TM₃ at peak, -24 ± 2 cmH₂O; PP at peak, -21 ± 2 cmH₂O) both within and between conditions. These observations validate the use of serial IC measurements to track changes in operating lung volumes during exercise in healthy pregnant and non-pregnant women. We also found that $P_{I_{max}}$ was not significantly different from its resting value at end-exercise within PP (-59 ± 4 versus -58 ± 5 cmH₂O, respectively; $P = 0.827$) and TM₃ (-57 ± 4 versus -53 ± 4 cmH₂O, respectively; $P = 0.316$); in this regard, pregnancy had no effect on pre-exercise, end-exercise or the exercise-induced change in $P_{I_{max}}$.

Dynamic operating lung volumes are shown in Fig. 2 (upper right panels) and Fig. 3. In contrast to PP where V_T continued to increase throughout exercise, a plateau in the V_T response was noted at the upper work rates in TM₃ secondary to a corresponding plateau in dynamic IRV at its minimal level (Fig. 2). In TM₃ compared with PP, IC increased by 0.37 l ($P < 0.001$) at rest (pre-exercise) and remained consistently larger during exercise up to

100 W, with no difference observed at the HEWR or at peak exercise (Table 2). Consequently, IC remained relatively constant throughout exercise in TM₃ and did not progressively increase from its resting value during exercise as it did in PP. Pregnancy-induced increases in V_T were accommodated from below (decreased EELV) at rest and throughout exercise (Fig. 3), and comprised a similar proportion (~72%) of the available IC at end-exercise in TM₃ compared with PP (Table 2).

The effects of pregnancy on P_{oes} -derived measures of respiratory mechanics during exercise are shown in Figs 2 and 4; measurements at the HEWR and at peak exercise are presented in Table 2. Tidal P_{oes} , tidal $P_{oes}/P_{I_{max}}$, W_{Eres} , W_{Ires} , W_{Iel} , W_{RES} and WOB were consistently higher at any given submaximal cycle work rate in TM₃ compared with PP, reflecting pregnancy-induced increases in exercise \dot{V}_E . The ratio of contractile respiratory muscle effort (tidal $P_{oes}/P_{I_{max}}$) to thoracic volume displacement (V_T/VC), an index of neuromechanical (un)coupling of the respiratory system, was not significantly different at any given work rate during incremental cycle exercise in TM₃ compared with PP (Fig. 5). Pulmonary resistance was not significantly different at rest, at the HEWR or at end-exercise in TM₃ compared with PP.

A V_T/\dot{V}_E inflection point was identified for all subjects in both TM₃ and PP. This inflection occurred at a

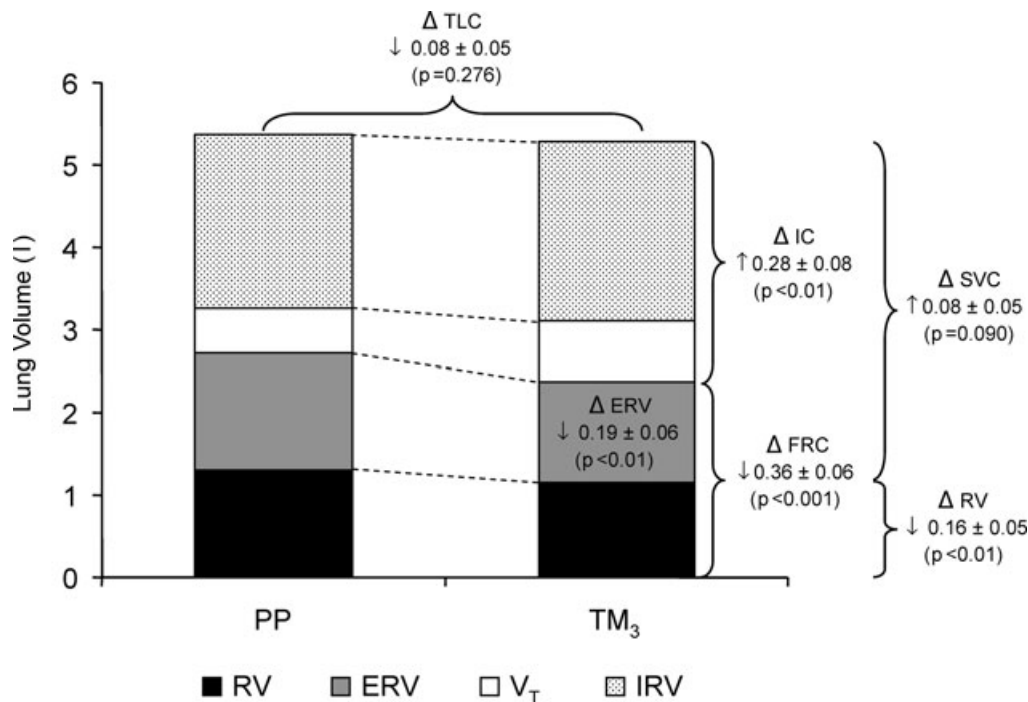


Figure 1. Effects of pregnancy on static lung volumes and capacities

In TM₃ compared with PP: FRC, ERV and RV decreased, while IC increased with no associated change in TLC. PP, postpartum; TM₃, third trimester; TLC, total lung capacity; ERV, expiratory reserve volume; IC, inspiratory capacity; FRC, functional residual capacity; SVC, slow vital capacity; RV, residual volume; V_T, tidal volume, IRV, inspiratory reserve volume; Δ, pregnancy-induced change (i.e. mean difference ± s.e.m. between values at TM₃ and PP); ↑, increase; ↓, decrease.

