Respiratory Physiology & Neurobiology 167 (2009) 87–100

Contents lists available at ScienceDirect

Respiratory Physiology & Neurobiology

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

Effects of pregnancy, obesity and aging on the intensity of perceived breathlessness during exercise in healthy humans

Dennis Jensen [a,*], Dror Ofir [b], Denis E. O'Donnell [a,c]

[a] Respiratory Investigation Unit, Department of Medicine, Queen's University and Kingston General Hospital, Kingston, ON, Canada
[b] School of Exercise and Sport Sciences, Zinman College of Physical Education and Sport Sciences, Wingate Institute, Israel
[c] Department of Physiology, Queen's University, Kingston, ON, Canada

ARTICLE INFO

Article history:
Accepted 30 January 2009

Keywords:
Breathlessness
Exercise
Pregnancy
Obesity
Aging
Respiratory mechanics

ABSTRACT

The healthy human respiratory system has impressive ventilatory reserve and can easily meet the demands placed upon it by strenuous exercise. Several acute physiological adaptations during exercise ensure harmonious neuromechanical coupling of the respiratory system, which allow healthy humans to reach high levels of ventilation without perceiving undue respiratory discomfort (breathlessness). However, in certain circumstances, such as pregnancy, obesity and natural aging, ventilatory reserve becomes diminished and exertional breathlessness is present. In this review, we focus on what is known about the mechanisms of increased activity-related breathlessness in these populations. Notwithstanding the obvious physiological differences between the three conditions, they share some common perceptual and ventilatory responses to exercise. Breathlessness intensity ratings (described as an increased "sense of effort") are consistently higher than normal at any given submaximal power output; and central motor drive to the respiratory muscles is consistently increased, reflecting increased ventilatory stimulation. The increased contractile respiratory muscle effort required to support the increased ventilatory requirements of exercise remains the most plausible source of increased activity-related breathlessness in pregnant, obese and elderly humans. In all three conditions, static and dynamic respiratory mechanical/muscular function is, to some extent, altered or impaired. Nevertheless, breathlessness intensity ratings are not significantly increased (compared to normal) at any given exercise ventilation in any of these three conditions. This strongly suggests that respiratory mechanical/muscular factors, *per se*, may be less important in the genesis of breathlessness. Moreover, in pregnancy and obesity, we present evidence that effective physiological adjustments exist to counterbalance the potentially negative sensory consequences of the altered respiratory mechanical/muscular function peculiar to these conditions.

1. Introduction

The healthy human respiratory system is generally regarded as being "overbuilt" with respect to the demands placed upon it, even during the most strenuous exercise (Dempsey, 1986). Indeed, the breathing apparatus (lungs, airways and respiratory musculature) admirably fulfills its primary task of ensuring that alveolar ventilation ($\dot{V}_A$) is precisely matched to muscle metabolic demand across a broad range of physical activities. Exercise-induced increases in minute ventilation ($\dot{V}_E$) and therefore contractile respiratory muscle effort is accompanied by "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity" (American Thoracic Society, 1999). It is clear that for most healthy young humans, it is the sense of intolerable leg discomfort – not breathing discomfort (breathlessness) – that is the proximate exercise-limiting symptom, at least during weight-supported cycle exercise (Killian, 1992a; Killian et al., 1992; Hamilton et al., 1996; Jones and Killian, 2000; O'Donnell et al., 2000). However, there is increasing evidence that troublesome activity-related breathlessness may arise in certain circumstances across the healthy human life span, including (1) during the course of pregnancy; (2) as a consequence of excessive weight gain/adiposity; and (3) with advancing age. The nature and source(s) of exertional breathlessness in these '*special*' populations are poorly understood and represent the primary focus of this review.

In this review, we will (1) discuss current neurophysiological concepts of exertional breathlessness; (2) summarize the physiological adaptations that are normally in place to minimize respiratory discomfort during exercise in healthy young individuals; and (3) review newer information about the mechanisms of exertional breathlessness in healthy pregnant, obese and elderly humans where ventilatory control and respiratory function are, to some extent, altered/impaired.

* Corresponding author. Tel.: +1 613 549 6666x4910; fax: +1 613 548 1307.
E-mail address: dennis.jensen@queensu.ca (D. Jensen).

1569-9048/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.resp.2009.01.011

2. Neurophysiology of exertional breathlessness: current concepts

Exercise requires an increase in $\dot{V}_A$ that is directly proportional to muscle metabolic requirements to replenish the O_2 extracted from the blood ($\dot{V}_{O_2}$), to eliminate the CO_2 added to the blood ($\dot{V}_{CO_2}$) and to partially compensate for the lactic acidosis that develops during exercise above the ventilatory threshold (Forster, 2000; Dempsey et al., 2006). The increase in $\dot{V}_A$ required to meet these metabolic demands must be achieved efficiently to minimize the work (WOB) and O_2 cost ($\dot{V}_{O_{2resp}}$) of breathing (Forster, 2000; Dempsey et al., 2006).

2.1. Mechanisms of exercise hyperpnea

The mechanisms underlying the precise matching of $\dot{V}_A$ to $\dot{V}_{CO_2}$ during exercise in healthy humans remain unclear and have been reviewed in detail elsewhere (Eldridge and Waldrop, 1991; Mateika and Duffin, 1995; Kaufman and Forster, 1996; Haouzi et al., 2004; Bell, 2006; Dempsey et al., 2006; Haouzi, 2006; Poon et al., 2007). Briefly, these include (1) a feedforward mechanism whereby motor output from higher (cortical) brain centers to the peripheral locomotor muscles provides a parallel stimulus to the medullary (brainstem) respiratory control center; (2) afferent feedback signals from the exercising muscles to the medullary respiratory control center which drives $\dot{V}_A$ in proportion to the neural activation of Type III and IV mechanoreptors and metaboreceptors residing within the active locomotor muscles and their vasculature; (3) a behavioral- and arousal-related mechanism whereby neural activation of cortical structures involved in the planning and anticipation of the motor act of exercise contributes to the voluntary control of the inspiratory pump muscles; (4) afferent feedback signals from the central and peripheral chemoreceptors in response to arterial and central (or brain tissue) acid–base disturbances during exercise above the ventilatory threshold; and (5) any combination thereof (Fig. 1).

2.2. Central corollary discharge: the proximate cause of exertional breathlessness?

During exercise in health, breathlessness intensity ratings measured by validated scales (e.g. Borg) increase in direct proportion with: (1) $\dot{V}_E$ expressed in L/min or as a % of maximal ventilatory capacity; (2) contractile respiratory muscle effort (tidal esophageal pressure swing expressed as a % of maximum inspiratory pressure, $\Delta P_{es}/P_{Imax}$); and (3) power output expressed in absolute terms (e.g. watts) or as a % of predicted maximum (Killian et al., 1984, 1992; LeBlanc et al., 1988; Killian, 1992b; O'Donnell et al., 2000). "Effort" has been defined as the "intensity of willed motor command" and is believed to reflect the conscious awareness of the central respiratory motor output command required to drive the active skeletal muscle (Killian et al., 1984; Killian, 1992b). Several studies have demonstrated that the intensity of perceived respira-

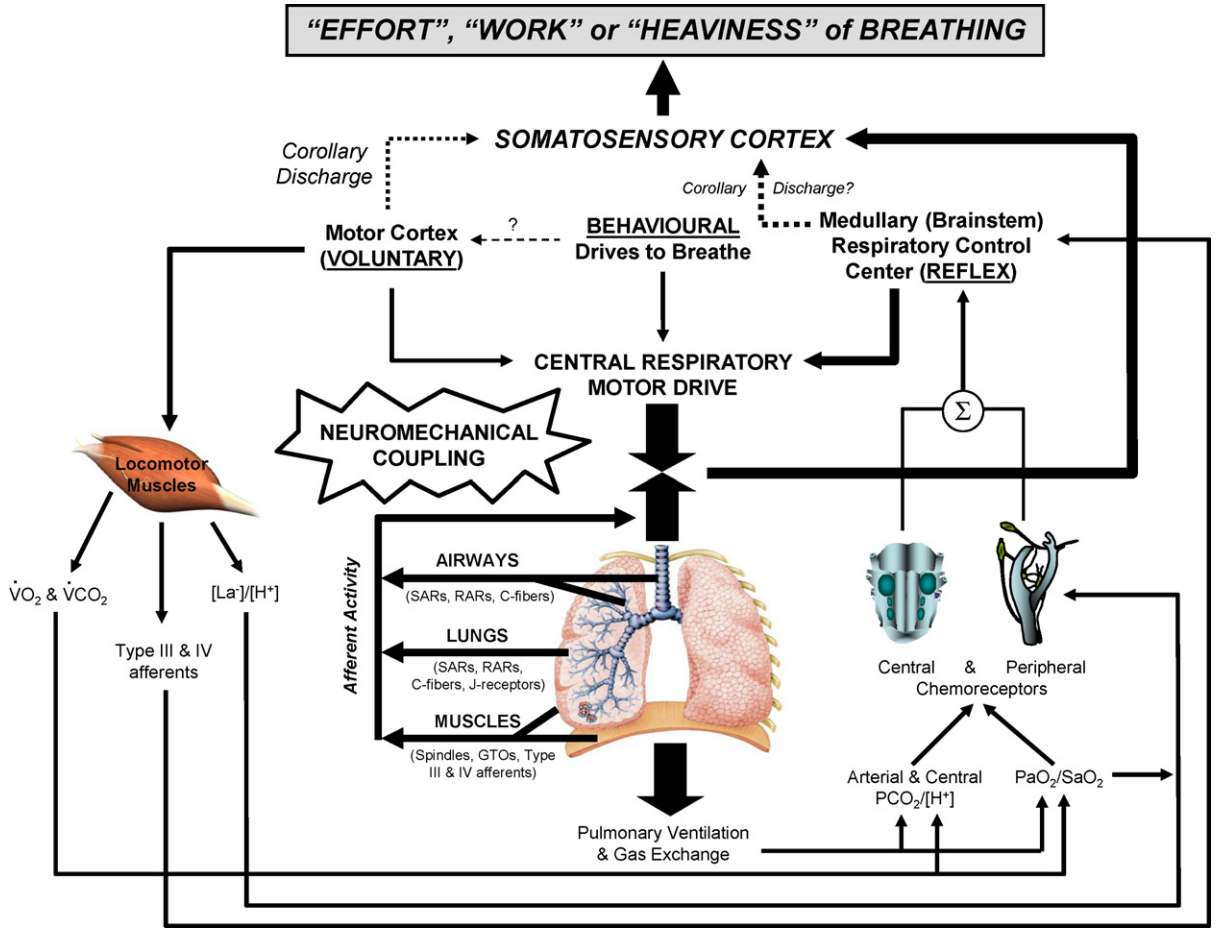

Fig. 1. Neurophysiological underpinnings of perceived respiratory discomfort (breathlessness) during exercise in healthy humans: a working hypothesis. Refer to text for details. $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$, metabolic rates of oxygen consumption and carbon dioxide production; Type III and IV mechano- and metabosensitive afferents in the peripheral locomotor (and respiratory) muscles and their vasculature; SARs, slowly adapting receptors; RARs, rapidly adapting receptors; C-fibers, bronchopulmonary C-fibers; J-receptors, juxtapulmonary capillary receptors; GTOs, Golgi tendon organs; PCO_2, partial pressure of carbon dioxide; $[H^+]$, hydrogen ion concentration; $[La^-]$, lactate ion concentration; PaO_2, arterial partial pressure of oxygen; SaO_2, arterial blood oxygen saturation.

tory "effort" is increased when: (1) $\dot{V}_E$ and $\Delta P_{es}/P_{Imax}$ are increased with exercise or reflex driven hyperventilation (O'Donnell et al., 2000); (2) the respiratory muscle load is increased (el-Manshawi et al., 1986); and/or (3) when the inspiratory pump muscles are functionally weakened by fatigue (Gandevia et al., 1981), acute partial paralysis (Moosavi et al., 2000) or lung hyperinflation (Killian et al., 1984). In healthy young individuals at the symptom-limited peak of exercise, breathlessness intensity is generally rated as "severe" and in qualitative terms is described as a heightened sense of "effort", "work" or "heaviness" of breathing (Simon et al., 1989; O'Donnell et al., 2000; Ofir et al., 2007). In general, these respiratory sensations are not inherently unpleasant, as they represent, based on learning and experience, the anticipated ventilatory response to heavy exercise. In this regard, intolerable breathlessness is rarely volunteered as the primary exercise-limiting symptom, at least during weight-supported cycle exercise in healthy young individuals (Killian, 1992a; Killian et al., 1992; Hamilton et al., 1996; Jones and Killian, 2000; O'Donnell et al., 2000).

The neurophysiological basis of increased "work", "effort" or "heaviness" of breathing is thought to be increased central corollary discharge to the somatosensory cortex, secondary to increased cortical (voluntary or willful) respiratory motor drive (Fig. 1) (Gandevia, 1988; O'Donnell et al., 2007). The role of increased brainstem (autonomic or reflex) respiratory motor drive in the genesis of perceived "effort" is less certain, but is likely integral to the "global" sense of increased central respiratory motor drive and corollary discharge (Fig. 1) (Chen et al., 1991, 1992; Killian, 1992b; Eldridge and Chen, 1996; Manning and Schwartzstein, 1995). Sensory afferent information arising from muscle spindles and Golgi tendon organs as well as from Type III and IV mechano- and metaboreceptors (all of which project directly to the somatosensory cortex) in the vigorously contracting respiratory muscles, including the diaphragm, may also contribute to the sense of increased "work", "effort" or "heaviness" of breathing during exercise when ventilatory requirements are high (Fig. 1) (Duron, 1981; Killian, 1992b; Jammes and Speck, 1995; Manning and Schwartzstein, 1995; O'Donnell et al., 2007). However, this possibility is more contentious since alterations in the mechanical/muscular response of the respiratory system are not obligatory to evoke breathlessness (specifically the qualitative sensation of "air hunger") in the setting of increased brainstem respiratory motor drive (Banzett et al., 1989, 1990; Gandevia et al., 1993).

