

Respiratory mechanics during exercise in endurance-trained men and women

Jordan A. Guenette¹, Jonathan D. Witt¹, Donald C. McKenzie^{1,2}, Jeremy D. Road² and A. William Sheel¹

¹School of Human Kinetics and ²Faculty of Medicine, The University of British Columbia, Vancouver, British Columbia, Canada

The purpose of this study was to compare the mechanics of breathing including the measurement of expiratory flow limitation, end-expiratory lung volume, end-inspiratory lung volume, and the work of breathing in endurance-trained men ($n = 8$) and women ($n = 10$) during cycle exercise. Expiratory flow limitation was assessed by applying a negative expiratory pressure at the mouth. End-expiratory lung volume and end-inspiratory lung volume were determined by having subjects perform inspiratory capacity manoeuvres. Transpulmonary pressure, taken as the difference between oesophageal and airway opening pressure, was plotted against volume and integrated to determine the work of breathing. Expiratory flow limitation occurred in nine females (90%) and three males (43%) during the final stage of exercise. Females had a higher relative end-expiratory lung volume (42 ± 8 versus $35 \pm 5\%$ forced vital capacity (FVC)) and end-inspiratory lung volume (88 ± 5 versus $82 \pm 7\%$ FVC) compared to males at maximal exercise ($P < 0.05$). Women also had a higher work of breathing compared to men across a range of ventilations. On average, women had a work of breathing that was twice that of men at ventilations above 90 l min^{-1} . These data suggest that expiratory flow limitation may be more common in females and that they experience greater relative increases in end-expiratory lung volume and end-inspiratory lung volume at maximal exercise compared to males. The higher work of breathing in women is probably attributed to their smaller lung volumes and smaller diameter airways. Collectively, these findings suggest that women utilize a greater majority of their ventilatory reserve compared to men and this is associated with a higher cost of breathing.

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Corresponding author A. W. Sheel: Health and Integrative Physiology Laboratory, University of British Columbia, 6108 Thunderbird Blvd, Vancouver, BC, Canada V6T-1Z3. Email: bill.sheel@ubc.ca

Expiratory flow limitation during exercise has been reported in both healthy men (Johnson *et al.* 1992) and women (McClaran *et al.* 1998). The presence of expiratory flow limitation may cause reflex inhibition of the hyperventilatory response and/or an alteration in operational lung volumes (Johnson *et al.* 1999). For example, with the onset of expiratory flow limitation, end-expiratory lung volume increases towards resting values. This dynamic hyperinflation permits increases in expiratory flow rates (Pellegrino *et al.* 1993b), but this comes at the expense of an increased elastic work of breathing because lung compliance is reduced as lung volume increases. Additionally, dynamic hyperinflation may hasten the fatigue of the respiratory muscles by requiring them to contract from a shorter length, which means that the muscular force required to ventilate the lungs is closer to the muscle's maximal capacity for force generation (Roussos *et al.* 1979).

The substantial ventilatory requirement of male endurance athletes may result in expiratory flow

limitation during strenuous exercise (Grimby *et al.* 1971; Johnson *et al.* 1992) although this is not necessarily a universal finding (Mota *et al.* 1999). Studies aimed at understanding the physiology of respiration during exercise have traditionally used male rather than female subjects. Only recently has there been an appreciable understanding that the respiratory responses to exercise in women may be different from that of men. Trained females may be particularly susceptible to developing expiratory flow limitation by virtue of their smaller diameter airways, smaller lung volumes and lower peak expiratory flow rates relative to age- and height-matched men (Mead, 1980; Thurlbeck, 1982; ATS, 1991; McClaran *et al.* 1998). These anatomically based differences ultimately result in a smaller maximum flow–volume loop which may cause women to experience expiratory flow limitation at a lower level of minute ventilation (\dot{V}_E) and oxygen consumption (\dot{V}_{O_2}) relative to men (McClaran *et al.* 1998; Hopkins & Harms, 2004). Increased susceptibility to expiratory flow limitation would presumably cause an increased level of

dynamic hyperinflation in women. Furthermore, it would be expected, based on mechanical grounds, that women would have a higher work of breathing for any level of absolute \dot{V}_E due to their smaller lung volumes and airways as it is well established that these factors increase pulmonary flow resistance (Briscoe & Dubois, 1958). However, there is no published evidence to show that trained women have a higher work of breathing during exercise compared to men.