lower cycle work rate during exercise in TM₃ compared with PP (120 ± 4 versus 133 ± 7 W; *P* = 0.013). Despite similar \dot{V}_E (56 ± 3 versus 53 ± 2 l min⁻¹ at TM₃ versus PP, respectively) and P_{oes} -derived mechanical measurements at this point, V_T was larger (*P* < 0.05) by an average of 0.26 l or 14% and occupied a greater (*P* < 0.05) proportion of both the available IC and VC in TM₃ than PP. Beyond the V_T/\dot{V}_E inflection point in TM₃, there was no further change (i.e. a plateau in the exercise response) in V_T , IC and IRV, despite continued increases in work rate, \dot{V}_{O_2} , \dot{V}_{CO_2} , \dot{V}_E , tidal P_{oes} , tidal $P_{oes}/P_{I_{max}}$ and work of breathing measurements. This is in contrast to PP, where V_T continued to increase after this inflection point as IRV continued to decline until it reached a similarly reduced level at end-exercise. As a result, further increases in the tidal P_{oes}/V_T (by 2.64

and 1.41 cmH₂O l⁻¹, *P* = 0.041) and effort–displacement ratios (by 0.22 and 0.13 units, *P* = 0.060) were consistently greater during exercise beyond the V_T/\dot{V}_E inflection point in TM₃ compared with PP (Fig. 5). Interestingly, the V_T/\dot{V}_E inflection point coincided with an inflection in the IRV/ \dot{V}_E relationship, indicating that respiratory mechanical constraints probably contributed to the saturation of V_T expansion near the limits of tolerance in TM₃.

Perceptual responses to symptom-limited incremental cycle exercise

Pregnancy had no effect on the distribution of the reasons for stopping exercise. In TM₃, two women stopped

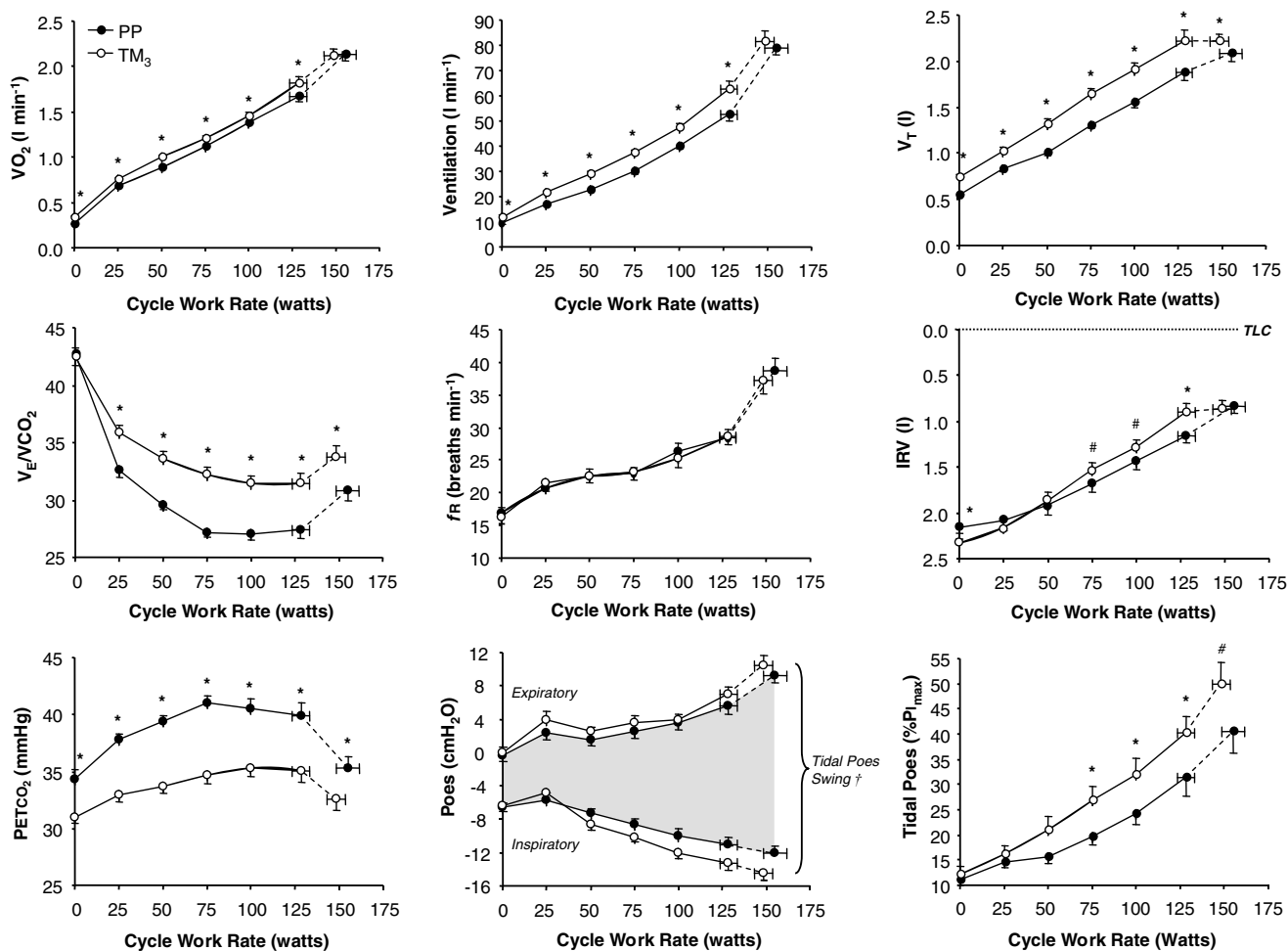


Figure 2. Effects of pregnancy on oxygen uptake, ventilation, breathing pattern and respiratory mechanical/muscular responses to incremental cycle exercise