2.3. Central corollary discharge: not the whole story!

Although the central corollary discharge ("sense of effort") hypothesis of exertional breathlessness is widely accepted, there are several experimental observations that it fails to explain. (1) If the intensity of perceived breathlessness was solely a function of the amplitude of cortical (voluntary) respiratory motor drive and attendant central corollary discharge, then it would be expected to vary *only* in intensity and *not* quality; however, this is not the case! Humans reliably detect, quantify and discriminate qualitatively distinct sensations of breathlessness provoked by different respiratory stimuli applied experimentally or resulting from cardiopulmonary disease (Zechman and Wiley, 1986; Simon et al., 1989, 1990; Elliot et al., 1991; American Thoracic Society, 1999; Lansing et al., 2000; O'Donnell et al., 2000; Scano et al., 2005). (2) Voluntarily increasing $\dot{V}_E$ and presumably therefore $\Delta P_{es}/P_{Imax}$ to the same level as that achieved spontaneously with hypercapnia (Adams et al., 1985) or during exercise (Lane et al., 1987) was not associated with perceived breathlessness in healthy humans, suggesting that increased brainstem (reflex) rather than cortical (voluntary) respiratory motor drive is the proximate source of respiratory discomfort. (3) Ward and Whipp (1989) previously showed that breathlessness intensity ratings were consistently higher during hypoxic-isocapnic compared with both hyperoxic–hypercapnic and hyperoxic-isocapnic cycle exercise, despite matched levels of $\dot{V}_E$ and presumably therefore $\Delta P_{es}/P_{Imax}$. (4) Harty et al. (1999) and O'Connor et al. (2000) reported that imposing a mechanical constraint to tidal volume (V_T) expansion by chest wall strapping significantly increased (compared with control) breathlessness intensity ratings at a standardized submaximal $\dot{V}_E$ during constant-load cycle exercise in healthy men. A more detailed mechanistic study by O'Donnell et al. (2000) found that, compared with control, chest wall strapping uncoupled the otherwise harmonious relationship between $\Delta P_{es}/P_{Imax}$ and thoracic volume displacement (i.e. neuromechanical uncoupling of the respiratory system), which in turn increased the intensity of perceived respiratory discomfort (described in qualitative terms as an increased sense of "unsatisfied inspiration") at any given submaximal $\dot{V}_E$, $\Delta P_{es}/P_{Imax}$, $\dot{V}_{O_2}$ and work rate during incremental cycle exercise in healthy men (refer to Figs. 3 and 4 in O'Donnell et al., 2000). In that study, the combination of chest wall strapping and increased central (brainstem) respiratory motor output command (by chemostimulation *via* added dead space), further hastened both neuromechanical uncoupling and the intensity of perceived "unsatisfied inspiration" with attendant reductions in peak aerobic working capacity. Based on these observations, O'Donnell et al. (2000) advanced the hypothesis that neuromechanical uncoupling may be relevant to the origin of the intensity and quality of exertional breathlessness under conditions of increased respiratory mechanical loading.

2.4. Respiratory mechanical and perceptual responses to exercise in health

During exercise in health, several acute physiological adaptations ensure harmonious neuromechanical coupling of the respiratory system with attendant minimization of perceived breathlessness, despite dramatic and progressive increases in ventilatory demand (>10 times resting values). These adaptations include: (1) the precise control of dynamic end-expiratory (EELV) and end-inspiratory (EILV) lung volumes; (2) reductions in intra- and extra-thoracic airway resistance; (3) breathing pattern optimization; and (4) enhanced matching of ventilation and perfusion (Dempsey et al., 1996, 2006, 2008; Poon et al., 2007). Collectively, these adaptations serve to maximize pulmonary gas exchange efficiency and maintain arterial blood gas/acid–base status near resting levels; partition the increased WOB between the inspiratory and expiratory muscles; and ensure that V_T expands within the most compliant (linear) portion of the respiratory system's sigmoid pressure-volume relation (by increasing EILV or encroaching on inspiratory reserve volume (IRV) and by decreasing EELV or encroaching on expiratory reserve volume (ERV)), where neuromechanical coupling is preserved and perceived breathlessness is minimized (Sharratt et al., 1987; Henke et al., 1988; Younes, 1991; Dempsey et al., 2006). It follows that if/when these physiological adaptations become undermined, such as may occur during exercise in pregnant, obese and elderly subjects, there is the potential for increased activity-related breathlessness.

2.5. Neurophysiology of exertional breathlessness: a working hypothesis

We contend that alterations in both central and peripheral sensory inputs and their complex integration within higher brain centers are fundamental to the experience of perceived respiratory discomfort during physical activity (Fig. 1). Briefly, the somatosensory cortex *calibrates* and *interprets* the appropriateness (or lack thereof) of the mechanical/muscular response of the respiratory system (conveyed *via* multiple sensory afferents in the respiratory

muscles, lungs, airways and chest wall) to the prevailing or pre-programmed level of central respiratory motor output command. The precise neural origin of central respiratory motor drive remains unclear, but available evidence suggests that it originates in any one or combination of several different central and peripheral neural substrates, which may or may not be directly sensed as central corollary discharge (Fig. 1).

As illustrated in Fig. 1, when the mechanical/muscular response of the respiratory system is commensurate with the prevailing level of central respiratory motor drive then breathlessness intensity increases in direct proportion to the level of central respiratory motor drive and is described as a heightened sense of "effort", "work" or "heaviness" of breathing. Alternatively, if the mechanical/muscular response of the respiratory system is constrained below the level dictated by central respiratory motor drive then breathlessness intensity increases in direct proportion to the widening disparity between ventilatory drive and mechanics and is described as the inherently unpleasant sense of "unsatisfied inspiration" (refer to Fig. 8 in O'Donnell et al., 2009, this issue).

In what situation(s) could these conditions exist in healthy humans so as to create other additional sources of activity-related breathlessness? It is reasonable to speculate that an abnormally increased central respiratory motor drive in conjunction with impairment in dynamic respiratory mechanics and muscle function might exist during exercise in healthy pregnant, obese and elderly humans (refer to Sections 3–5 below, respectively). If this were true, then (1) the intensity of perceived breathlessness would be consistently higher during exercise at any given submaximal $\dot{V}_E$, $\Delta P_{es}/P_{Imax}$, $\dot{V}_{O_2}$, power output, etc. in these groups compared with control and (2) the experience of exertional breathlessness in these groups might encompass other qualitatively distinct perceptions (beyond increased "effort", "work" or "heaviness" of breathing) that allude to "unsatisfied inspiration."

3. Breathlessness in healthy human pregnancy

Activity-related breathlessness is a common complaint of as many as 75% of healthy pregnant women by ~30 weeks gestation (Milne et al., 1978; Moore et al., 1987). The normal physiological breathlessness of pregnancy is rarely severe enough to be of any clinical significance, and does not usually interfere with activities of daily living or compromise peak aerobic working capacity (Weinberger et al., 1980; Tenholder and South-Paul, 1989; Elkus and Popovich, 1992; Zeldis, 1992; Crapo, 1996; Wise et al., 2006; Jensen et al., 2008b). However, experimental evidence suggests that the severity of activity-related breathlessness (measured by the Medical Research Council scale) varies considerably among otherwise healthy pregnant women (Milne et al., 1978; Moore et al., 1987). Furthermore, clinical experience tells us that a minority of pregnant women seek medical attention when breathlessness begins to interfere with their ability to engage in activities of daily living. Under these circumstances, the care giver is faced with the difficult challenge of distinguishing physiological from pathophysiological (e.g. airway hyper-responsiveness, cardiovascular dysfunction, pulmonary hypertension, etc.) and/or psychophysiological (e.g. anxiety) causes of this symptom. The clinical assessment and management of pregnant women is further complicated by the fact that the nature and source(s) of gestational breathlessness are not completely understood.

3.1. Mechanical adaptations of the respiratory system in pregnancy

The effects of pregnancy and advancing gestation on resting pulmonary function have been reviewed in detailed elsewhere (Weinberger et al., 1980; Elkus and Popovich, 1992; Crapo, 1996; Wise et al., 2006; Jensen et al., 2007a) and are summarized in Table 1. Briefly, progressive changes in the shape and configuration of the abdomen, diaphragm and chest wall (secondary to the gravid uterus) are only partially compensated for by relaxation of ligamentous attachments of the ribs such that chest wall and therefore total respiratory system compliance are reduced (Farman and Thorpe, 1969; Marx et al., 1970). Consequently, resting EELV or functional residual capacity (FRC), ERV and residual volume (RV) decrease, while resting inspiratory capacity (I_C) increases by ~0.35–0.50 L with no associated change in total lung capacity (TLC) (Gee et al., 1967; Knuttgen and Emerson, 1974; Gilroy et al., 1988; Berry et al., 1989; Contreras et al., 1991; Jensen et al., 2008b). Despite progressive thoraco-abdominal distortion, static inspiratory and expiratory muscle strength is well preserved in pregnancy (Gilroy et al., 1988; Contreras et al., 1991; Jensen et al., 2008b). Although pregnancy-induced reductions in resting EELV and arterial PCO_2 might be expected to increase both airway resistance and airway hyper-responsiveness, the available research suggests that neither pregnancy nor advancing gestation decreases FEV_1 or peak and mid-maximal expiratory flow rates (Knuttgen and Emerson, 1974; Berry et al., 1989; Garcia-Rio et al., 1997; Jensen et al., 2008b). In fact, resting measures of airway resistance have actually been shown to decrease or improve during pregnancy (Rubin et al., 1956; Gee et al., 1967; Garrard et al., 1978; Jensen et al., 2008b).

Table 1
Effects of pregnancy, obesity and aging on resting pulmonary function in healthy humans.

Variable	Pregnancy	Obesity	Aging
Chest wall compliance	↓	↓	↓
Lung compliance	↔	↓	↑
Total respiratory system compliance	↓	↓	↓
FEV_1	↔↑	↓	↓
Airway/pulmonary resistance	↔↓	↑	↑
TLC	↔	↔	↔↓
V_C	↔↑	↔	↓
I_C	↑	↑	↓
EELV or FRC	↓	↓	↑
ERV	↓	↓	↓
RV	↓	↔	↑
Inspiratory muscle strength	↔	↓	↓
Expiratory muscle strength	↔	↓	↓
D_LCO	↔	↔	↓

Arrows represent direction of change in relation to healthy, young control subjects. FEV_1, forced expiratory volume in one second; TLC, total lung capacity; V_C, vital capacity; I_C, inspiratory capacity; EELV, end-expiratory lung volume; FRC, functional residual capacity; ERV, expiratory reserve volume; RV, residual volume; D_LCO, diffusing capacity of the lung for carbon monoxide; ↓, decrease; ↑, increase; ↔, no change; ↔↑, no change or slight increase; ↔↓, no change or slight decrease.

3.2. Gestational breathlessness: normal awareness of maternal hyperventilation?

Pregnancy is characterized by increased $\dot{V}_E$ both at rest (by 3–5 L/min or 35–55%) and during standard submaximal exercise (by 5–15 L/min or 10–40%) (Fig. 2), as a result of increased V_T expansion with little/no change in breathing frequency (Field et al., 1991; Wolfe et al., 1994; Ohtake and Wolfe, 1998; Jensen et al., 2008b). The mechanisms of the increased ventilatory response to exercise in pregnancy remain unclear and have not yet been examined in detail. Preliminary findings from our laboratory suggest, however, that pregnancy-induced increases in exercise hyperpnea can be explained in large part by reductions in the respiratory control system's resting PCO_2 equilibrium point (Jensen et al., 2008c), which in turn results from a complex interaction of alterations in female sex steroid hormone concentrations, central chemoreflex and non-