The limited number of studies that have attempted to assess expiratory flow limitation in exercising women have utilized the technique of superimposing tidal breaths within the maximum flow–volume loop (McClaran *et al.* 1998; Walls *et al.* 2002). Although this is a widely used method, it may lead to a false detection or overestimation of expiratory flow limitation for two primary reasons. First, the thoracic gas compression artefact of the maximum flow–volume loop may underestimate the true capacity for flow generation (Ingram & Schilder, 1966). Second, the differences in the volume and time history that precede tidal expiration and forced expiratory manoeuvres may lead to a false detection of expiratory flow limitation (D'Angelo *et al.* 1993; Mota *et al.* 1999). An alternative method to determine expiratory flow limitation is to apply a negative expiratory pressure at the mouth and compare the flow–volume curve of the ensuing expiration with the preceding control breath (Valta *et al.* 1994; Mota *et al.* 1999). Unlike the traditional method, the negative expiratory pressure technique does not require forced expiratory efforts or the correction for gas compression. Furthermore, the volume history of the control expiration and the subsequent expiration with the negative expiratory pressure is the same. To our knowledge, the negative expiratory pressure technique, which avoids these caveats, has not been used to assess expiratory flow limitation in female athletes.

Based on the above brief summary, we hypothesized that female endurance athletes with smaller lungs would be at an increased risk of developing expiratory flow limitation at maximal exercise. We also hypothesized that women would have a higher relative increase in operational lung volumes and a higher absolute work of breathing during progressive exercise compared to male endurance athletes.

Methods

Subjects

All experimental procedures and protocols were approved by the Clinical Screening Committee for Research and Other Studies Involving Human Subjects of the University of British Columbia, conforming to the *Declaration of Helsinki*. Each subject provided written informed consent prior to participating in this study. All subjects ($n = 8$ male; $n = 10$ female) were highly trained endurance athletes

(1 runner, 1 rower, 3 triathletes, 13 cyclists) and were excluded on the basis of any previous history of asthma, smoking, or cardiopulmonary disease. Progesterone combined with oestrogen raises both alveolar ventilation and chemosensitivity (Bayliss & Millhorn, 1992; Tatsumi *et al.* 1997). As such, testing of females was limited to the early follicular phase (days 3–8) (Lebrun *et al.* 1995) as determined via a self-reported menstrual history questionnaire. The use of oral contraceptives did not result in exclusion from this investigation.

General protocol

On Day 1 subjects underwent general pulmonary function testing and then sat quietly for 10 min while resting cardiorespiratory and metabolic measures were collected. After a 5 min self-selected warm-up, subjects underwent an incremental cycle test to exhaustion to determine maximal oxygen consumption ($\dot{V}_{O_{2max}}$). Throughout the exercise test, subjects became familiar with performing inspiratory capacity manoeuvres. Following a brief recovery, subjects then performed 5 min of steady-state submaximal exercise ($\sim 70\%$ of maximum work) in order to become familiar with the negative expiratory pressure test. On Day 2, a balloon-tipped catheter was inserted into the oesophagus followed by 10 min of baseline measures. Subjects then performed the identical exercise protocol to that of Day 1. Experimental days were separated by a minimum of 48 h.

Pulmonary function

Forced vital capacity (FVC), forced expiratory volume in 1 s ($FEV_{1.0}$), $FEV_{1.0}/FVC$, and peak expiratory flow were determined using a portable spirometer (Spirolab II, Medical International Research, Vancouver, BC, Canada). Measurements were obtained with subjects seated, utilizing standard protocols and expressed as percentage predicted (ATS, 2002). Subjects with an $FEV_{1.0}/FVC < 80\%$ of predicted were excluded from the investigation. Upon completion of these tests, subjects were instructed to perform several inspiratory capacity manoeuvres from functional residual capacity for familiarization purposes.