Data points are mean ± S.E.M. values at rest, at standardized cycle work rates during exercise and at peak exercise. PP, postpartum; TM₃, third trimester; \dot{V}_{O_2} , metabolic rate of O₂ uptake; \dot{V}_E/\dot{V}_{CO_2} , ventilatory equivalent for CO₂; P_{ETCO_2} , end-tidal partial pressure of CO₂; V_T , tidal volume; IRV, inspiratory reserve volume; f_R , breathing frequency; P_{oes} , oesophageal pressure; tidal P_{oes} (% $P_{I_{max}}$), tidal oesophageal pressure expressed as a percentage of maximum inspiratory pressure (an index of contractile respiratory muscle effort). **P* < 0.05; #*P* ≤ 0.07 TM₃ versus PP; † tidal P_{oes} swings increased from PP to TM₃ (*P* < 0.05) during exercise at cycle work rates ≥ 75 W.

Table 2. Effects of pregnancy on perceptual, cardio-metabolic, ventilatory and respiratory mechanical/muscular responses at the symptom-limited peak (i.e. last 30 s of loaded pedalling) and at the highest equivalent work rate (HEWR) of cycle exercise

	Peak exercise		HEWR	
	PP	TM ₃	PP	TM ₃
Breathlessness (Borg scale)	5.4 ± 0.6	6.5 ± 0.5*	3.2 ± 0.4	4.1 ± 0.3*
Leg discomfort (Borg scale)	6.6 ± 0.7	6.5 ± 0.6	4.1 ± 0.5	4.5 ± 0.5
Work rate (W)	155 ± 7	148 ± 5	128 ± 5	128 ± 5
\dot{V}_{O_2} (l min ⁻¹)	2.13 ± 0.08	2.12 ± 0.08	1.67 ± 0.06	1.82 ± 0.07†
\dot{V}_{O_2} (% predicted max)	111 ± 4	110 ± 3	87 ± 2	94 ± 3†
\dot{V}_{CO_2} (l min ⁻¹)	2.58 ± 0.08	2.40 ± 0.08*	1.91 ± 0.07	1.99 ± 0.08
HR (beats min ⁻¹)	174 ± 3	168 ± 3‡	158 ± 4	157 ± 2
O ₂ pulse (ml beat ⁻¹)	12.3 ± 0.5	12.7 ± 0.5	10.7 ± 0.5	11.6 ± 0.5*
MAP (mmHg)	104 ± 1	107 ± 1	102 ± 2	105 ± 5
\dot{V}_E (l min ⁻¹)	79.1 ± 2.6	81.5 ± 4.1	52.5 ± 2.6	62.7 ± 3.2‡
\dot{V}_E /MVC (%)	72.8 ± 3.2	71.5 ± 3.5	48.3 ± 2.7	54.7 ± 2.4†
V _T (l)	2.08 ± 0.08	2.22 ± 0.07†	1.88 ± 0.09	2.22 ± 0.12‡
V _T /IC (%)	71.8 ± 2.2	72.4 ± 2.3*	61.8 ± 2.0	71.2 ± 2.8‡
IC (l)	2.92 ± 0.11	3.08 ± 0.08	3.04 ± 0.12	3.11 ± 0.08
IC change from rest (l)	0.21 ± 0.09	-0.00 ± 0.10#	0.33 ± 0.10	0.03 ± 0.09†
IRV (l)	0.84 ± 0.08	0.86 ± 0.08	1.16 ± 0.08	0.89 ± 0.09†
f _R (breaths min ⁻¹)	38.7 ± 1.9	37.2 ± 2.0	28.4 ± 1.3	28.6 ± 1.3
T _I /T _{TOT} (%)	50.4 ± 0.9	48.7 ± 0.8	46.5 ± 0.7	47.3 ± 0.8
V _T /T _I (l s ⁻¹)	2.57 ± 0.11	2.77 ± 0.13	1.87 ± 0.07	2.20 ± 0.10†
V _T /T _E (l s ⁻¹)	2.61 ± 0.09	2.65 ± 0.16	1.65 ± 0.10	1.98 ± 0.11‡
S _{pO₂} (%)	94.5 ± 1.0	95.1 ± 0.6	95.5 ± 0.4	95.0 ± 0.6
P _{ETCO₂} (mmHg)	35.3 ± 0.9	32.6 ± 1.1*	39.9 ± 1.1	35.1 ± 1.0‡
\dot{V}_E / \dot{V}_{O_2}	37.5 ± 1.4	38.6 ± 1.4	31.5 ± 1.2	34.5 ± 1.1†
\dot{V}_E / \dot{V}_{CO_2}	30.8 ± 0.9	33.8 ± 1.0†	27.4 ± 0.8	31.5 ± 0.8‡
Peak inspiratory P _{oes} (cmH ₂ O)	-12.1 ± 0.9	-14.4 ± 0.9	-11.0 ± 0.9	-13.3 ± 0.8#
Peak expiratory P _{oes} (cmH ₂ O)	9.3 ± 0.9	10.5 ± 1.2	5.6 ± 1.0	7.0 ± 0.9
Tidal P _{oes} (cmH ₂ O)	21.4 ± 1.3	24.8 ± 1.7*	16.9 ± 1.2	20.3 ± 1.2†
Tidal P _{oes} /P _I max (%)	40.6 ± 4.3	49.8 ± 4.4#	31.5 ± 3.9	40.2 ± 3.1*
Tidal P _{oes} /P _I max: V _T /VC	0.81 ± 0.11	0.94 ± 0.09	0.69 ± 0.09	0.76 ± 0.06
Tension time index	0.08 ± 0.01	0.08 ± 0.01	0.06 ± 0.01	0.07 ± 0.01
W _I res (joules min ⁻¹)	45.1 ± 3.3	54.1 ± 8.2	23.0 ± 3.5	30.4 ± 5.4*
W _E res (joules min ⁻¹)	76.2 ± 6.6	79.2 ± 11.2	30.4 ± 5.8	41.8 ± 6.5‡
W _{RES} (joules min ⁻¹)	121.3 ± 9.2	133.3 ± 8.8	53.5 ± 9.1	72.1 ± 11.5†
W _I el (joules min ⁻¹)	110.3 ± 6.5	132.2 ± 13.5#	77.5 ± 4.1	109.1 ± 11.4†
WOB (joules min ⁻¹)	155.5 ± 8.2	186.3 ± 18.6#	110.6 ± 6.3	139.5 ± 14.2†
R _L (cmH ₂ O l ⁻¹ s ⁻¹)	2.55 ± 0.15	2.65 ± 0.17	2.41 ± 0.16	2.55 ± 0.29