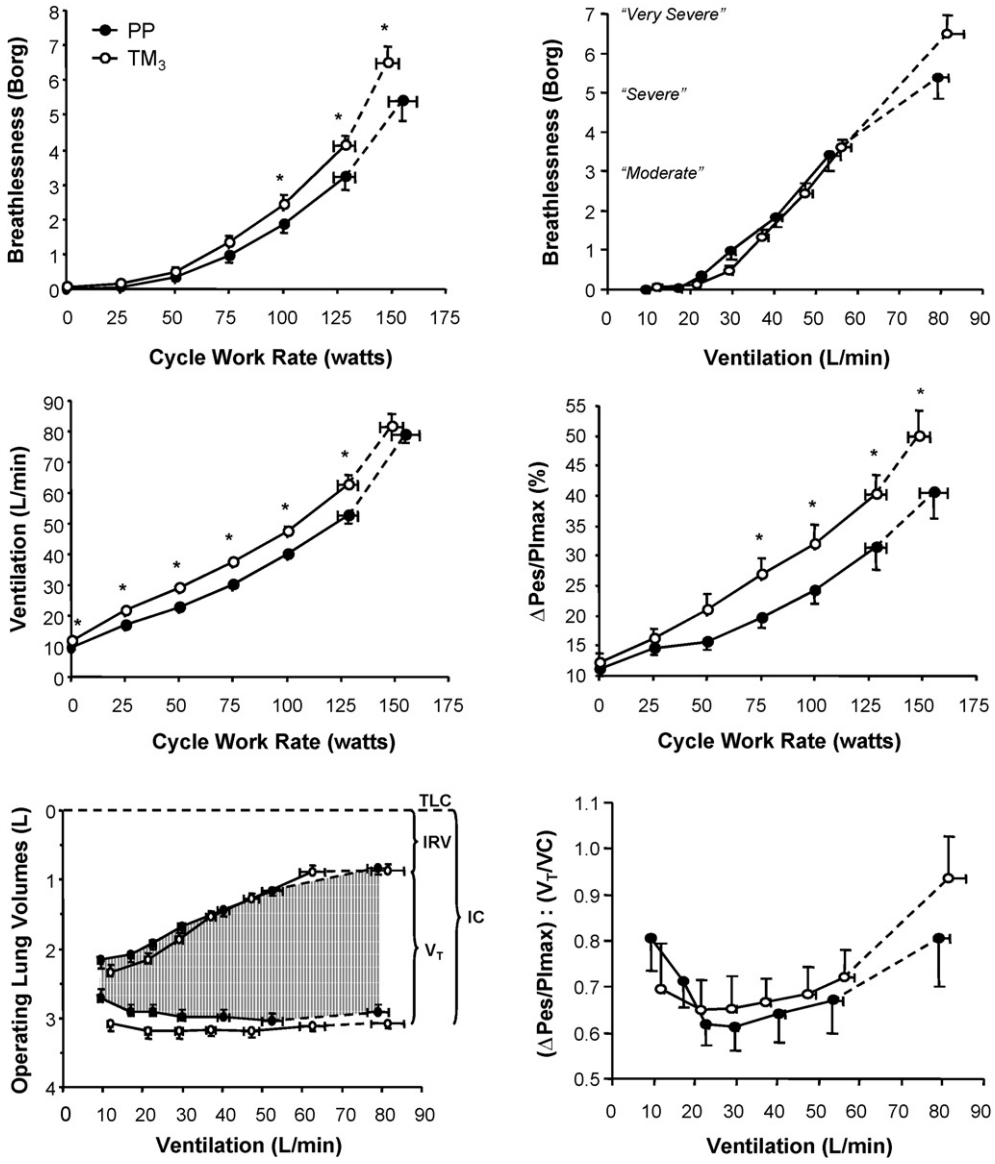

Fig. 2. Effects of pregnancy on perceptual, ventilatory and respiratory mechanical/muscular responses to incremental weight-supported cycle exercise. Refer to text for details. Data points are mean ±SEM at rest, at standardized cycle work rates during exercise and at end-exercise. PP, post-partum; TM_3, third trimester; ΔP_{es}, tidal esophageal pressure; $\Delta P_{es}/P_{Imax}$, tidal esophageal pressure expressed as a percentage of maximal inspiratory pressure (an estimate of contractile respiratory muscle effort); TLC, total lung capacity; IRV, inspiratory reserve volume; V_T, tidal volume; I_C, inspiratory capacity; V_C, vital capacity. $^*p < 0.05$ TM3 vs. PP Adapted and modified from Jensen et al., 2008b with permission.

chemoreflex drives to breathe, acid–base balance, cerebral blood flow and $\dot{V}_{CO_2}$ (Jensen et al., 2005, 2007a, 2008a).

Regardless of the mechanism(s) of maternal hyperventilation, it is reasonable to postulate that gestational breathlessness reflects, at least in part, the normal (conscious) awareness of increased $\dot{V}_E$ and $\Delta P_{es}/P_{Imax}$ (Fig. 1). Indeed, Field et al. (1991) found that V_T, inspiratory esophageal pressure (an estimate of contractile inspiratory muscle effort) and breathlessness intensity ratings were consistently higher during cycle exercise in the third trimester (TM_3) compared with the post-partum (PP) state. In that study, however, comparisons were made at a standardized submaximal cycle work rate of only 48 watts, corresponding to breathlessness intensity ratings of "very slight" to "slight" (i.e. 1–2 Borg units) in TM_3 and PP, respectively. Thus, the concern remains that the exercise testing protocol employed by Field and colleagues was too conservative to unmask potential dynamic mechanical ventilatory constraints relevant to the origin of exertional breathlessness in pregnancy.

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

Conventional wisdom suggests that the progressive thoracoabdominal distortion of pregnancy may alter the normal mechanical/muscular response of the respiratory system to exercise (refer to Section 2.4 above), thereby constraining V_T expansion especially when ventilatory requirements are high. It is also possible that the mechanical encumbrance of the gravid uterus may impair the ability of healthy pregnant women to reduce EELV during exercise, thereby compromising power-sharing between the inspiratory and expiratory muscles, and forcing dynamic EILV closer to TLC where there is increased elastic loading and functional weakening of the inspiratory pump muscles. Based on our previous work in both health (O'Donnell et al., 2000) and disease (O'Donnell et al., 2006), we can predict that these restrictive mechanical ventilatory constraints, in the setting of increased central (brainstem) respiratory motor drive (Jensen et al., 2005, 2007a, 2008a, 2008c),

would cause neuromechanical uncoupling. Consequently, breathlessness intensity ratings would be expected to increase at any given $\dot{V}_E$, particularly during strenuous exercise in TM_3 when ventilatory requirements are high and the mechanical encumbrance of the gravid uterus is the greatest. Contrary to our expectations, we found that neither pregnancy nor advancing gestation altered breathlessness–$\dot{V}_E$ relationships during symptom-limited incremental cycle exercise (Jensen et al., 2007b). This strongly suggested the existence of specific respiratory mechanical adaptations that accommodated the increased central respiratory motor drive of pregnancy, while preserving effort-displacement relationships.

Indeed, we recently reported that recruitment of resting I_C (by ~0.40 L) and reduced airway resistance helped the respiratory system to accommodate the increased demand for V_T expansion during incremental cycle exercise in TM_3, despite failure to dynamically decrease EELV (Fig. 2) (Jensen et al., 2008b). These remarkable respiratory mechanical adaptations helped to prevent further encroachment of dynamic EILV on TLC as well as to preserve both effort-displacement and breathlessness–$\dot{V}_E$ relationships throughout much of exercise in TM_3 compared with PP (Fig. 2). Interestingly, we also found that dynamic mechanical constraints on V_T expansion contributed to the perception of exertional breathlessness in TM_3, but only at the limits of tolerance when ventilatory requirements approached maximal levels. Nevertheless, pregnancy had no significant effect on peak aerobic working capacity nor did it alter the quality of perceived breathlessness at end-exercise, which was described primarily as an increased sense of respiratory "effort/work."

3.4. Summary

The results of the abovementioned studies strongly suggest that progressive changes in the shape and configuration of the abdomen, diaphragm and chest wall (secondary to the gravid uterus) do not contribute importantly to perceived respiratory discomfort during exercise in healthy pregnant women, even in late gestation. In fact, it appears that mechanically advantageous adaptations of the respiratory system, including recruitment of resting I_C and reduced airway resistance, may actually help to minimize the sensory consequences of increased respiratory mechanical loading and increased central ventilatory drive during exercise in pregnancy. These impressive respiratory mechanical adaptations may also help to preserve cardiopulmonary interactions and thus peak aerobic working capacity during maternal exercise. Therefore, we conclude, in accordance with the neurophysiological construct of perceived respiratory discomfort illustrated in Fig. 1, that pregnancy-induced increases in activity-related breathlessness ultimately reflect the normal awareness of increased $\dot{V}_E$ and $\Delta P_{es}/P_{Imax}$ that accompanies the increased central (reflex) ventilatory drive, at least during weight-supported cycle exercise.

4. Exertional breathlessness in obesity

Obesity (OB) is a well-recognized public health threat in developed countries. In addition to the long list of adverse cardiovascular and metabolic consequences, OB is associated with consistent alterations in static and dynamic respiratory mechanical/muscular function as well as increases in central ventilatory drive (refer to Sections 4.1 and 4.2 below, respectively). These changes may be at least partly responsible for the increased perception of activity-related breathlessness that characterizes this condition (Karason et al., 2000; Sin et al., 2002; Aaron et al., 2004; Collet et al., 2007; Ofir et al., 2007). Nevertheless, only recently have studies been conducted to elucidate the underlying cause(s) of this symptom in OB (Sahebjami, 1998; El-Gamal et al., 2005; Lotti et al., 2005; Collet et al., 2007; Ofir et al., 2007; Salome et al., 2007; Babb et al., 2008a; Romagnoli et al., 2008).

4.1. Effects of obesity on resting pulmonary function

The effects of OB on resting pulmonary function have been reviewed in detail elsewhere (Luce, 1980; Gibson, 2000; Koenig, 2001; Parameswaran et al., 2006; Cherniack, 2008; Lavietes, 2008) and include (Table 1): (1) reductions in chest wall, lung and total respiratory system compliance, which reflect the accumulation of excess adipose tissue in and around the ribs, diaphragm and abdomen, increased pulmonary blood volume and microatelectasis; (2) little or no change in TLC, V_C and RV; (3) reductions in resting ERV and EELV (or FRC), secondary to reductions in total respiratory system compliance and increased deposition of intra-abdominal and intra-thoracic adipose tissue; (4) increases in resting I_C by ~0.35–0.55 L (Fig. 3); (5) increases in airway/pulmonary resistance and reductions in FEV_1, with little/no change in bronchial reactivity; (6) increased prevalence and severity of expiratory flow limitation with attendant increases in intrinsic positive end-expiratory pressure; (7) reduced static inspiratory and expiratory muscle strength/endurance; (8) increased WOB and $\dot{V}_{O_{2resp}}$; (9) little/no change in the diffusing capacity of the lung for carbon monoxide (D_LCO); (10) increased ventilation-perfusion mismatching; and (11) reduced resting arterial PO_2 and increased alveolar-to-arterial PO_2 difference (Fritts et al., 1959; Dempsey et al., 1966a, 1966b; Holley et al., 1967; Barrera et al., 1969, 1973; Ray et al., 1983; Babb et al., 1989, 2002, 2008b; Thomas et al., 1989; Rubinstein et al., 1990; Pelosi et al., 1996, 1997, 1998, 1999; Pankow et al., 1998; Weiner et al., 1998; Kress et al., 1999; Eichenberger et al., 2002; Aaron et al., 2004; Chlif et al., 2005, 2007; DeLorey et al., 2005; Watson and Pride, 2005; Jones and Nzekwu, 2006; Collet et al., 2007; Ofir et al., 2007; Salome et al., 2007; Sutherland et al., 2008; Zavorsky and Hoffman, 2008).

4.2. Ventilatory response to exercise in obesity

It is well established that $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ – expressed in L/min – are consistently higher at rest and during both weight-bearing and weight-supported exercise in OB compared with normal weight (NW) subjects (Fig. 4) (Dempsey et al., 1966a; Whipp and Davis, 1984; Babb et al., 1991, 2002; Hulens et al., 2001; Lafortuna et al., 2006, 2008; Seres et al., 2006; Ofir et al., 2007). OB-related increases in exercise $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ have been attributed to increased O_2 cost of moving heavier limbs; reduced mechanical efficiency of the peripheral locomotor muscles; and increased WOB and $\dot{V}_{O_{2resp}}$ (Fritts et al., 1959; Dempsey et al., 1966a, 1966b; Whipp and Davis, 1984; Pelosi et al., 1996, 1998; Kress et al., 1999; Hulens et al., 2001; Lafortuna et al., 2006, 2008; Seres et al., 2006).

The increased metabolic requirements of exercise in OB provoke an increase in $\dot{V}_E$ (Fig. 4) and presumably therefore $\Delta P_{es}/P_{Imax}$ at any given submaximal work rate during exercise compared with NW controls (Whipp and Davis, 1984; Hulens et al., 2001; Ofir et al., 2007; Romagnoli et al., 2008). Thus, central (brainstem or reflex) respiratory motor drive is increased during exercise in OB as a result of increased peripheral locomotor (and respiratory) muscle metabolic requirements. The increased ventilatory response to exercise in OB is characterized by a relatively rapid and shallow breathing pattern (Fig. 4), which is likely a compensatory/optimization strategy adopted by these individuals to minimize excessive increases in the elastic WOB and $\dot{V}_{O_{2resp}}$, particularly during strenuous exercise when ventilatory requirements are high (Babb et al., 1991; Hulens et al., 2001; Chlif et al., 2007; Ofir et al., 2007). Despite the shallow breathing pattern and increased $\dot{V}_{O_{2resp}}$, pulmonary gas exchange and arterial blood gas/acid–base status are relatively well preserved throughout exercise in the

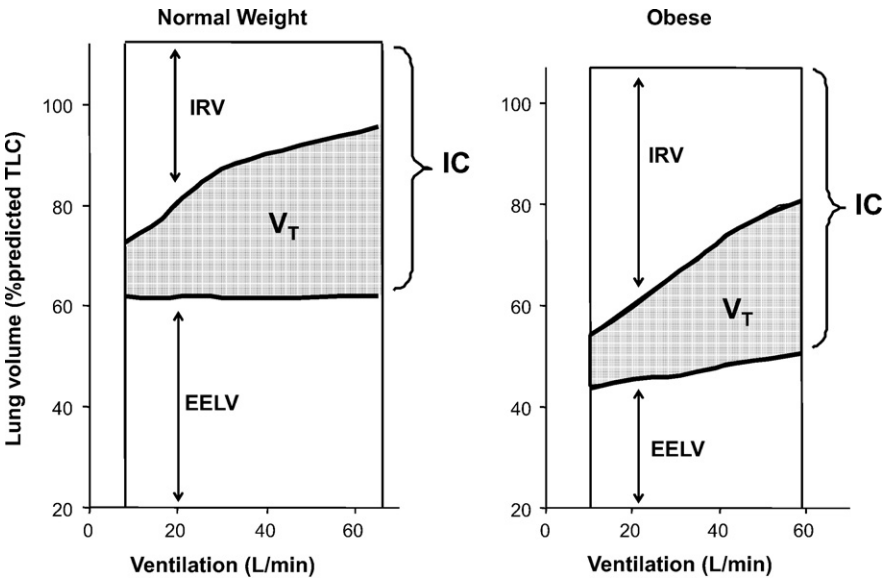

Fig. 3. Operating lung volumes from rest to the symptom-limited peak of incremental cycle exercise in obese and normal weight women. Refer to text for details. Note the progressive increase in dynamic end-expiratory lung volume (EELV) from rest to peak exercise in the obese group only and the larger resting and dynamic inspiratory capacity (I_C) in the obese compared with normal weight group. TLC, total lung capacity; IRV, inspiratory reserve volume; V_T, tidal volume. Adapted and modified from Ofir et al., 2007 with permission.

majority of OB subjects (Dempsey et al., 1966b; Zavorsky and Hoffman, 2008).