Exercise protocol

Exercise was performed on an electronically braked cycle ergometer (Excalibur Sport, Lode, Gronigen, The Netherlands). Males and females started the test at 200 W and 100 W, respectively, with the workload increasing in a stepwise fashion by 30 W every 3 min until volitional exhaustion. This protocol was designed such that men and women would exercise for the same duration. Three minute stages were chosen in order to have steady-state

\dot{V}_E such that expiratory flow limitation and changes in lung volumes could be determined. To determine $\dot{V}_{O_2\max}$ on Day 1, subjects wore a nose clip and breathed through a mouthpiece connected to a non-rebreathing valve (model 2700B, Hans-Rudolph, Kansas City, MO, USA). Mixed expired gases were measured using calibrated CO_2 and O_2 analysers (Model CD-3A and Model S-3-A/I, respectively, Applied Electrochemistry, Pittsburgh, PA, USA). Inspiratory flow was measured using a calibrated pneumotachograph (model 3813, Hans Rudolph). The flow signal was integrated to obtain volume, breath timing and frequency, and to determine \dot{V}_E . Heart rate was obtained from a telemetric heart rate monitor (Polar Electro, Kempele, Finland) every 30 s. All ventilatory and expired gas data during the exercise test were recorded continuously at 200 Hz (PowerLab/16SP model ML 795, ADI, Colorado Springs, CO, USA) and stored on a computer for subsequent analysis (Chart v5.3, ADInstruments, Colorado Springs, CO, USA).

Expiratory flow limitation

Expiratory flow limitation was determined using the negative expiratory pressure technique as described by Mota *et al.* (1999). Briefly, the negative expiratory pressure technique involves the connection of a Venturi device (207A, model, Raytech Instruments, Vancouver, BC, Canada) to a tank of compressed gas capable of generating a range of negative pressures. A control box operated by the experimenter was used to activate and deactivate the negative expiratory pressure when it received a signal from the pneumotachograph. After expiration was initiated, the system took ~ 50 ms to reach the desired negative pressure which was set at approximately -10 cmH₂O (Mota *et al.* 1999). The valve remained opened for the entire expiration and was closed immediately at the onset of the next inspiration. The Venturi device was placed at the distal end of the pneumotachograph, which recorded the tidal flow–volume loops. Volume was obtained by numerical integration of the flow signal. The flow signal was corrected for any offset, using the assumption that inspired and expired volumes of the control breaths preceding the test breaths are the same (Koulouris *et al.* 1995). A minimum of three negative expiratory pressure tests were performed during the final workload as subjects were approaching volitional exhaustion. Expiratory flow limitation was considered present when there was an overlap between the negative expiratory pressure breath and preceding control expiration (Valta *et al.* 1994; Mota *et al.* 1999). The negative expiratory pressure technique has been validated in mechanically ventilated patients with concomitant determination of isovolume flow–pressure relationships (Valta *et al.* 1994) and in resting subjects with chronic obstructive pulmonary disease (Koulouris *et al.* 1995). The negative

expiratory pressure technique has been shown to be a simple and reliable method for determining expiratory flow limitation during exercise (Koulouris *et al.* 1997a; Mota *et al.* 1999).

Operational lung volumes

Changes in end-expiratory lung volume and end-inspiratory lung volume were evaluated from measurements of inspiratory capacity at rest, at the end of each exercise stage and immediately prior to cessation of exercise. End-expiratory lung volume was calculated by subtracting the resting FVC from the inspiratory capacity with the assumption that total lung capacity remains constant throughout exercise (Johnson *et al.* 1999). End-inspiratory lung volume was calculated by adding end-expiratory lung volume to the tidal volume. After a full explanation and demonstration to each subject, satisfactory technique and reproducibility of the inspiratory capacity manoeuvres ($\pm \sim 5\%$) were obtained during the familiarization day at rest and also during exercise. Subjects were given additional practice during the warm-up and rest period of Day 2. Prior to performing an inspiratory capacity manoeuvre, subjects were given a verbal prompt for the manoeuvre and encouragement throughout the manoeuvre (O'Donnell *et al.* 1998). Inspiratory capacity trials were considered acceptable when peak inspiratory oesophageal pressure matched those obtained at rest (Younes & Kivinen, 1984; Babb *et al.* 1991; Johnson *et al.* 1995). If subjects failed to achieve the pre-exercise target pressures, they were required to repeat the inspiratory capacity manoeuvre. When analysing the inspiratory capacity data, six breaths were selected prior to the inspiratory capacity manoeuvre in order to monitor changes in pneumotachograph drift and any alterations in breathing pattern immediately prior to the manoeuvre.