*P < 0.05; †P < 0.01; ‡P < 0.001; #P ≤ 0.07 TM₃ versus PP. Values are means ± s.e.m. PP, postpartum; TM₃, third trimester; O₂, oxygen; CO₂, carbon dioxide; \dot{V}_{O_2} , metabolic rate of O₂ uptake; \dot{V}_{CO_2} , metabolic rate of CO₂ production; HR, heart rate; MAP, mean arterial pressure; \dot{V}_E , minute ventilation; MVC, maximal ventilatory capacity estimated as FEV₁ × 35; V_T, tidal volume; IC, inspiratory capacity; IRV, inspiratory reserve volume; f_R, breathing frequency; T_I/T_{TOT}, inspiratory duty cycle; V_T/T_I and V_T/T_E, mean tidal inspiratory and expiratory flow, respectively; S_{pO₂}, arterial O₂ saturation; P_{ETCO₂}, end-tidal CO₂ tension; \dot{V}_E / \dot{V}_{O_2} and \dot{V}_E / \dot{V}_{CO_2} , ventilatory equivalent for O₂ and CO₂, respectively; P_{oes}, oesophageal pressure; P_Imax, maximum inspiratory (negative) oesophageal pressure; VC, vital capacity; W_Ires, inspiratory flow resistive work of breathing; W_Eres, expiratory flow resistive work of breathing; W_{RES}, total resistive work of breathing; W_Iel, inspiratory elastic work of breathing; WOB, total inspiratory work of breathing; R_L, pulmonary resistance.

primarily due to breathing discomfort, eight due to leg discomfort and five due to a combination of both breathing and leg discomfort. In PP, one woman stopped due to breathing discomfort, 13 due to leg discomfort

and one due to a combination of breathing and leg discomfort. The selection frequency of breathlessness descriptor phrases at end-exercise was similar in TM₃ and PP. The majority (80%) of women in both TM₃ and PP

described their breathlessness at this point as an increased sense of respiratory 'work/effort'. Borg ratings of perceived leg discomfort were not significantly different at any given work rate during exercise in TM₃ compared with PP (Fig. 6). Breathlessness intensity ratings were significantly greater at 100 W (by 0.6 Borg units, $P = 0.045$), at the HEWR and at peak exercise in TM₃ compared with PP (Fig. 6, Table 2). Breathlessness– \dot{V}_E relationships, however, were essentially superimposed throughout much of exercise in TM₃ and PP (Fig. 5). Breathlessness intensity was similar at the V_T/\dot{V}_E inflection point during exercise in TM₃ and PP (Fig. 5). Similar to the response pattern seen with the tidal P_{oes}/V_T and effort–displacement ratios (discussed above), progressive increases in breathlessness intensity ratings (by 2.9 and 2.1 Borg units, $P = 0.024$) were significantly greater during exercise beyond the V_T/\dot{V}_E inflection point in TM₃ compared with PP (Fig. 5).

Discussion

The main findings of this study were: (1) pregnancy-induced increases in exertional breathlessness reflected the normal awareness of increased \dot{V}_E and contractile respiratory muscle effort; (2) mechanical adaptations of the respiratory system, including recruitment of resting IC and increased bronchodilatation, accommodated the increased V_T expansion during exercise in pregnancy, while preserving effort–displacement and breathlessness– \dot{V}_E relationships; and (3) dynamic mechanical ventilatory constraints (as evidenced by a plateau in the V_T and IRV response during exercise beyond the V_T/\dot{V}_E inflection point) contributed to perceived respiratory discomfort near the limits of tolerance in late gestation.