4.3. Respiratory mechanical/muscular and perceptual responses to exercise in obesity

Reductions in resting ERV and EELV force OB patients to breathe close to RV where (1) there is increased resistive loading of the respiratory system as a result of breathing on the lower, non-compliant (alinear) portion of the respiratory systems sigmoid pressure-volume relation and (2) the capacity of the respiratory system to increase expiratory flow rates in the setting of increased ventilatory requirements is compromised. In this regard, maintaining or further decreasing EELV into an already reduced ERV during exercise in OB would be mechanically disadvantageous with attendant negative sensory consequences, particularly in the face of an increased central (reflex) ventilatory drive. Alternatively, it is reasonable to postulate, on both theoretical and physiological grounds, that OB patients may actually *pseudo-normalize* their pulmonary function to meet the increased ventilatory requirements of exercise (thereby minimizing the intensity of perceived exertional breathlessness) by simply increasing dynamic EELV to a more normal (predicted) relaxation volume of the respiratory system.

Babb et al. (1989) previously reported that, in contrast to NW controls, EELV did not decrease from its reduced resting value during incremental treadmill exercise in healthy young overweight women. They subsequently reported that EELV actually decreased from its already reduced resting level during moderate intensity cycle exercise and returned to its resting (pre-exercise) level at end-exercise in healthy OB men (DeLorey et al., 2005) and women (Babb et al., 2002). Unfortunately, the effects of OB on breathlessness-work rate, breathlessness–$\dot{V}_E$ and breathlessness–$\dot{V}_{O_2}$ relationships were not examined in these studies.

Babb et al. (2008a) recently tested the hypothesis that exertional breathlessness in otherwise healthy OB women reflects increased $\dot{V}_{O_{2resp}}$. In this study, $\dot{V}_{O_{2resp}}$ (estimated as the change in $\dot{V}_{O_2}$ from rest during eucapnic voluntary hyperventilation) was 40–70% higher in OB women with vs. without exertional breathlessness (defined as a Borg rating of perceived breathlessness of $\geq$4 and $\leq$2 units at a standardized submaximal cycle work rate of 60 watts, respectively), even though ventilatory, breathing pattern, dynamic operating lung volume and esophageal pressure-derived respiratory mechanical/muscular responses to exercise were no different between-groups (Babb et al., 2008a; Wood et al., 2008). In this regard, the positive correlation between $\dot{V}_{O_{2resp}}$ and Borg ratings of exertional breathlessness reported by Babb et al. (2008a) could not be easily accounted for. Furthermore, it is difficult to reconcile both the mean and correlative results of this study with the following observations: (1) experimentally decreasing the WOB and $\dot{V}_{O_{2resp}}$ did not alleviate the intensity of perceived breathlessness during constant-load cycle exercise in patients with stable congestive heart failure (O'Donnell et al., 1999) and (2) increases in the WOB and $\dot{V}_{O_{2resp}}$ are not obligatory to provoke breathlessness under controlled experimental conditions (Banzett et al., 1989, 1990; Gandevia et al., 1993).

A study from our laboratory by Ofir et al. (2007) recently examined the contribution of increased central ventilatory drive, respiratory mechanical/muscular factors and their interaction to exertional breathlessness in OB by comparing detailed ventilatory and perceptual responses to incremental cycle exercise in 18 middle-aged OB and 13 age-matched NW control subjects. In that study, Borg ratings of perceived breathlessness were consistently higher at any given submaximal work rate during exercise in the former; however, breathlessness–$\dot{V}_E$ and breathlessness–$\dot{V}_{O_2}$ relationships were essentially superimposed between-groups (Fig. 4). These findings were subsequently confirmed by Romagnoli et al. (2008) and strongly suggested that (1) the increased perception of exertional breathlessness in OB reflected the normal awareness of increased $\dot{V}_E$ and $\Delta P_{es}/P_{lmax}$ that accompanied the increased central (reflex) ventilatory drive (Fig. 1) and (2) respiratory mechanical/muscular factors, *per se*, did not contribute importantly to exertional breathlessness in OB.

Why were respiratory mechanical/muscular factors not contributory? First, Ofir et al. (2007) and Romagnoli et al. (2008) demonstrated that, in contrast to NW controls, dynamic EELV progressively increased from its reduced resting level to a value that was closer to the normal (predicted) relaxation volume of

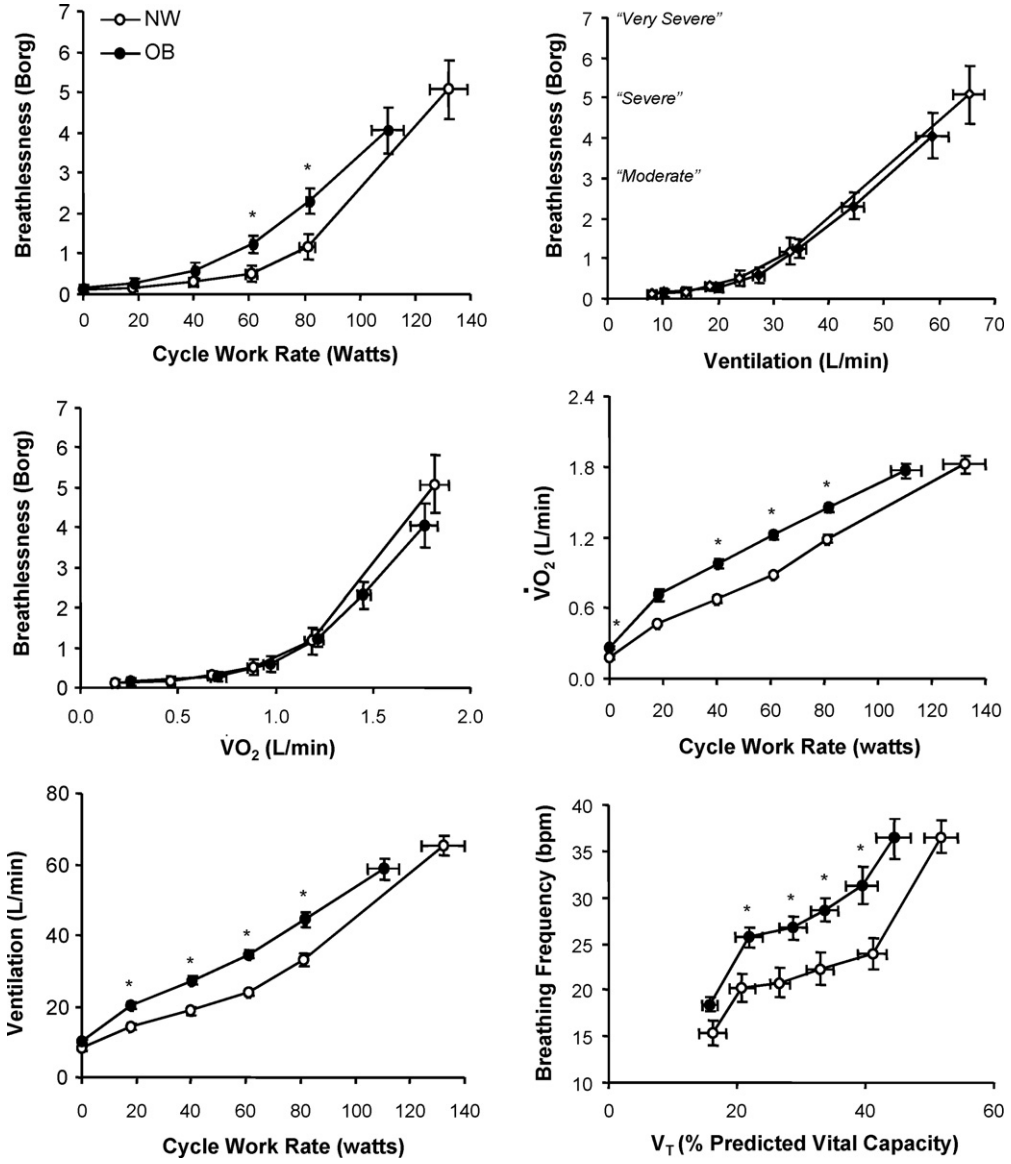

Fig. 4. Effects of obesity on perceptual, metabolic and ventilatory responses to incremental cycle exercise. Refer to text for details. Data points are mean ±SEM at rest, at standardized cycle work rates during exercise and at end-exercise. NW, normal weight control group; OB, obese group; $\dot{V}_{O_2}$, metabolic rate of oxygen consumption; V_T, tidal volume $^*p < 0.05$ OB vs. NW. Adapted and modified from Ofir et al., 2007 with permission.

the respiratory system during exercise in OB (Fig. 3). This is in keeping with the documented behavior of dynamic EELV during both hypercapnia-induced hyperventilation (Lotti et al., 2005) and methacholine challenge (Salome et al., 2007) in healthy OB vs. NW subjects. Ofir et al. (2007) argued that dynamic increases in EELV may have salutary effects on exertional breathlessness by (1) attenuating the anticipated rise in expiratory flow limitiation and thus intrinsic positive end-expiratory pressure as $\dot{V}_E$ increased during exercise in OB and (2) preserving effort-displacement relationships (or neuromechanical coupling) throughout exercise in OB without disadvantaging the inspiratory pump muscles, thereby helping to preserve their ability to meet the increased demand for tidal respiratory flow rate generation. Second, Ofir et al. (2007) proposed that recruitment of resting I_C (which represents the true operating limits for V_T expansion during exercise in flow-limited patients) may help the respiratory system to accommodate the increased demand for $\dot{V}_E$ within the most compliant (linear) portion of the respiratory system's pressure-volume relation throughout exercise in OB, while preventing further encroachment of dynamic EILV on TLC, despite progressive increases in dynamic EELV.

4.4. Summary

The increased prevalence and severity of activity-related breathlessness in OB compared with NW subjects cannot be easily explained by respiratory mechanical/muscular factors, but ultimately reflects the normal awareness of increased $\dot{V}_E$ and $\Delta P_{es}/P_{Imax}$ that accompanies the increased metabolic and ventilatory requirements of moving heavier limbs, at least during weight-supported cycle exercise (Fig. 1). Whether or not these observations apply to weight-bearing (e.g. treadmill) exercise when the ventilatory requirements are further exaggerated requires investigation.

5. Activity-related breathlessness in the healthy elderly

A number of studies have indicated that ~30% of healthy elderly (aged ≥65 years) subjects experience breathlessness during activities of daily living, and that this symptom (measured by the Medical Research Council scale) is an independent predictor of both morbidity and mortality (Horsley et al., 1991; Ho et al., 2001; Tessier et al.,

2001; Waterer et al., 2001; Mahler et al., 2003; Mahler and Baird, 2005; Huijnen et al., 2006; Medbo and Melbye, 2008). Although the physiological effects of normal healthy aging on the respiratory system are well established (refer to Section 5.1 below), only a handful of published studies have attempted to elucidate the nature and source(s) of breathlessness in this population (Tack et al., 1981, 1982, 1983; Altose et al., 1985; Killian et al., 1992; Akiyama et al., 1993; Mahler et al., 2003; Mahler and Baird, 2005; Ofir et al., 2008). A more detailed understanding of the physiological mechanism(s) of exertional breathlessness in healthy elderly men and women becomes important if we are to optimize diagnosis and management of various cardiopulmonary disorders in this rapidly increasing demographic of patients.

5.1. Normative aging of the respiratory system

The physiological effects of aging on the structure and function of the respiratory system have been reviewed in detail elsewhere (Johnson and Dempsey, 1991; Tolep and Kelsen, 1993; Johnson et al., 1994; Janssens et al., 1999; Janssens, 2005). Briefly, these include (Table 1): (1) progressive increases in lung compliance (reflecting loss of lung elastic recoil due to enlargement of alveolar airspaces and a decrease in their elastic fibers) and decreases in chest wall compliance (reflecting calcification of the intervetebral spaces and/or progressive osteoporosis-induced changes in the shape and configuration of the thorax); (2) progressive increases in closing volume (i.e. the lung volume at which dependent lung zones cease to ventilate as a result of airway closure) and therefore RV, resulting in static lung hyperinflation; (3) reductions in V_C, reflecting increases in RV with little/no change in TLC; (4) reductions in ERV and increases in EELV (or FRC), which in the setting of a relatively preserved TLC, significantly decreases resting I_C by 0.45–0.50 L (Fig. 5); (5) narrowing of the central and peripheral airways, which in turn increases airway/pulmonary flow resistance, and decreases FEV_1 as well as peak and mid-maximal expiratory flow rates; (6) increased prevalence and severity of expiratory flow limitation; (7) reductions in inspiratory and expiratory muscle strength/endurance, reflecting general loss of skeletal muscle mass/strength, physical deconditioning and/or malnutrition; (8) increased WOB and $\dot{V}_{O_{2resp}}$; (9) reductions in alveolar surface area and D_LCO as a result of enlargement of the alveolar airspaces; (10) progressive increases in both physiological dead space and ventilation-perfusion mismatching; and (11) little/no change in resting arterial blood gas/acid–base status (Tenney and Miller, 1956; Cohn and Donoso, 1963; Raine and Bishop, 1963; Holland et al., 1968; Turner et al., 1968; Anthonisen et al., 1969/1970; Thurlbeck, 1969; Bode et al., 1976; Estenne et al., 1985; Fowler et al., 1987; Hagberg et al., 1988; Takishima et al., 1990; Johnson et al., 1991a; Verbeken et al., 1992a, 1992b; Gillooly and Lamb, 1993; Tolep and Kelsen, 1993; Enright et al., 1994; McClaren et al., 1995; Tolep et al., 1995; Cardus et al., 1997; Polkey et al., 1997; DeLorey and Babb, 1999; Babb and Rodarte, 2000; Topin et al., 2003; Hardie et al., 2004; de Bisschop et al., 2005; Ofir et al., 2008).