Work of breathing

Measurement of oesophageal pressure was obtained using a balloon-tipped catheter (no. 47-9005, Ackrad Laboratory, Cranford, NJ, USA) attached to piezoelectric pressure transducer (± 100 cmH₂O; Raytech Instruments Vancouver, BC, Canada). Airway opening pressure was obtained via a port located in the mouthpiece and transferred by polyethylene tubing to a differential piezoelectric pressure transducer (± 100 cmH₂O; Raytech Instruments, Vancouver, BC, Canada). Transducers were calibrated using a digital manometer (2021P, Digitron, Torquay UK). Viscous lidocaine (lignocaine) hydrochloride (2%) (Xylocaine, AstraZeneca Canada Inc. Mississauga, Ontario, Canada) was applied in the nasal and pharyngeal passages to minimize discomfort. The catheter was inserted through the nose and positioned

~45 cm down from the nostril (Milic-Emili *et al.* 1964). After the balloon was inserted, all the air was evacuated by pulling back on a syringe plunger until the plunger returned to a non-vacuum position. One millilitre of air was injected in order to partially inflate the balloon and catheter according to the manufacturer's specifications. Validity of the balloon pressure was checked by having the subjects blow against an occluded airway (Baydur *et al.* 1982). If trans-pulmonary pressure remained constant while airway opening pressure increased, placement was considered appropriate. Trans-pulmonary pressure was calculated as the difference between oesophageal pressure and airway opening pressure. The work of breathing was obtained by ensemble averaging several breaths and then using a customized software program (LabVIEW software V6.1, National Instruments) to integrate the averaged trans-pulmonary pressure–tidal volume loop (Otis, 1964). The work of breathing was then multiplied by breathing frequency to represent the amount of work done per minute by the respiratory system. The method for analysing the work of breathing was similar to previous studies where the work of breathing was compared between two groups (Milic-Emili *et al.* 1962; Cibella *et al.* 1999). The individual raw work of breathing data was plotted against a range of ventilations obtained during exercise. To facilitate comparison between men and women, curves corresponding to each subject were calculated assuming the following relationship between the work of breathing (W_b) and \dot{V}_E :

$$W_b = a\dot{V}_E^3 + b\dot{V}_E^2 \quad (1)$$

This equation is based on the original work of Rohrer (1915) and is described in the classic work of Otis *et al.* (1950). The term $b\dot{V}_E^2$ represents the mechanical work done in overcoming the viscous resistance offered by the lung tissues to deformation and by the respiratory tract to the laminar flow of air. The term $a\dot{V}_E^3$ represents the work done in overcoming the resistance to turbulent flow. A value for constants a and b was then determined for each individual subject. All flow and pressure signals were amplified, filtered (low-pass) at 50 Hz, and digitized at 200 Hz by a 16-bit analog-to-digital converter (200B, Direc Physiologic Recording System; Raytech Instruments) using the data acquisition software program (Direc/Win version 2.21, Raytech Instruments Inc.) and stored for subsequent analysis.

Statistical analysis

Repeated measures ANOVA (Statistica 6.1, Stat Soft Inc., Tulsa, OK, USA) was used to examine differences in end-expiratory lung volume and end-inspiratory lung volume across different workloads. If significant F -ratios were detected, Tukey's *post hoc* test was applied to determine where the differences occurred.

Table 1. Subject characteristics

	Men ($n = 8$)	Women ($n = 10$)
Age (years)	25.9 ± 4.9	24.7 ± 2.8
Height (cm)	183.9 ± 6.6	168.6 ± 4.7*
Mass (kg)	76.6 ± 9.8	63.3 ± 4.2*
BMI (kg m ⁻²)	22.6 ± 1.8	22.3 ± 0.9
BSA (m ²)	1.99 ± 0.15	1.72 ± 0.08*
FVC (l)	5.6 ± 1.0	4.5 ± 0.5*
FVC (%predicted)	105 ± 14	108 ± 13
FEV _{1.0} (l)	5.1 ± 1.0	3.8 ± 0.5*
FEV _{1.0} (%predicted)	106 ± 18	107 ± 13
FEV _{1.0} /FVC (%)	85.3 ± 4.2	84.5 ± 5.3
FEV _{1.0} /FVC (%predicted)	101 ± 5	98 ± 6
PEF (l s ⁻¹)	12.6 ± 1.4	8.0 ± 1.1*
PEF (%predicted)	124 ± 11	116 ± 18

Values are means ± s.d. Definitions of abbreviations: BMI, body mass index; BSA, body surface area; FVC, forced vital capacity; FEV_{1.0}, forced expiratory volume in 1 s; FEV_{1.0}/FVC, forced expiratory volume in 1 s/forced vital capacity; PEF, peak expiratory flow. *Significantly different from men ($P < 0.001$).