Normal awareness of an increased contractile respiratory muscle effort

The women in our study reported mild-to-moderate persistent activity-related breathlessness, as evidenced by a ~ 3.5 unit decrease in the BDI focal score from PP to TM₃. Consistent with the results of previous studies (Sady *et al.* 1989; Lotgering *et al.* 1995), however, aerobic working capacity was well preserved in late gestation: women exercised to at least 100% of their predicted maximum work rate and \dot{V}_{O_2} in TM₃ and PP, respectively.

In keeping with the results of Field *et al.* (1991), we found that \dot{V}_E , tidal P_{oes}/P_{Imax} and breathlessness intensity ratings were significantly higher at any given work rate during incremental cycle exercise in TM₃ compared with PP (e.g. by 10.2 l min^{-1} (20%), $8.8\%P_{Imax}$ (28%) and 0.9 Borg units (28%) at the HEWR). We also found that breathlessness– \dot{V}_E relationships were similar throughout exercise in TM₃ compared with PP; and that pregnancy-induced increases in breathlessness at the HEWR correlated significantly with concomitant changes in indices of maternal hyperventilation, namely \dot{V}_E/\dot{V}_{CO_2} (Pearson $r = 0.576$, $P = 0.025$) and P_{ETCO_2} (Pearson $r = -0.744$, $P = 0.002$). Collectively, these findings support the hypothesis that pregnancy-induced increases in exertional breathlessness reflect the normal conscious awareness of increased \dot{V}_E and contractile respiratory muscle effort. The neurophysiological basis of breathlessness in this circumstance is thought to be increased central corollary discharge to the somatosensory cortex, secondary to increased brainstem (autonomic) and cortical respiratory motor drive (Chen *et al.* 1991, 1992; Manning & Schwartzstein, 1995; O'Donnell *et al.* 2007). Direct sensory afferent information arising from mechano- and metaboreceptors in the vigorously contracting inspiratory pump muscles may also contribute

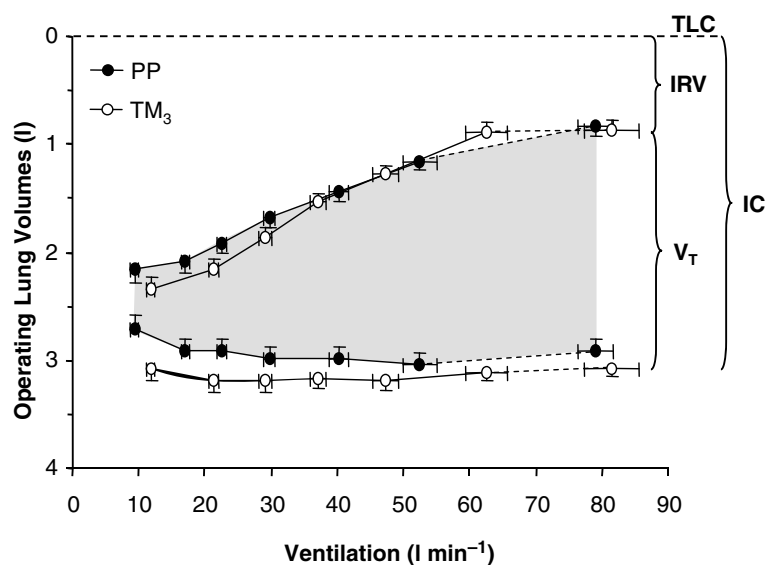


Figure 3. Effects of pregnancy on the behaviour of dynamic operating lung volumes during incremental cycle exercise

Data points are mean \pm s.e.m. values at rest, at standardized cycle work rates during exercise and at peak exercise. PP, postpartum; TM₃, third trimester; TLC, total lung capacity; IRV, inspiratory reserve volume; V_T , tidal volume; IC, inspiratory capacity.

to the sense of increased respiratory 'work/effort' when ventilatory requirements are high (Manning & Schwartzstein, 1995).

Role of respiratory mechanical factors in gestational breathlessness

This is the first study to examine the potential contribution of respiratory mechanical factors to perceived respiratory discomfort during exercise in human pregnancy. It is reasonable to assume that the progressive thoraco-abdominal distortion of pregnancy may, in the setting of an increased central ventilatory drive, uncouple the otherwise harmonious relationship between contractile respiratory muscle effort and thoracic volume displacement, i.e. neuromechanical uncoupling. Thus, it is possible that restrictive mechanical constraints on exercise hyperpnoea may develop during exercise in TM₃ with attendant amplification of breathlessness intensity ratings at any given \dot{V}_E . In support of this idea, previous studies have found that imposing a mechanical constraint to V_T expansion (by chest wall strapping), in the face of an increased central ventilatory drive (by dead space loading), significantly increased (*versus* control) the intensity of perceived breathlessness at any given \dot{V}_E during incremental cycle exercise in healthy subjects (Harty *et al.* 1999; O'Donnell *et al.* 2000). Surprisingly, we found that breathlessness- \dot{V}_E and effort-displacement relationships (Fig. 5) were essentially superimposed throughout much of exercise in TM₃ compared with PP. This suggests that respiratory mechanical factors did not contribute importantly to gestational breathlessness and/or that physiological adaptations were in place in TM₃ to minimize the sensory consequences of increased respiratory mechanical loading.