5.2. Ventilatory, respiratory mechanical/muscular and perceptual responses to exercise in the healthy elderly

Compared with younger subjects, $\dot{V}_E$, $\dot{V}_E/\dot{V}_{O_2}$ and $\dot{V}_E/\dot{V}_{CO_2}$ responses to exercise are consistently higher in healthy elderly adults (Fig. 5) (Brischetto et al., 1984; Johnson et al., 1991a; McConnell and Davies, 1992; McConnell et al., 1993; Inbar et al., 1994; Poulin et al., 1994; McClaren et al., 1995; Hadebank et al., 1998; DeLorey and Babb, 1999; Prioux et al., 2000; Sun et al., 2002; Ofir et al., 2008). The accelerated ventilatory response to exercise in the elderly cannot be easily explained by increases in central and/or peripheral chemoreflex drives to breathe, but ultimately reflect the combination of (1) increased physiological dead space and ventilation-perfusion mismatching, (2) earlier onset of lactic acidosis, i.e., reduced ventilatory threshold and (3) reduced mechanical efficiency of the peripheral locomotor muscles (Peterson et al., 1981; Brischetto et al., 1984; Posner et al., 1987; McConnell and Davies, 1992; McConnell et al., 1993; Poulin et al., 1993; Inbar et al., 1994; Hadebank et al., 1998; DeLorey and Babb, 1999; Prioux et al., 2000; Sun et al., 2002).

The combined results of several previous studies (Johnson et al., 1991a, 1991b; McClaren et al., 1995; Babb, 1997; DeLorey and Babb, 1999; Babb et al., 2003), including our own (Ofir et al., 2008), have demonstrated that the increased ventilatory requirements of exercise and the relatively reduced maximal ventilatory reserve in healthy elderly compared with younger adults results in: (1) significant expiratory flow limitation, even during mild-to-moderate exercise (refer to Fig. 5 in Ofir et al., 2008); (2) relative static and dynamic lung hyperinflation, as evidenced by increases in both resting and dynamic EELV (reduced I_C) and EILV (reduced IRV) (Fig. 5); (3) increased elastic and flow-resistive WOB with higher $\dot{V}_{O_{2resp}}$; (4) increased contractile inspiratory muscle effort (i.e., higher pressure generation by the inspiratory muscles as a % of maximal available inspiratory pressure); and (5) greater dynamic mechanical constraints on V_T expansion during exercise, as indicated by increased V_T/V_C, V_T/I_C, EELV/TLC and EILV/TLC ratios (Fig. 5).

Psychophysiological studies by Tack et al. (1981, 1982, 1983) and Altose et al. (1985) suggest that the perception of resistive and elastic respiratory mechanical loading is consistently reduced, while the sensation of respiratory muscle force development is no different in healthy elderly compared with younger adults during quiet resting breathing. Akiyama et al. (1993) reported that the intensity of perceived respiratory discomfort at hyperoxic–hypercapnic end-tidal PCO_2 levels of 45 and 50 mmHg was consistently higher in healthy elderly compared with younger subjects, despite similar levels of $\dot{V}_E$. Unfortunately, the physiological significance of these observations as they relate specifically to age-related increases activity-related breathlessness remains largely unknown (O'Donnell et al., 2009, this issue).

Killian et al. (1992) were the first to clearly demonstrate progressive age-related increases in the intensity of perceived breathlessness during incremental cycle exercise in healthy men and women (refer to Fig. 3a and b in Killian et al., 1992). We recently reported that breathlessness intensity ratings were consistently higher (by 1–2 Borg units) at a standardized submaximal $\dot{V}_{O_2}$ of 20–25 mL/kg/min during incremental treadmill exercise in healthy elderly (aged 60–80 years) compared with younger (aged 40–59 years) adults (Fig. 5) (Ofir et al., 2008). We showed that this difference could be explained in large part by: (1) the normal awareness of increased $\dot{V}_E$; that is, advancing age had no demonstrable effect on breathlessness–$\dot{V}_E$ slopes (Fig. 5); (2) reduced static inspiratory muscle strength; and (3) relative lung hyperinflation (as indicated by a 0.35–0.55 L reduction in both resting and dynamic I_C) with greater dynamic mechanical constraints on V_T expansion, particularly during heavy exercise when ventilatory requirements approached maximal levels (Fig. 5). In keeping with these observations, Johnson and Dempsey (1991) reported a significant positive correlation between breathlessness intensity ratings and the magnitude of contractile inspiratory muscle effort during incremental treadmill exercise in 12 physically fit elderly subjects.

5.3. Summary

Progressive increases in activity-related breathlessness with advancing age, although multifactorial, can be explained in large

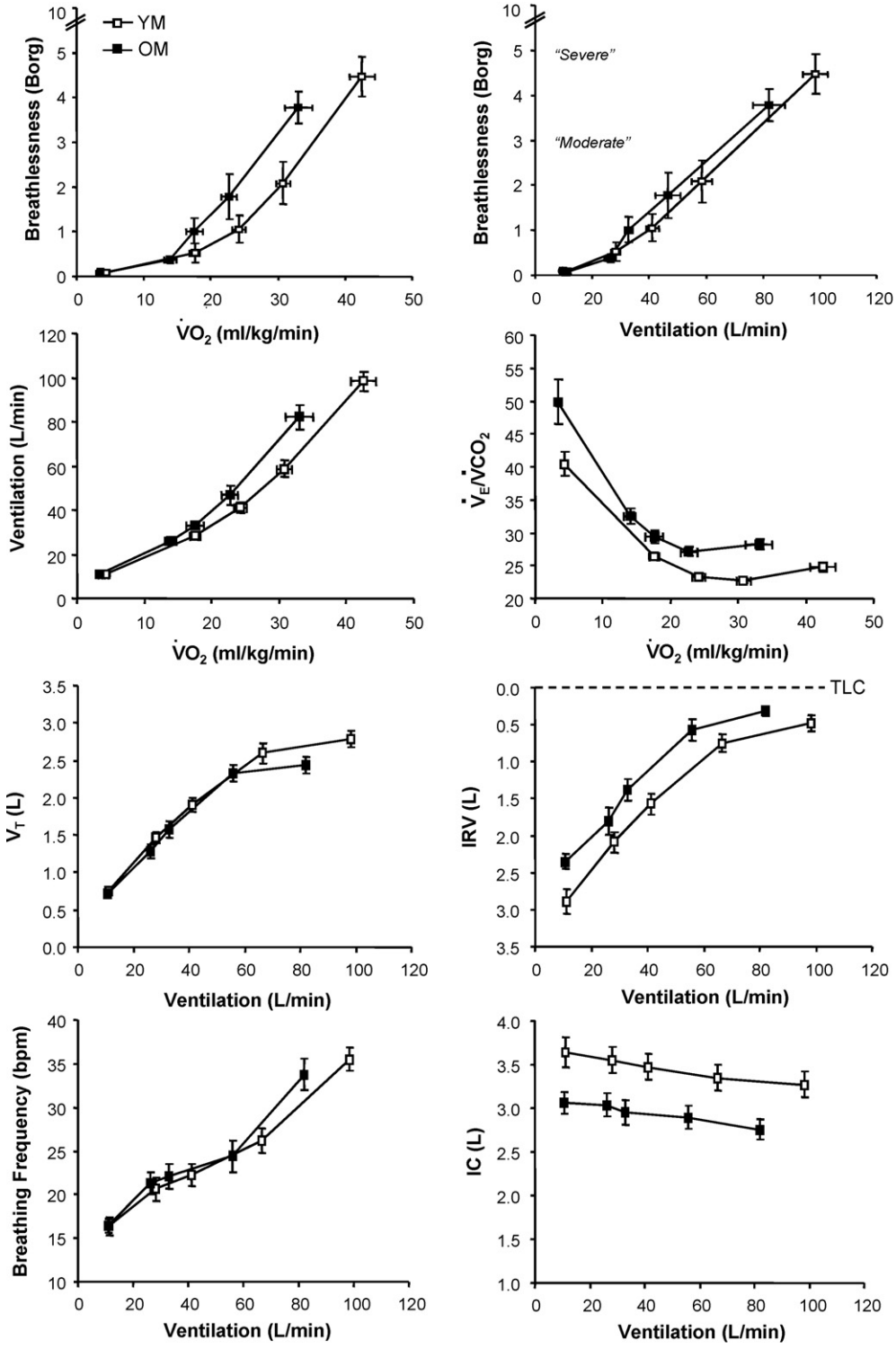

Fig. 5. Perceptual, ventilatory and respiratory mechanical responses to incremental treadmill exercise in healthy older (OM, aged 60–80 years) compared with younger men YM, aged 40–59 years). Refer to text for details. Data points are mean ±SEM for measurements at rest, during each stage of exercise and at peak exercise. $\dot{V}_{O_2}$, metabolic rate of oxygen consumption; $\dot{V}_E/\dot{V}_{CO}$, ventilatory equivalent for carbon dioxide; V_T, tidal volume; IRV, inspiratory reserve volume; TLC, total lung capacity; I_C, inspiratory capacity. Adapted and modified from Ofir et al., 2008 with permission.

part by the normal awareness of increased $\dot{V}_E$ and $\Delta P_{es}/P_{Imax}$ (Fig. 1) that accompanies reductions in pulmonary gas exchange efficiency, peripheral locomotor muscle efficiency/conditioning and contractile respiratory muscle strength. Surprisingly, respiratory mechanical/muscular factors, *per se*, do not appear to contribute importantly to age-related increases exertional breathlessness, except perhaps at the limits of tolerance.

6. Conclusions

Several acute physiological adaptations during exercise ensure harmonious neuromechanical coupling of the respiratory system, which allow healthy humans to reach high levels of ventilation without experiencing intolerable respiratory discomfort (breathlessness). However, in certain circumstances throughout the human

life span, such as pregnancy, during excessive weight gain and as a result of natural aging, ventilatory reserve becomes diminished and activity-related breathlessness may be present. In all of these conditions, central (reflex) motor drive to the respiratory muscles is consistently increased, reflecting increased ventilatory stimulation from various sources. In pregnancy, hyperventilation is humorally mediated, whereas in obesity, increased peripheral locomotor muscle metabolic requirements are the dominant source of increased exercise hyperpnea. In elderly subjects, pulmonary gas exchange derangements, including high physiological dead space and increased ventilation-perfusion mismatching, are ultimately responsible for the exaggerated ventilatory response to exercise. The increased contractile respiratory muscle effort (and the attendant increased central corollary discharge) required to support the increased exercise ventilation remains the most plausible source of increased activity-related breathlessness in each of these three populations. Indeed, qualitative descriptors of perceived respiratory discomfort that allude to an increased sense of "effort", "work" or "heaviness" of breathing are commonly selected at the symptom-limited peak of exercise in all of these conditions. Alterations in the operating characteristics of the respiratory muscles (i.e. muscle strength, force-velocity and length-tension properties) may also underlie the increased effort requirements of ventilation during exercise in healthy pregnant, obese and elderly subjects.

The nature of altered static and dynamic respiratory mechanical/muscular function is fundamentally different in pregnant, obese and elderly humans. We anticipated that the combination of (1) reduced contractile respiratory muscle strength, (2) increased intrinsic mechanical loading of the respiratory muscles and (3) dynamic mechanical constraints on tidal volume expansion during exercise would contribute importantly to the increased intensity of activity-related breathlessness that characterizes these three conditions. Surprisingly, breathlessness intensity ratings are not increased at any given ventilation during exercise in any of these three conditions. This strongly suggests that respiratory mechanical/muscular factors, *per se*, are less important than expected. In pregnancy, remarkable respiratory mechanical adaptations, including recruitment of resting inspiratory capacity and reduced airway resistance, help to ensure that neuromechanical coupling of the repiratory system is admirably preserved during weight-supported exercise, thereby obviating significant respiratory discomfort. Similarly, in obesity, the combination of (1) resting inspiratory capacity recruitment, (2) dynamic increases in end-expiratory lung volume (closer to the predicted relaxation volume of the respiratory system) and (3) a relatively shallow breathing pattern, may help the respiratory system to accommodate the increased demand for ventilation during weight-supported exercise, while helping to minimize the intensity of perceived breathlessness. Increased exertional breathlessness intensity in healthy elderly compared with younger subjects reflects increased ventilatory demand and relative weakness and increased intrinsic mechanical loading of the respiratory muscles. Although current wisdom dictates that the healthy human respiratory system is truly "overbuilt" with respect to the demands placed upon it during exercise, it is clear that significant dynamic mechanical ventilatory constraints exist at the limits of tolerance in healthy pregnant, obese and elderly subjects. Fortunately, in reality, the respiratory system is rarely called upon to meet the excessive ventilatory demands of heavy exercise during activities of daily living in these three conditions.