Mean comparisons between groups were performed using unpaired t tests with Bonferroni corrections where appropriate. Pearson product moment correlations were used to determine linear relationships between selected dependent variables. The level of significance was set at $P < 0.05$ for all statistical comparisons.

Results

Subject characteristics

Twenty-one endurance-trained subjects volunteered to participate in this study but two (1 male, 1 female) were excluded on the basis of an FEV_{1.0}/FVC < 80% of predicted and another was excluded on the basis of an irregular menstrual cycle. Subject characteristics are shown in Table 1. Women were significantly smaller in terms of height, mass and body surface area ($P < 0.001$). Women had a significantly smaller FVC, FEV_{1.0} and peak expiratory flow compared to men ($P < 0.001$). All subjects were within or greater than predicted values for all pulmonary function variables and there were no significant differences between men and women ($P > 0.05$).

Exercise data

Table 2 shows metabolic, ventilatory and performance characteristics at maximal exercise on Day 1. Men had a significantly higher absolute and relative $\dot{V}_{O_{2,max}}$ compared to women ($P < 0.01$). Men had a significantly higher V_T ($P < 0.05$) and \dot{V}_E ($P < 0.001$) compared to women at maximal exercise. Men achieved a higher power output at maximal exercise ($P < 0.001$). By design, duration of exercise tests were the same between men and women.

Table 2. Peak exercise values on Day 1

	Men (n = 8)	Women (n = 10)
\dot{V}_{O_2} (ml kg ⁻¹ min ⁻¹)	69.5 ± 7.8	59.8 ± 4.8*
\dot{V}_{O_2} (l min ⁻¹)	5.3 ± 0.7	3.8 ± 0.4*
\dot{V}_{CO_2} (l min ⁻¹)	5.7 ± 0.6	4.1 ± 0.5*
RER	1.08 ± 0.07	1.07 ± 0.04
F_b (breaths min ⁻¹)	59 ± 9	58 ± 5
V_T (l)	3.1 ± 0.4	2.3 ± 0.3*
\dot{V}_E (l min ⁻¹)	161 ± 25	120 ± 18*
\dot{V}_E/\dot{V}_{O_2}	30.6 ± 4.9	31.6 ± 3.0
\dot{V}_E/\dot{V}_{CO_2}	28.2 ± 3.0	29.6 ± 3.0
\dot{V}_E/BSA (%)	81 ± 9	69 ± 9*
T_i (s)	0.47 ± 0.04	0.47 ± 0.07
T_e (s)	0.51 ± 0.07	0.52 ± 0.11
T_{tot} (s)	0.98 ± 0.09	0.99 ± 0.17
T_i/T_{tot}	0.48 ± 0.03	0.48 ± 0.03
T_e/T_{tot}	0.52 ± 0.03	0.52 ± 0.03
HR (beats min ⁻¹)	189 ± 8	190 ± 11
Exercise duration (s)	1273 ± 189	1229 ± 163
Peak power (W)	376 ± 30	265 ± 26*

*Significantly different from men ($P < 0.05$). Values are means ± s.d. Definitions of abbreviations: \dot{V}_{O_2} , oxygen consumption; \dot{V}_{CO_2} , carbon dioxide production; RER, respiratory exchange ratio; F_b , breathing frequency; V_T , tidal volume; \dot{V}_E , minute ventilation; \dot{V}_E/\dot{V}_{O_2} , ventilatory equivalent for oxygen; \dot{V}_E/\dot{V}_{CO_2} , ventilatory equivalent for carbon dioxide; \dot{V}_E/BSA , minute ventilation/body surface area; HR, heart rate; T_i , inspiratory time; T_e , expiratory time; T_{tot} , total time ($T_i + T_e$).