In keeping with the results of several previous studies (Gilroy *et al.* 1988; Berry *et al.* 1989; Contreras *et al.* 1991; Garcia-Rio *et al.* 1996, 1997), we found that pre-exercise resting IC increased (by 0.37 l or ~14%) and EELV decreased (by 0.45 l or ~17%) from PP to TM₃ (Fig. 3). Thus, IC increased because EELV decreased with no associated change in TLC. Static (and dynamic) lung compliance and inspiratory muscle strength were not affected by pregnancy. Preserved inspiratory muscle strength probably reflects the combined physiological effects of an increased area of apposition (Gilroy *et al.* 1988) and increased diaphragmatic mid-position (Thomson & Cohen, 1938) with attendant improvement in the length-tension relationship of the diaphragm, secondary to reductions in resting EELV. The reduced resting EELV in TM₃ may be explained by reductions in chest wall and therefore total respiratory system compliance (Marx *et al.* 1970).

This is the first study to document the behaviour of dynamic operating lung volumes during exercise in

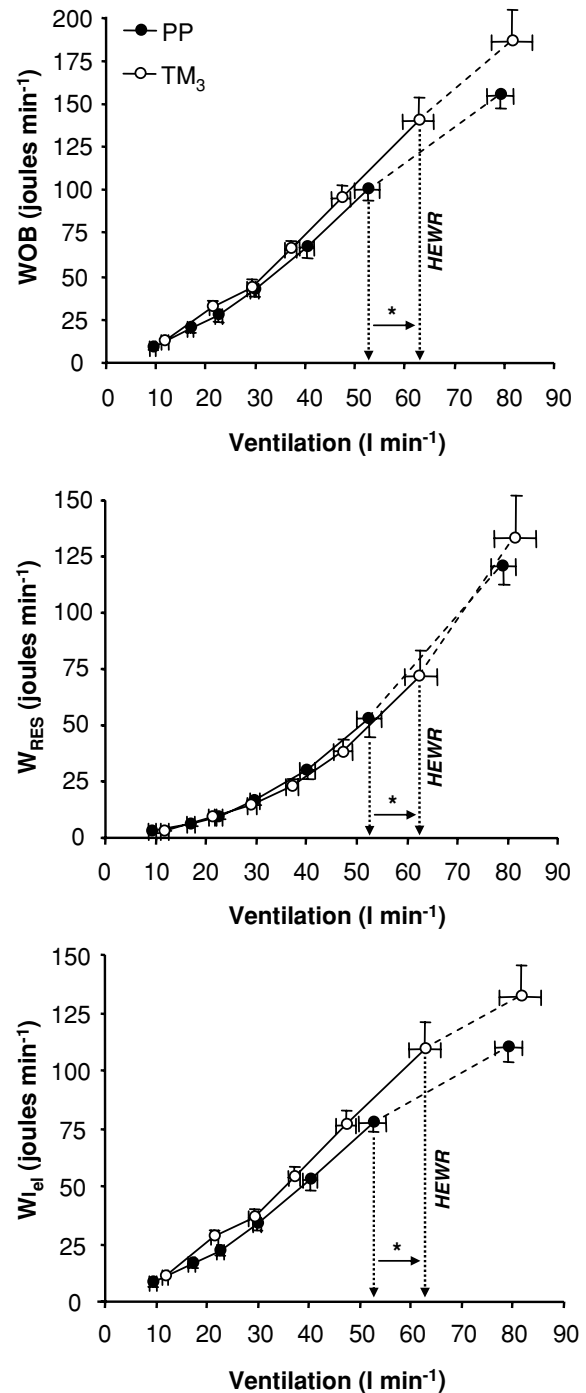


Figure 4. Effects of pregnancy on the relationship between ventilation and the total inspiratory work of breathing (WOB); total resistive work of breathing (W_{RES}); and inspiratory elastic work of breathing (W_{eli}) during incremental cycle exercise. Data points are mean \pm s.e.m. values at rest, at standardized cycle work rates during exercise and at peak exercise. Measurements of WOB, W_{RES} and W_{eli} were significantly higher in TM₃ compared with PP during exercise at the highest equivalent work rate (HEWR = 128 ± 5 W); however, these differences were no longer significant when expressed against ventilation. PP, postpartum; TM₃, third trimester. * $P < 0.05$ TM₃ versus PP during exercise at the HEWR.