Acknowledgement

Dennis Jensen, Ph.D., was supported by the John Alexander Stuart Fellowship (Deparment of Medicine, Queen's University and Kingston General Hospital).

References

Aaron, S.D., Fergusson, D., Dent, R., Chen, Y., Vandemheen, K.L., Dales, R.E., 2004. Effect of weight reduction on respiratory function and airway reactivity in obese women. Chest 125, 2046–2052.

Adams, L., Lane, R., Shea, S.A., Cockcroft, A., Guz, A., 1985. Breathlessness during different forms of ventilatory stimulation: a study of mechanisms in normal subjects and respiratory patients. Clin. Sci. 69, 663–672.

Akiyama, Y., Nishimura, M., Kokayashi, S., Yamamoto, M., Miyamoto, K., Kawakami, Y., 1993. Effect of again on respiratory load compensation and dyspnea sensation. Am. Rev. Respir. Dis. 148, 1586–1591.

Altose, M.D., Leitner, J., Cherniack, N.S., 1985. Effect of age and respiratory efforts on the perception of resistive ventilatory loads. J. Gerontol. 40, 147–153.

American Thoracic Society, 1999. Dyspnea. Mechanisms, assessment and management: a consensus statement. Am. J. Respir. Crit. Care Med. 159, 321–340.

Anthonisen, N.R., Danson, J., Robertson, P.C., Ross, W.R.D., 1969. Airway closure as a function of age. Respir. Physiol. 8, 58–65.

Babb, T.G., 1997. Ventilatory response to exercise in subjects breathing CO_2 or HeO_2. J. Appl. Physiol. 82, 746–754.

Babb, T.G., Buskirk, E.R., Hodgson, J.L., 1989. Exercise end-expiratory lung volume in lean and moderately obese women. Int. J. Obes. 13, 11–19.

Babb, T.G., DeLorey, D.S., Wyrick, B.L., 2003. Ventilatory response to exercise in aged runners breathing $He–O_2$ or inspired CO_2. J. Appl. Physiol. 94, 685–693.

Babb, T.G., DeLorey, D.S., Wyrick, B.L., Gardner, P.P., 2002. Mild obesity does not limit change in end-expiratory lung volume during cycling in young women. J. Appl. Physiol. 92, 2483–2490.

Babb, T.G., Korzick, D., Meador, M., Hodgson, J.L., Buskirk, E.R., 1991. Ventilatory response of moderately obese women to submaximal exercise. Int. J. Obes. 15, 59–65.

Babb, T.G., Ranasinghe, K.G., Comeau, L.A., Semon, T.L., Schwartz, B., 2008a. Dyspnea on exertion in obese women: association with an increased oxygen cost of breathing. Am. J. Respir. Crit. Care Med. 178, 116–123.

Babb, T.G., Rodarte, J.R., 2000. Mechanism of reduced maximal expiratory flow with aging. J. Appl. Physiol. 89, 505–511.

Babb, T.G., Wyrick, B.L., DeLorey, D.S., Chase, P.J., Feng, M.Y., 2008b. Fat distribution and end-expiratory lung volume in lean and obese men and women. Chest, doi:10.1378/chest.07-1728.

Banzett, R.B., Lansing, R.W., Brown, R., Topolus, G.P., Yager, D., Steele, S.M., Londono, B., Loring, S.H., Reid, M.B., Adams, L., Nations, C.S., 1990. 'Air hunger' arising from increased PCO_2 persists after complete neuromuscular block in humans. Respir. Physiol. 81, 1–18.

Banzett, R.B., Lansing, R.W., Reid, M.B., Adams, L., Brown, R., 1989. Air hunger' arising from increased PCO_2 in mechanically ventilated quadriplegics. Respir. Physiol. 76, 53–68.

Barrera, F., Hillyer, P., Ascanio, G., Bechtel, J., 1973. The distribution of ventilation, diffusion, and blood flow in obese patients with normal and abnormal blood gases. Am. Rev. Respir. Dis. 108, 819–830.

Barrera, F., Reidenberg, M.M., Winters, W.L., Hungspreugs, S., 1969. Ventilation-perfusion relationships in the obese patient. J. Appl. Physiol. 26, 420–426.

Bell, H.J., 2006. Respiratory control at exercise onset: an integrated systems perspective. Respir. Physiol. Neurobiol. 152, 1–15.

Berry, M.J., McMurray, R.G., Katz, V.L., 1989. Pulmonary and ventilatory responses to pregnancy, immersion and exercise. J. Appl. Physiol. 66, 857–862.

Bode, F.R., Dosman, J., Martin, R.R., Ghezzo, H., Macklem, P.T., 1976. Age and sex differences in lung elasticity, and in closing capacity in nonsmokers. J. Appl. Physiol. 41, 129–135.

Brischetto, M.J., Millman, R.P., Peterson, D.D., Silage, D.A., Pack, A.I., 1984. Effect of aging on ventilatory response to exercise and CO_2. J. Appl. Physiol. 56, 1143–1150.

Cardus, J., Burgos, F., Diaz, O., Roca, J., Barbera, J.A., Marrades, R.M., Rodriguez-Roisin, R., Wagner, P.D., 1997. Increase in pulmonary ventilation-perfusion inequality with age in healthy individuals. Am. J. Respir. Crit. Care Med. 156, 648–653.

Chen, Z., Eldridge, F.L., Wagner, P.G., 1991. Respiratory-associated rhythmic firing of midbrain neurons in cats: relation to level of respiratory drive. J. Physiol. 437, 305–325.

Chen, Z., Eldridge, F.L., Wagner, P.G., 1992. Respiratory-associated thalamic activity is related to the level of respiratory drive. Respir. Physiol. 90, 99–113.

Cherniack, E.P., 2008. Obesity and the aging respiratory system. Curr. Respir. Med. Rev. 4, 116–121.

Chlif, M., Keochkerian, D., Feki, Y., Vaidie, A., Choquet, D., Ahmaidi, S., 2007. Inspiratory muscle activity during incremental exercise in obese men. Int. J. Obes. 31, 1456–1463.

Chlif, M., Keochkerian, D., Mourlhon, C., Choquet, D., Ahmaidi, S., 2005. Noninvasive assessment of the tension-time index of inspiratory muscles at rest in obese male subjects. Int. J. Obes. 29, 1478–1483.

Cohn, J.E., Donoso, H.D., 1963. Mechanical properties of the lung in normal men over 60 years old. J. Clin. Invest. 42, 1406–1410.

Collet, F., Mallart, A., Bervar, J.F., Bautin, N., Matran, R., Pattou, F., Romon, M., Perez, T., 2007. Physiologic correlates of dyspnea in patients with morbid obesity. Int. J. Obes. 31, 700–706.

Contreras, G., Cutiernex, M., Beroiza, T., Fantin, A., Oddo, M., Vallarroel, L., Cruz, E., Lisboa, C., 1991. Ventilatory drive and respiratory muscle function in pregnancy. Am. Rev. Respir. Dis. 144, 837–841.

Crapo, R.O., 1996. Normal cardiopulmonary physiology during pregnancy. Clin. Obstet. Gynecol. 39, 3–16.