Expiratory flow limitation

Figure 1A and B shows individual flow–volume curves at maximal exercise in women and men, respectively. Subjects were considered flow limited if part of the negative expiratory pressure breath overlapped the preceding control breath. One male subject (subject 3) was excluded in the analysis of expiratory flow limitation because the negative expiratory pressure caused a sustained decrease in expiratory flow using previously defined criteria (Valta *et al.* 1994; Tantucci *et al.* 1999). Expiratory flow limitation was shown to occur in 3 of the 7 male subjects and 9 of the 10 female subjects during the final stage of exercise. Subject 3 (Fig. 1A) was the only female that did not develop expiratory flow limitation. Of all female subjects she also had the largest lungs (134% predicted FVC).

Overcoming expiratory flow limitation

Since multiple negative expiratory pressure tests were obtained throughout the final exercise stage, it could be determined if subjects could become flow limited early in a given exercise stage and later in the same stage, become non-flow limited. Several subjects who demonstrated

expiratory flow limitation (6 female, 1 male) during the initial portion of the final stage of exercise were later able to overcome the expiratory flow limitation. Figure 2 is representative of a single female subject (subject 9) who experienced expiratory flow limitation early during the final exercise stage but was later able to avoid the expiratory flow limitation through an alteration in her breathing pattern. As expected, in those subjects who demonstrated expiratory flow limitation and then did not later in the same exercise stage, there was no appreciable decline in \dot{V}_E as the exercise progressed, but V_T decreased slightly and was coupled with an increase in F_b .

Operational lung volumes

Figure 3 shows changes in end-expiratory lung volume and end-inspiratory lung volume expressed as percentage of FVC at rest and during exercise in men and women. One female subject was not included in the analysis of lung volumes due to her inability to correctly perform inspiratory capacity manoeuvres. Mean values for end-expiratory lung volume decreased from rest in men and women with the onset of exercise. End-expiratory lung volume remained significantly below resting end-expiratory lung volume in men throughout all exercise intensities whereas females increased end-expiratory lung volume at 89% and 100% of maximum exercise workload (W_{max}), such that end-expiratory lung volume was no longer significantly different from rest. At maximum exercise, women had a significantly higher relative end-expiratory lung volume compared to men (42 ± 8 versus $35 \pm 5\%$ FVC, $P < 0.05$). Mean end-inspiratory lung volume in men continued to increase from rest and throughout exercise but plateaued between 90 and 100% of W_{max} whereas mean end-inspiratory lung volume rose throughout all exercise intensities in women. At maximal exercise, relative end-inspiratory lung volume was significantly higher in women compared to men (88 ± 5 versus $82 \pm 7\%$ FVC, $P < 0.05$).

Work of breathing

Figure 4 shows the individual raw traces relating the mechanical work of breathing and \dot{V}_E . The curves are of a continually increasing slope meaning that the mechanical work of breathing per any additional unit of air ventilated ($dW_b/d\dot{V}_E$) increases progressively with increasing \dot{V}_E . Without exception, the curve for each subject fits eqn (1) where the mean $r^2 = 0.99$. Mean values for constants a and b are shown in Table 3. Constant a was significantly higher in women compared to men ($P < 0.05$) but no differences were detected for constant b ($P > 0.05$). A mean curve for men and women was constructed based on the average values for each constant (Fig. 5). The curves

have been extrapolated to 200 l min^{-1} for theoretical and visual purposes only. Constant b did not correlate with any variables in this study. However, constant a was significantly correlated with a number of variables as

shown in Table 4. The majority of significant correlations were only demonstrated when men and women were pooled into a single group. No variables were significantly correlated with constant a in men. However, $\text{FEV}_{1.0}$ and