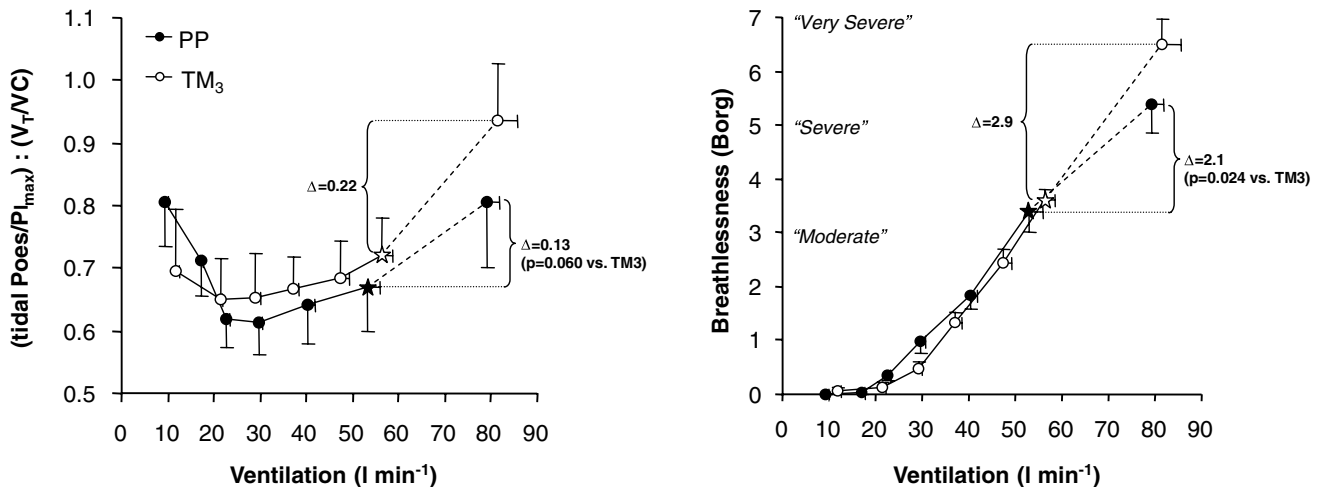


Figure 5. Effects of pregnancy on the relationship between contractile respiratory muscle effort (tidal $P_{\text{oes}}/P_{\text{Imax}}$) and thoracic volume displacement (V_T/V_C), i.e. neuromechanical (un)coupling of the respiratory system; and Borg ratings of perceived breathlessness at the limits of exercise tolerance

Data points are mean \pm S.E.M. values at rest, at standardized cycle work rates and the V_T/\dot{V}_E inflection point (\star) during exercise and at peak exercise. Effort–displacement ratios were similar at any given work rate during incremental cycle exercise in TM₃ compared with PP. The effort–displacement ratio and breathlessness intensity ratings were similar during exercise at the V_T/\dot{V}_E inflection point in TM₃ and PP. However, there was a progressively greater rise in the effort–displacement ratio and breathlessness intensity ratings after the V_T/\dot{V}_E inflection point was exceeded in TM₃ compared with PP, despite similar continued increases in ventilation. PP, postpartum; TM₃, third trimester; tidal $P_{\text{oes}}/P_{\text{Imax}}$, tidal oesophageal pressure expressed as a percentage of maximum inspiratory pressure; V_T/V_C , tidal volume expressed as a percentage of vital capacity.

pregnancy. In contrast to PP, dynamic EELV did not decrease from its resting value during incremental cycle exercise in TM₃ (Fig. 3), despite similar progressive increases in expiratory effort in both conditions (Fig. 2). We postulate that further decreasing EELV into an already reduced ERV during exercise in TM₃ would be mechanically disadvantageous (with negative sensory consequences), particularly in the setting of an increased

central ventilatory drive. In this regard, reductions in dynamic EELV would position V_T closer to RV where tidal expiratory flow generation may become compromised. Considered together, the recruitment of resting IC (Fig. 3) and the preserved relationship between contractile respiratory muscle effort and thoracic volume displacement throughout much of exercise in TM₃ (Fig. 5) strongly suggests that the greater demand for V_T

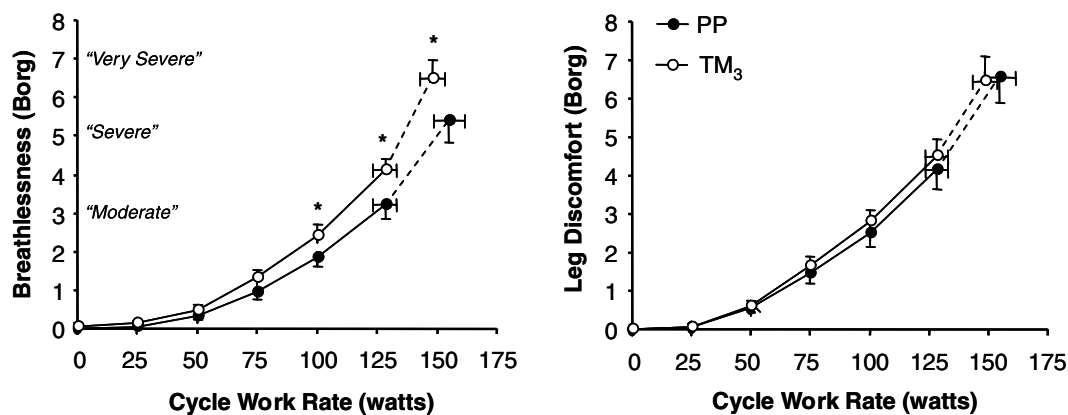


Figure 6. Effects of pregnancy on the intensity of perceived breathlessness and leg discomfort during incremental cycle exercise

Data points are mean \pm S.E.M. values at rest, at standardized cycle work rates during exercise and at peak exercise. Borg ratings of perceived breathlessness intensity were consistently higher at any given work rate during incremental cycle exercise in TM₃ compared with PP. PP, postpartum; TM₃, third trimester. $\star P < 0.05$ TM₃ versus PP.

expansion was accommodated within the most compliant portion of the respiratory system's pressure–volume relation. Interestingly, because of adequate IC recruitment at rest, the reduced ability to dynamically decrease EELV during exercise in TM₃ did not result in further encroachment on dynamic IRV (Fig. 3). It follows that if pregnant women failed to recruit resting IC, then V_T would expand to reach a critical minimal IRV even earlier in exercise. The attendant earlier onset of increased elastic loading of the inspiratory muscles would be expected to have important negative sensory consequences.