de Bisschop, C., Marty, M.L., Tessier, J.F., Barberger-Gateau, P., Dartgues, J.F., Guenard, H., 2005. Expiratory flow limitation and obstruction in the elderly. Eur. Respir. J. 26, 594–601.
DeLorey, D.S., Babb, T.G., 1999. Progressive mechanical ventilatory constraints with aging. Am. J. Respir. Crit. Care Med. 160, 169–177.
DeLorey, D.S., Wyrick, B.L., Babb, T.G., 2005. Mild-to-moderate obesity: implications for respiratory mechanics at rest and during exercise in young men. Int. J. Obes. 29, 1039–1047.
Dempsey, J.A., 1986. Is the lung built for exercise? Med. Sci. Sports Exerc. 18, 143–155.
Dempsey, J.A., Adams, L., Ainsworth, D.M., Fregosi, R.F., Gallagher, C.G., Guz, A., Johnson, B.D., Powers, S.K., 1996. Airway, lung, and respiratory function during exercise. In: Rowell, L.B., Shephard, J.T. (Eds.), Handbook of Physiology. Oxford University Press, New York, pp. 448–514.
Dempsey, J.A., McKenzie, D., Haverkamp, H., Eldridge, M., 2008. Update in the understanding of respiratory limitations to exercise performance in fit, active adults. Chest 134, 613–622.
Dempsey, J.A., Miller, J.D., Romer, L.E., 2006. The respiratory system. In: Tipton, C.M., Sawka, M.N., Tate, C.A., Terjung, R.L. (Eds.), ACSM's Advanced Exercise Physiology. Lippincott, Williams and Wilkins, Baltimore, MD, pp. 246–299 (Chapter 10).
Dempsey, J.A., Reddan, W., Balke, B., Rankin, J., 1966a. Work capacity determinants and physiologic cost of weight-supported work in obesity. J. Appl. Physiol. 21, 1815–1820.
Dempsey, J.A., Reddan, W., Rankin, J., Balke, B., 1966b. Alveolar-arterial gas exchange during muscular work in obesity. J. Appl. Physiol. 21, 1807–1814.
Duron, B., 1981. Intercostal and diaphragmatic muscle afferents. In: Hornbein, T.F. (Ed.), Regulation of Breathing, Part I. Marcel Dekker, Inc., New York, pp. 473–540.
Eichenberger, A.S., Proietti, S., Wicky, S., Frascarolo, P., Suter, M., Spahn, D.R., Magnusson, L., 2002. Morbid obesity and postoperative pulmonary atelectasis: an underestimated problem. Anesth. Analg. 95, 1788–1792.
Eldridge, F.L., Waldrop, T.G., 1991. Neural control of breathing during exercise. In: Whipp, B., Wasserman (Eds.), Exercise, Pulmonary Physiology and Pathophysiology. Dekker, New York, pp. 309–370.
Eldridge, F.L., Chen, Z., 1996. Respiratory sensation: a neurophysiological perspective. In: Adams, L., Guz, A. (Eds.), Respiratory Sensation. Lung Biology in Health and Disease, 90. Marcel Dekker, New York, NY, pp. 19–67.
El-Gamal, H., Khayat, A., Shikora, S., Unterborn, J.N., 2005. Relationship of dyspnea to respiratory drive and pulmonary function tests in obese patients before and after weight loss. Chest 128, 3870–3874.
Elkus, R., Popovich, J., 1992. Respiratory physiology in pregnancy. Clin. Chest Med. 13, 555–565.
Elliot, M.W., Adams, L., Cockcroft, A., Macrae, K.D., Murphy, K., Guz, A., 1991. The language of breathlessness: use of verbal descriptors by patients with cardiopulmonary disease. Am. Rev. Respir. Dis. 144, 826–832.
el-Manshawi, A., Killian, K.J., Summers, E., Jones, N.L., 1986. Breathlessness during exercise with and without resistive loading. J. Appl. Physiol. 61, 896–905.
Enright, P.L., Kronmal, R.A., Manolio, T.A., Schenker, M.B., Hyatt, R.E., 1994. Respiratory muscle strength in the elderly: correlates and reference values. Am. J. Respir. Crit. Care Med. 149, 430–438.
Estenne, M., Yernault, J.C., De Troyer, A., 1985. Rib cage and diaphragm-abdomen compliance in humans: effects of age and posture. J. Appl. Physiol. 59, 1842–1848.
Farman, J.V., Thorpe, M.H., 1969. Compliance changes during caesarean section: a study of forty cases. Br. J. Anaesth. 41, 999–1001.
Field, S.K., Bell, S.G., Cenaiko, D.F., Whitelaw, W.A., 1991. Relationship between inspiratory effort and breathlessness in pregnancy. J. Appl. Physiol. 71, 1897–1902.
Forster, H.V., 2000. Exercise hyperpnea: where do we go from here? Exerc. Sport Sci. Rev. 28, 133–137.
Fowler, R.W., Pluck, R.A., Hetzel, M.R., 1987. Maximal expiratory flow-volume curves in Londeners aged 60 years and over. Thorax 42, 173–182.
Fritts, H.W., Filler, J., Fishman, A.P., Courland, A., 1959. The efficiency of ventilation during voluntary hyperpnea: studies in normal subjects and in dyspneic patients with either chronic pulmonary emphysema or obesity. J. Clin. Invest. 38, 1339–1348.
Gandevia, S.C., 1988. Neural mechanisms underlying the sensation of breathlessness: kinesthetic parallels between respiratory and limb muscles. Aust. N. Z. J. Med. 18, 83–91.
Gandevia, S.C., Killian, D.J., Campbell, E.J.M., 1981. The effect of respiratory muscle fatigue on respiratory sensations. Clin. Sci. 60, 463–466.
Gandevia, S.C., Killian, K., McKenzie, D.K., Crawford, M., Allen, G.M., Gorman, R.B., Hales, J.P., 1993. Respiratory sensations, cardiovascular control, kinaesthesia and transcranial stimulation during paralysis in humans. J. Physiol. 470, 85–107.
Garcia-Rio, F., Pino-Garcia, J.M., Serrano, S., Racionero, M.A., Terreros-Caro, J.G., Alvarez-Sala, R., Vilasante, C., Villamor, J., 1997. Comparison of helium dilution and plethysmographic lung volumes in pregnant women. Eur. Respir. J. 10, 2371–2375.
Garrard, G.S., Littler, W.A., Redman, C.W.G., 1978. Closing volume during normal pregnancy. Thorax 33, 488–492.
Gee, J.B.L., Packer, B.S., Millen, J.E., Robin, E.D., 1967. Pulmonary mechanics during pregnancy. J. Clin. Invest. 46, 945–952.
Gibson, G.J., 2000. Obesity, respiratory function and breathlessness. Thorax 55 (Suppl. 1), S41–S44.
Gillooly, M., Lamb, D., 1993. Airspace size in lungs of lifelong non-smokers: effect of age and sex. Thorax 48, 39–43.
Gilroy, R.J., Mangura, B.T., Lavietes, M.H., 1988. Rib cage and abdominal volume displacements during breathing in pregnancy. Am. Rev. Respir. Dis. 137, 668–672.
Hadebank, D., Reindl, I., Vietzke, G., Bauer, U., Sperfeld, A., Glaser, S., Wernecke, K.D., Kleber, F.X., 1998. Ventilatory efficiency and exercise tolerance in 101 healthy volunteers. Eur. J. Appl. Physiol. 77, 421–426.
Hagberg, J.M., Yerg, J.E., Seals, D.R., 1988. Pulmonary function in young and older athletes and untrained men. J. Appl. Physiol. 65, 101–105.
Hamilton, A.L., Killian, K.J., Summers, E., Jones, N.L., 1996. Symptom intensity and subjective limitation to exercise in patients with cardiorespiratory disorders. Chest 110, 1255–1263.
Haouzi, P., 2006. Theories on the nature of the coupling between ventilation and gas exchange during exercise. Respir. Physiol. Neurobiol. 151, 267–279.
Haouzi, P., Chenuel, B., Huszczuk, A., 2004. Sensing vascular distention in skeletal muscle by slow conducting afferent fibers: neurophysiological basis and implication for respiratory control. J. Appl. Physiol. 96, 407–418.
Hardie, J.A., Vollmer, W.M., Buist, A.S., Ellingsen, I., Morkve, O., 2004. Reference values for arterial blood gases in the elderly. Chest 125, 2053–2060.
Harty, H.R., Corfield, D.R., Schwartzstein, R.M., Adams, L., 1999. External thoracic restriction, respiratory sensation, and ventilation during exercise in men. J. Appl. Physiol. 86, 1142–1150.
Henke, K.G., Sharrat, M., Pegelow, D., Dempsey, J.A., 1988. Regulation of end-expiratory lung volume during exercise. J. Appl. Physiol. 64, 135–146.
Ho, S.F., O'Mahony, M.S., Steward, J.A., Breay, P., Buchalter, M., Burr, M.L., 2001. Dyspnoea and quality of life in older people at home. Age Ageing 30, 155–159.
Holland, J., Milic-Emili, J., Macklem, P.T., Bates, D.V., 1968. Regional distribution of pulmonary ventilation and perfusion in elderly subjects. J. Clin. Invest. 47, 81–92.
Holley, H.S., Milic-Emili, J., Becklake, M.R., Bates, D.V., 1967. Regional distribution of pulmonary ventilation and perfusion in obesity. J. Clin. Invest. 46, 475–481.
Horsley, J.R., Sterling, I.J., Waters, W.E., Howell, J.B., 1991. Respiratory symptoms among elderly people in the New Forest area as assessed by postal questionnaire. Age Ageing 20, 325–331.
Huijnen, B., van der Horst, F., van Amelsvoort, L., Wesseling, G., Lansbergen, M., Aarts, P., Nicolson, N., Knottnerus, A., 2006. Dyspnea in elderly family practice patients: occurrence, severity, quality of life and mortality over an 8-year period. Fam. Pract. 23, 34–39.
Hulens, M., Vansant, G., Lysens, R., Claessens, A.L., Muls, E., 2001. Exercise capacity in lean versus obese women. Scand. J. Med. Sci. Sports 11, 305–309.
Inbar, O., Oren, A., Scheinowitz, M., Rotstein, A., Dlin, R., Casaburi, R., 1994. Normal cardiopulmonary responses during incremental exercise in 20- to 70-yr-old men. Med. Sci. Sports. Exerc. 26, 538–546.
Jammes, Y., Speck, D.F., 1995. Respiratory contol by respiratory and diaphragmatic muscle afferents. In: Dempsey, J.A., Pack, A.I. (Eds.), Regulation of Breathing. Marcel Dekker, Inc., New York, pp. 543–582.
Janssens, J.P., 2005. Aging of the respiratory system: impact on pulmonary function tests and adaptation to exertion. Clin. Chest Med. 26, 469–484.
Janssens, J.P., Pache, J.C., Nicod, L.P., 1999. Physiological changes in respiratory function associated with ageing. Eur. Respir. J. 13, 197–205.
Jensen, D., Duffin, J., Lam, Y.M., Webb, K.A., Simpson, J.A., Davies, G.A.L., Wolfe, L.A., O'Donnell, D.E., 2008a. Physiological mechanisms of hyperventilation during human pregnancy. Respir. Physiol. Neurobiol. 161, 76–86.
Jensen, D., Webb, K.A., Davies, G.A.L., O'Donnell, D.E., 2008b. Mechanical ventilatory constraints during incremental cycle exercise in human pregnancy: implications for respiratory sensation. J. Physiol. 586, 4735–4750.
Jensen, D., Webb, K.A., O'Donnell, D.E., 2007a. Chemical and mechanical adaptations of the respiratory system at rest and during exercise in human pregnancy. Appl. Physiol. Nutr. Metab. 32, 1239–1250.
Jensen, D., Webb, K.A., O'Donnell, D.E., 2008c. The increased ventilatory response to exercise in pregnancy reflects alterations in the respiratory control system's resting PCO_2 equilibrium point. Appl. Physiol. Nutr. Metab. 33, s49.
Jensen, D., Webb, K.A., Wolfe, L.A., O'Donnell, D.E., 2007b. Effects of human pregnancy and advancing gestation on respiratory discomfort during exercise. Respir. Physiol. Neurobiol. 156, 85–93.
Jensen, D., Wolfe, L.A., Slatkovska, L., Webb, K.A., Davies, G.A.L., O'Donnell, D.E., 2005. Effects of human pregnancy on the ventilatory chemoreflex response to carbon dioxide. Am. J. Physiol. -Regul. Integr. Comp. Physiol. 288, R1369–R1375.
Johnson, B.D., Badr, M.S., Dempsey, J.A., 1994. Impact of the aging pulmonary system on the response to exercise. Clin. Chest Med. 15, 229–246.
Johnson, B.D., Dempsey, J.A., 1991. Demand vs. capacity in the aging pulmonary system. Exerc. Sport Sci. Rev. 19, 171–210.
Johnson, B.D., Reddan, W.G., Pegelow, D.F., Seow, K.C., Dempsey, J.A., 1991a. Flow limitation and regulation of functional residual capacity during exercise in a physically active aging population. Am. Rev. Respir. Dis. 143, 960–967.
Johnson, B.D., Reddan, W.G., Seow, K.C., Dempsey, J.A., 1991b. Mechanical constraints on exercise hyperpnea in a fit aging population. Am. Rev. Respir. Dis. 143, 968–977.
Jones, N.M., Killian, K.J., 2000. Exercise limitation in health and disease. N. Eng. J. Med. 343, 632–641.
Jones, R.L., Nzekwu, M.M.U., 2006. The effects of body mass index on lung volumes. Chest 130, 827–833.
Karason, K., Lindroos, A.K., Stenlof, K., Sjostrom, L., 2000. Relief of cardiorespiratory symptoms and increased physical activity after surgically induced weight loss. Arch. Intern. Med. 160, 1797–1802.
Kaufman, M.P., Forster, H.V., 1996. Reflexes controlling circulatory, ventilatory and airway responses to exercise. In: Rowell, L.B., Shepherd, J.T. (Eds.), Handbook of Physiology. Oxford University Press, Oxford, pp. 381–447.
Killian, K.J., 1992a. Symptoms limiting exercise. In: Jones, N.L., Killian, K.J. (Eds.), Breathlessness: The Campbell Symposium. Boehringer Ingelheim, Canada, pp. 132–142 (Chapter 17).