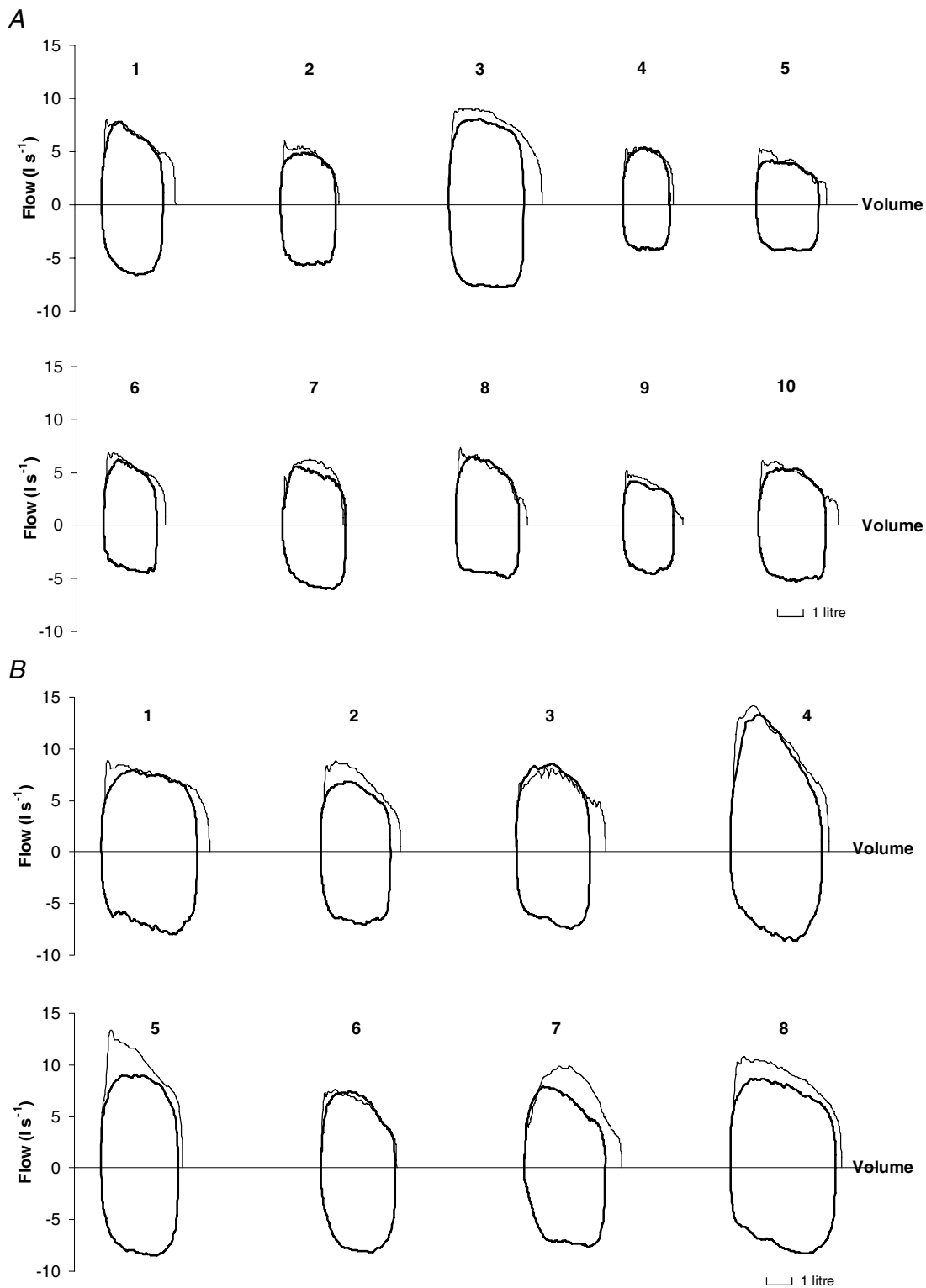


Figure 1

Individual tidal flow-volume loops during the final stage of exercise in women (A; $n = 10$) and men (B; $n = 8$). Dark lines represent the control breath and thin lines represent the negative expiratory pressure breath.

peak expiratory flow were correlated with constant a in women. There was also a trend for $FEV_{1.0}/FVC$ to be related to constant a in women ($r = -0.62$; $P = 0.08$). Figure 6 shows the work of breathing plotted against relative values of $\dot{V}_{O_{2max}}$. The work of breathing was not different between men and women at 75, 90 and 100% of $\dot{V}_{O_{2max}}$.

Discussion

This study was designed to systematically compare the mechanics of breathing in male and female endurance athletes during progressive exercise to exhaustion. Ours is the first investigation to utilize the negative expiratory pressure technique to assess expiratory flow limitation and is the only study which has measured the mechanical work of breathing in a group of female endurance athletes during exercise. The principle findings of this study are threefold. First, female endurance athletes experience expiratory flow limitation more frequently and at a lower level of \dot{V}_E compared to male endurance athletes. Second, females experience greater dynamic hyperinflation during heavy exercise. Third, the total mechanical work of breathing is higher in females compared to males during progressive exercise. Our findings point to a female pulmonary system which is at a mechanical disadvantage compared to their male counterparts during exercise.