Reductions in EELV, alone or in combination with a reduced P_{aCO_2} , would be expected to increase airway resistance at rest and during exercise in pregnancy (Briscoe & Dubois, 1958; Newhouse *et al.* 1964; Sterling, 1968). Consistent with the results of previous studies (Rubin *et al.* 1956; Gee *et al.* 1967; Garrard *et al.* 1978), however, we found that resting and dynamic airway function was modestly, but consistently improved in late gestation: FEV₁ and FEF_{25%–75%} increased, while RV and sRaw decreased from PP to TM₃. Moreover, pulmonary resistance was not significantly different at rest or during exercise in pregnancy, despite substantial increases in \dot{V}_E , V_T/T_I and V_T/T_E (e.g. by ~20%, 18% and 21% at the HEWR, respectively). Even relatively minor reductions in airway diameter would be expected to have substantial deleterious effects on breathing mechanics (and therefore perceived respiratory discomfort) in the setting of high ventilatory requirements during exercise in healthy individuals. The corollary of this is that the above-mentioned improvements in resting and dynamic airway function probably contributed to the preservation of effort–displacement and breathlessness– \dot{V}_E relationships throughout much of exercise in TM₃ compared with PP (Fig. 5).

The physiological mechanisms of bronchodilatation in pregnancy remain highly conjectural and were not explored in this study. Based on the collective results of several previous studies, we postulate that pregnancy-induced reductions in pulmonary vagal efferent activity (Severinghaus & Stupfel, 1955; Butler *et al.* 1960; Newhouse *et al.* 1964; Sterling, 1968; Avery *et al.* 2001; Ito *et al.* 2006), alone or in combination with progesterone-mediated alterations in airway smooth muscle tone (Foster *et al.* 1983; Perusquia *et al.* 1997) and/or genioglossus muscle activity (Popovic & White, 1998) may be responsible.

Mechanisms of breathlessness near the limits of tolerance in late gestation

The present study is the first to examine the physiological events at high exercise intensities when breathlessness intensity ratings became 'severe' to 'very severe'. Recent studies from our laboratory have suggested

that attainment of the V_T/\dot{V}_E inflection point (at a critically reduced dynamic IRV) during exercise represents a critical mechanical event with important sensory consequences (Ofir *et al.* 2007, 2008). In the present study, \dot{V}_E , tidal $P_{oes}/P_{I_{max}}$, the effort–displacement ratio and breathlessness intensity ratings were similar during exercise at the V_T/\dot{V}_E inflection point in TM₃ and PP (Fig. 5). However, clear pregnancy-related differences emerged after this point was exceeded: V_T expansion was more constrained, and effort–displacement ratios and breathlessness intensity ratings were consistently higher (Fig. 5), despite similar levels of \dot{V}_E , tidal $P_{oes}/P_{I_{max}}$ and \dot{V}_{O_2} in TM₃ compared with PP. We have previously argued that exertional breathlessness intensity ratings increase abruptly when dynamic IRV reaches a minimal value of ~0.5–1.0 l below TLC and a widening disparity emerges between increased central ventilatory drive and the simultaneous mechanical/muscular response of the respiratory system, i.e. neuromechanical uncoupling (O'Donnell *et al.* 1997, 2000, 2006, 2007; Ofir *et al.* 2007, 2008).

Critique of methods

Weight-supported cycle exercise tests were employed to minimize the risk of falls as well as the potentially confounding effects of maternal weight gain on P_{oes} -derived measures of dynamic ventilatory mechanics during weight-bearing (e.g. treadmill) exercise. Pregnancy-induced increases in body mass (by an average of ~11.5 kg in the present study) would be expected to increase the metabolic cost of locomotion during weight-bearing activities (e.g. stair climbing) with attendant increases in \dot{V}_E , tidal $P_{oes}/P_{I_{max}}$ and therefore perceived breathlessness. In this regard, our results probably underestimate the effects of healthy human pregnancy on respiratory discomfort during activities of daily living. Furthermore, we acknowledge that the aetiology of breathlessness is multifactorial and we cannot rule out the possibility that during the course of human pregnancy psychological or affective factors (e.g. temporal sensitization) modulated the quality and intensity of exertional respiratory discomfort. Nevertheless, if these factors were contributory then one would expect both breathlessness– \dot{V}_E and leg discomfort–work rate relationships to be altered in TM₃ compared with PP; however, this was not the case.

Summary

In conclusion: (1) pregnancy-induced increases in exertional breathlessness reflected the normal awareness of increased (humorally mediated) ventilation and contractile respiratory muscle effort; (2) mechanical adaptations of the respiratory system, including

recruitment of resting inspiratory capacity and increased bronchodilatation, permitted the respiratory system to accommodate the demand for greater tidal volume expansion during exercise in pregnancy, while preserving effort–displacement (i.e. neuromechanical coupling) and breathlessness–ventilation relationships; and (3) dynamic mechanical ventilatory constraints became evident only at the limits of tolerance in late gestation with attendant negative sensory consequences. These novel findings have potentially important implications for the clinical assessment of pregnant women who seek medical attention for troublesome activity-related breathlessness. In this regard, variation in the severity of gestational breathlessness may reflect variation in the amplitude of central ventilatory drive and/or impaired respiratory mechanical adaptations, including inadequate inspiratory capacity recruitment and/or bronchodilatation.

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