Killian, K.J., 1992b. Nature of breathlessness and its measurement. In: Jones, N.L., Killian, K.J. (Eds.), Breathlessness: The Campbell Symposium. Boehringer Ingelheim, Canada, pp. 74–87 (Chapter 11).
Killian, K.J., Gandevia, S.C., Summers, E., Campbell, E.J.M., 1984. Effect of increased lung volume on perception of breathlessness, effort, and tension. J. Appl. Physiol. 57, 686–691.
Killian, K.J., Summers, E., Jones, N.L., Campbell, E.J.M., 1992. Dyspnea and leg effort during incremental cycle ergometry. Am. Rev. Respir. Dis. 145, 1339–1345.
Knuttgen, H.G., Emerson Jr., K., 1974. Physiological response to pregnancy at rest and during exercise. J. Appl. Physiol. 36, 549–553.
Koenig, S.M., 2001. Pulmonary complications of obesity. Am. J. Med. Sci. 321, 249–279.
Kress, J.P., Pohlman, A.S., Alverdy, J., Hall, J.B., 1999. The impact of morbid obesity on oxygen cost of breathing ($\dot{V}_{O_{2resp}}$) at rest. Am. J. Respir. Crit. Care Med. 160, 883–886.
Lafortuna, C.L., Agosti, F., Galli, R., Busti, C., Lazzer, S., Sartorio, A., 2008. The energetic and cardiovascular response to treadmill walking and cycle ergometer exercise in obese women. Eur. J. Appl. Physiol. 103, 707–717.
Lafortuna, C.L., Proietti, M., Agosti, F., Sartorio, A., 2006. The energy cost of cycling in young obese women. Eur. J. Appl. Physiol. 97, 16–25.
Lane, R., Cockcroft, A., Guz, A., 1987. Voluntary isocapnic hyperventilation and breathlessness during exercise in normal subjects. Clin. Sci. 73, 519–523.
Lansing, R.W., Im, B.S.H., Thwing, J.I., Legedza, A.T.R., Banzett, R.B., 2000. The perception of respiratory work and effort can be independent of the perception of air hunger. Am. J. Respir. Crit. Care Med. 162, 1690–1696.
Lavietes, M.H., 2008. Obesity: its consequences upon respiratory system function. Curr. Respir. Med. Rev. 4, 90–94.
LeBlanc, P., Summers, E., Inman, M.D., Jones, N.L., Campbell, E.J.M., Killian, K.J., 1988. Inspiratory muscles during exercise: a problem of supply and demand. J. Appl. Physiol. 64, 2482–2489.
Lotti, P., Gigliotti, F., Tesi, F., Stenardi, L., Grazzini, M., Duranti, R., Scano, G., 2005. Respiratory muscles and dyspnea in obese nonsmoking subjects. Lung 183, 311–323.
Luce, J.M., 1980. Respiratory complications of obesity. Chest 78, 626–631.
Mahler, D.A., Baird, J.C., 2005. Dyspnea in the elderly. In: Mahler, D.A., O'Donnell, D.E. (Eds.), Lung Biology in Health and Diseease: Dyspnea: Mechanisms, Measurement and Management, 208, 2nd ed. Taylor & Francis Group, Boca Raton, FL, pp. 19–28 (Chapter 2).
Mahler, D.A., Fierro-Carrion, G., Baird, J.C., 2003. Evaluation of dyspnea in the elderly. Clin. Geriatr. Med. 19, 19–33.
Manning, H.L., Schwartzstein, R.M., 1995. Pathophysiology of dyspnea. N. Eng. J. Med. 33, 1547–1553.
Marx, G.F., Murthy, P.K., Orkin, L.R., 1970. Static compliance before and after vaginal delivery. Brit. J. Anaesth. 42, 1100–1104.
Mateika, J.H., Duffin, J., 1995. A review on the control of breathing during exercise. Eur. J. Appl. Physiol. 71, 1–27.
McClaren, S.R., Babcock, M.A., Pegelow, D.F., Reddan, W.G., Dempsey, J.A., 1995. Longitudinal effects of aging on lung function at rest and exercise in healthy active fit elderly adults. J. Appl. Physiol. 78, 1957–1968.
McConnell, A.K., Davies, C.T.M., 1992. A comparison of the ventilatory responses to exercise of elderly and younger humans. J. Gerontol. 47, B137–B141.
McConnell, A.K., Semple, E.S.G., Davies, C.T.M., 1993. Ventilatory responses to exercise and carbon dioxide in elderly and younger humans. Eur. J. Appl. Physiol. 66, 332–337.
Medbo, A., Melbye, H., 2008. What role may symptoms play in the diagnosis of airflow limitation? A study in an elderly population. Scand. J. Prim. Health Care. 26, 2–98.
Milne, J.A., Howie, A.D., Pack, A.I., 1978. Dyspnea during normal pregnancy. Br. J. Obstet. Gynaecol. 85, 260–263.
Moore, L.G., McCullough, R.E., Weil, J.V., 1987. Increased HVR in pregnancy: relationship to hormonal and metabolic changes. J. Appl. Physiol. 62, 158–163.
Moosavi, S.H., Topulos, G.P., Hafer, A., Lansing, R.W., Adams, L., Brown, R., Banzett, R.B., 2000. Acute partial paralysis alters perceptions of air hunger, work and effort at constant PCO_2 and $\dot{V}_E$. Respir. Physiol. 122, 45–60.
O'Connor, S., McLoughlin, P., Gallagher, C.G., Harty, H.R., 2000. Ventilatory response to incremental and constant-workload exercise in the presence of thoracic restriction. J. Appl. Physiol. 89, 2179–2186.
O'Donnell, D.E., Banzett, R.B., Carrieri-Kohlman, V., Casaburi, R., Davenport, P.W., Gandevia, S.C., Gelb, A.G., Mahler, D.A., Webb, K.A., 2007. Pathophysiology of dyspnea in chronic obstructive pulmonary disease: a roundtable. Proc. Am. Thorac. Soc. 4, 145–168.
O'Donnell, D.E., D'Arsigny, C., Raj, S., Abdollah, H., Webb, K.A., 1999. Ventilatory assistance improves exercise endurance in stable congestive heart failure. Am. J. Respir. Crit. Care Med. 160, 1804–1811.
O'Donnell, D.E., Hamilton, A.L., Webb, K.A., 2006. Sensory-mechanical relationships during high-intensity constant-work-rate exercise in COPD. J. Appl. Physiol. 101, 1025–1035.
O'Donnell, D.E., Hong, H.H., Webb, K.A., 2000. Respiratory sensation during chest wall restriction and dead space loading in exercising men. J. Appl. Physiol. 88, 1859–1869.
O'Donnell, D.E., Ora, J., Webb, K.A., Laveneziana, P., Jensen, D., 2009. Mechanisms of activity-related dyspnea in pulmonary diseases. Respir. Physiol. Neurobiol. (this issue).
Ofir, D., Laveneziana, P., Webb, K.A., Lam, Y.M., O'Donnell, D.E., 2008. Sex differences in the perceived intensity of breathlessness during exercise with advancing age. J. Appl. Physiol. 104, 1583–1593.
Ofir, D., Laveneziana, P., Webb, K.A., O'Donnell, D.E., 2007. Ventilatory and perceptual responses to cycle exercise in obese women. J. Appl. Physiol. 102, 2217–2226.
Ohtake, P.J., Wolfe, L.A., 1998. Physical conditioning attenuates respiratory responses to steady-state exercise in late gestation. Med. Sci. Sports Exerc. 30, 17–27.
Pankow, W., Podszus, T., Gutheil, T., Penzel, T., Peter, J.H., Von Wichert, P., 1998. Expiratory flow limitation and intrinsic positive end-expiratory pressure in obesity. J. Appl. Physiol. 85, 1236–1243.
Parameswaran, K., Todd, D.C., Soth, M., 2006. Altered respiratory physiology in obesity. Can. Respir. J. 13, 203–210.
Pelosi, P., Croci, M., Ravagnan, I., Cerisara, M., Vicardi, P., Lissoni, A., Gattinoni, L., 1997. Respiratory system mechanics in sedated, paralyzed morbidly obese patients. J. Appl. Physiol. 82, 811–818.
Pelosi, P., Croci, M., Ravagnan, I., Tredici, S., Pedoto, A., Lissoni, A., Gattinoni, L., 1998. The effects of body mass on lung volumes, respiratory mechanics, and gas exchange during general anesthesia. Anesth. Analg. 87, 654–660.
Pelosi, P., Croci, M., Ravagnan, I., Vicardi, P., Gattinoni, L., 1996. Total respiratory system, lung, and chest wall mechanics in sedated-paralyzed postoperative morbidly obese patients. Chest 109, 144–151.
Pelosi, P., Ravagnan, I., Giurati, G., Panigada, M., Bottino, N., Tredici, S., Eccher, G., Gattinoni, L., 1999. Positive end-expiratory pressure improves respiratory function in obese but not in normal subjects during anesthesia and paralysis. Anesthesiology 91, 1221–1231.
Peterson, D.D., Pack, A.I., Silage, D.A., Fishman, A.P., 1981. Effects of aging on ventilatory and occlusion pressure responses to hypoxia and hypercapnia. Am. Rev. Respir. Dis. 124, 387–391.
Polkey, M.I., Harris, M.L., Hughes, P.D., Hamnegard, C.H., Lyons, D., Green, M., Moxham, J., 1997. The contractile properties of the elderly human diaphragm. Am. J. Respir. Crit. Care Med. 155, 1560–1654.
Poon, C.S., Tin, C., Yu, Y., 2007. Homeostasis of exercise hyperpnea and optimal sensorimotor integration: the internal model paradigm. Respir. Physiol. Neurobiol. 159, 1–13.
Posner, J.D., Gorman, K.M., Klein, H.S., Cline, C.J., 1987. Ventilatory threshold: measurement and variation with age. J. Appl. Physiol. 63, 1519–1525.
Poulin, M.J., Cunningham, D.A., Paterson, D.H., Kowalchuk, J.M., Smith, W.D.F., 1993. Ventilatory sensitivity to CO_2 in hyperoxia and hypoxia in older aged humans. J. Appl. Physiol. 75, 2209–2216.
Poulin, M.J., Cunningham, D.A., Paterson, D.H., Rechnitzer, P.A., Ecclestone, N.A., Koval, J.J., 1994. Ventilatory response to exercise in men and women 55 to 86 years of age. Am. J. Respir. Crit. Care Med. 149, 408–415.
Prioux, J., Romonatxo, M., Hayot, M., Mucci, P., Prefaut, C., 2000. Effect of ageing on the ventilatory response and lactate kinetics during incremental exercise in man. Eur. J. Appl. Physiol. 81, 100–107.
Raine, J.M., Bishop, J.M., 1963. A-a difference in O_2 tension and physiological dead space in normal man. J. Appl. Physiol. 18, 284–288.
Ray, C.S., Sue, D.Y., Bray, G., Hansen, J.E., Wasserman, K., 1983. Effects of obesity on respiratory function. Am. Rev. Respir. Dis. 128, 501–506.
Romagnoli, I., Laveneziana, P., Clini, E.M., Palange, P., Valli, G., de Blasio, F., Gigliotti, F., Scano, G., 2008. Role of hyperinflation vs. deflation in dyspnoea in severely to extremely obese subjects. Acta. Physiol. 193, 393–402.
Rubin, A., Russo, N., Goucher, D., 1956. The effect of pregnancy upon pulmonary function in normal women. Am. J. Obstet. Gynecol. 72, 963–969.
Rubinstein, I., Zamel, N., DuBarry, L., Hoffstein, V., 1990. Airflow limitation in morbidly obese, nonsmoking men. Ann. Intern. Med. 112, 828–832.
Sahebjami, H., 1998. Dyspnea in obese healthy men. Chest 114, 1373–1377.
Salome, C.M., Munoz, P.A., Berend, N., Thorpe, C.W., Schachter, L.M., King, G.G., 2007. Effect of obesity on breathlessness and airway responsiveness to methacholine in non-asthmatic subjects. Int. J. Obes. 32, 502–509.
Scano, G., Stenardi, L., Grazzini, M., 2005. Understanding dyspnea by its language. Eur. Respir. J. 25, 380–385.
Seres, L., Lopez-Ayerbe, J., Coll, R., Rodriguez, O., Vila, J., Formiguera, X., Alastrue, A., Rull, M., Valle, V., 2006. Increased exercise capacity after surgically induced weight loss in morbid obesity. Obesity 14, 273–279.
Sharratt, M.T., Henke, K.G., Aaron, E.A., Pegelow, D.F., Dempsey, J.A., 1987. Exercise-induced changes in functional residual capacity. Respir. Physiol. 70, 313–326.
Simon, P.M., Schwartzstein, R.M., Weiss, J.W., Lahive, K., Fencl, V., Teghtsoonia, M., Weinberger, S.E., 1989. Distinguishable sensations of breathlessness induced in normal volunteers. Am. Rev. Respir. Dis. 140, 1021–1027.
Simon, P.M., Schwartzstein, R.M., Weiss, K., Fencl, M., Teghtsoonian, M., Weinberger, S.E., 1990. Distinguishable types of breathlessness in patients with shortness of breath. Am. Rev. Respir. Dis. 142, 1009–1014.
Sin, D.D., Jones, R.L., Man, P., 2002. Obesity is a risk factor for dyspnea but not airflow obstruction. Arch. Intern. Med. 162, 1477–1481.
Sun, X.G., Hansen, J.E., Garatachea, N., Storer, T.W., Wasserman, K., 2002. Ventilatory efficiency in healthy subjects. Am. J. Respir. Crit. Care Med. 166, 1443–1448.
Sutherland, T.J., Goulding, A., Grant, A.M., Cowan, J.O., Williamson, A., Willams, S.M., Skinner, M.A., Taylor, D.R., 2008. The effect of adiposity measured by dual-energy X-ray absorptiometry on lung function. Eur. Respir. J. 32, 85–91.
Tack, M., Altose, M.D., Cherniack, N.S., 1981. Effect of aging on respiratory sensations produced by elastic loads. J. Appl. Physiol. 50, 844–850.
Tack, M., Altose, M.D., Cherniack, N.S., 1982. Effect of aging on the perception of resistive ventilatory loads. Am. Rev. Respir. Dis. 126, 463–467.
Tack, M., Altose, M.D., Cherniack, N.S., 1983. Effects of aging on sensation of respiratory force and displacement. J. Appl. Physiol. 55, 1433–1440.
Takishima, T., Shindoh, C., Kikuchi, Y., Hida, W., Inoue, H., 1990. Aging effect on oxygen consumption of respiratory muscles in humans. J. Appl. Physiol. 69, 14–20.
Tenholder, M.F., South-Paul, J.E., 1989. Dyspnea in pregnancy. Chest 96, 381–388.

Tenney, S.M., Miller, R.M., 1956. Dead space ventilation in old age. J. Appl. Physiol. 9, 321–327.
Tessier, J.F., Nejjari, C., Letenneur, L., Filleul, L., Marty, M.L., Gateau, P.B., Dartigues, J.F., 2001. Dyspnea and 8-year mortality among elderly men and women: the PAQUID cohort study. Eur. J. Epidemiol. 17, 223–229.
Thomas, P.S., Owen, E.R.T.C., Hulands, G., Milledge, J.S., 1989. Respiratory function in the morbidly obese before and after weight loss. Thorax 44, 382–386.
Thurlbeck, W.M., 1969. The internal surface area of nonemphysematous lung. Am. Rev. Respir. Dis. 95, 765–773.
Tolep, K., Higgins, N., Muza, S., Criner, G., Kelsen, S.G., 1995. Comparison of diaphragm strength between healthy adult elderly and young men. Am. J. Respir. Crit. Care Med. 152, 677–682.
Tolep, K., Kelsen, S.G., 1993. Effect of aging on respiratory skeletal muscles. Clin. Chest Med. 14, 363–378.
Topin, N., Mucci, P., Hayot, M., Prefaut, C., Ramonatxo, M., 2003. Gender influence on the oxygen consumption of the respiratory muscles in young and older healthy individuals. Int. J. Sports Med. 24, 559–564.
Turner, J., Mead, J., Wohl, M., 1968. Elasticity of human lungs in relation to age. J. Appl. Physiol. 25, 664–671.
Verbeken, E.K., Cauberghs, M., Mertens, I., Clement, J., Lauweryns, J.M., Van de Woestijne, K.P., 1992a. The senile lung, Comparison with normal and emphysematous lungs. 1. Structural aspects. Chest 101, 793–799.
Verbeken, E.K., Cauberghs, M., Mertens, I., Clement, J., Lauweryns, J.M., Van de Woestijne, K.P., 1992b. The senile lung Comparison with normal and emphysematous lungs. 2. Functional aspects. Chest 101, 800–809.
Ward, S.A., Whipp, B.J., 1989. Effects of peripheral and central chemoreflex activation on the isopnoeic rating of breathing in exercising humans. J. Physiol. 411, 27–43.
Waterer, G.W., Wan, J.Y., Kritchevsky, S.B., Wunderink, R.G., Satterfield, S., Bauer, D.C., Newman, A.B., Taaffe, D.R., Jensen, R.L., Crapo, R.O., for the Health ABC Study, 2001. Airflow limitation is underrecognized in well-functioning older people. J. Am. Geriatr. Soc. 49, 1032-1038.
Watson, R.A., Pride, N.B., 2005. Postural changes in lung volumes and respiratory resistance in subjects with obesity. J. Appl. Physiol. 98, 512–517.
Weinberger, S.E., Weiss, S.T., Cohen, W.R., Weiss, J.W., Johnson, T.S., 1980. Pregnancy and the lung. Am. Rev. Respir. Dis. 121, 559–581.
Weiner, P., Waizman, J., Weiner, M., Rabner, M., Magadle, R., Zamir, D., 1998. Influence of excessive weight loss after gastroplasty for morbid obesity on respiratory muscle performance. Thorax 53, 39–42.
Whipp, B.J., Davis, J.A., 1984. The ventilatory stress of exercise in obesity. Am. Rev. Respir. Dis. 129, S90–S92.
Wise, R.A., Polito, A.J., Krishnan, V., 2006. Respiratory physiologic changes in pregnancy. Immunol. Allergy Clin. North Am. 26, 1–12.
Wolfe, L.A., Walker, R.M., Bonen, A., McGrath, M.J., 1994. Effects of pregnancy and chronic exercise on respiratory responses to graded exercise. J. Appl. Physiol. 76, 1928–1936.
Wood, H.E., Semon, T.L., Comeau, L.A., Schwartz, B., MacDougall, R.M., Klocko, M.N., Babb, T.G., 2008. The ventilatory response to exercise does not differ between obese women with and without dyspnea on exertion. Adv. Exp. Med. Biol. 605, 514–518.
Younes, M., 1991. Determinants of thoracic excursions during exercise. In: Whipp, B.J., Wasserman, K. (Eds.), Lung Biology in Health and Disease. Exercise Pulmonary Physiology and Pathophysiology. Marcel Dekker, New York, pp. 1–65.
Zavorsky, G.S., Hoffman, S.L., 2008. Pulmonary gas exchange in the morbidly obese. Obes. Rev. 9, 326–339.
Zechman, F.W., Wiley, R.L., 1986. Afferent inputs to breathing: respiratory sensation. In: Fishman, A.P. (Ed.), Handbook of Physiology Section 3, Vol. II Part 2: The Respiratory System. American Physiological Society, Bethesda, MD, pp. 449–474.
Zeldis, S.M., 1992. Dyspnea during pregnancy: distinguishing cardiac from pulmonary causes. Clin. Chest Med. 13, 567–585.