Expiratory flow limitation

We found that expiratory flow limitation occurs in both endurance-trained men and women at maximal exercise. However, expiratory flow limitation occurred more frequently in trained women even though maximal \dot{V}_E was considerably lower than in the men. Nearly all women experienced expiratory flow limitation (90%) at maximal exercise, whereas expiratory flow limitation only occurred in 43% of males. This difference is probably attributable to the inherent differences in the structural and functional characteristics of the male and female pulmonary systems (Mead, 1980; Thurlbeck, 1982; ATS, 1991; McClaran *et al.* 1998). The women in this study had significantly smaller lungs and lower peak expiratory flow rates compared to men. The findings in the present study extend those of McClaran *et al.* (1998) and Guenette *et al.* (2004) that suggest women are more likely to utilize a greater percentage of their ventilatory reserve during exercise compared to men.

Endurance-trained humans are a unique model to understand respiratory mechanics during exercise because they have extremely high metabolic and ventilatory demands even though their pulmonary function (i.e. lung volumes and flow rates) is not markedly different from that of sedentary individuals (Reuschlein *et al.* 1968). The high ventilatory requirement could predispose them to

expiratory flow limitation. However, the few investigations that have assessed expiratory flow limitation in endurance athletes have reported conflicting results with no studies making direct comparisons between men and women. Mota *et al.* (1999) suggest that expiratory flow limitation is rare in male endurance athletes whereas Johnson *et al.* (1992) have shown the opposite. The discrepancy may be due, in part, to methodological considerations associated with the assessment of expiratory flow limitation. As mentioned, the traditional method of assessing expiratory flow limitation involves the placement of tidal flow–volume loops within a maximum flow–volume loop and positioned according to end-expiratory lung volume. Koulouris (2002) has summarized a number of methodological concerns with this method. For example,

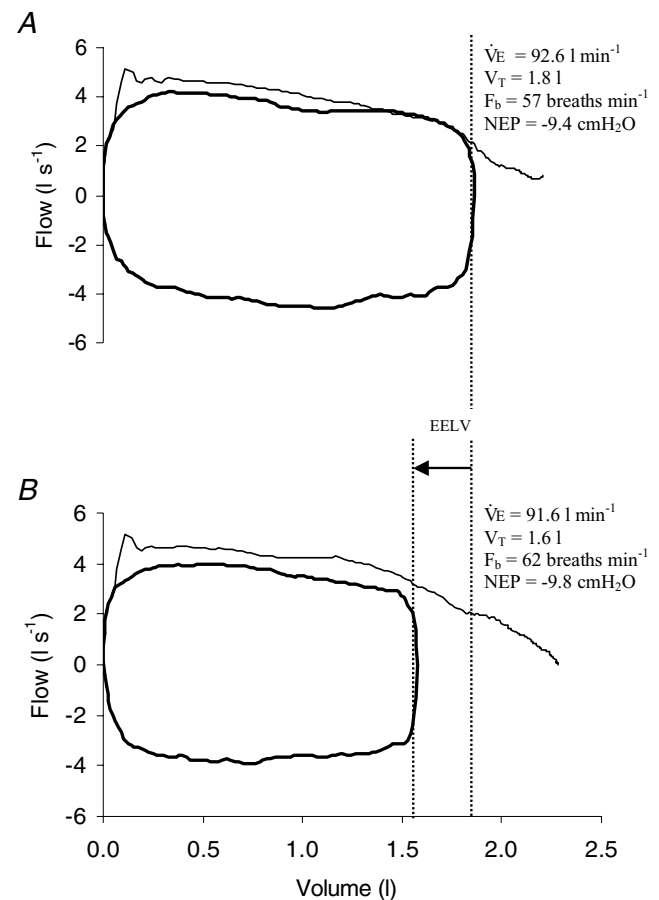


Figure 2

A, representative flow–volume loops of a single female subject (subject 9) experiencing expiratory flow limitation during the final stage of exercise as evidenced by the overlap between the control breath (dark line) and the negative expiratory pressure breath (thin line). B, flow–volume loops collected later during the final stage of exercise in the same subject. She is no longer flow limited because the negative expiratory pressure increased expiratory flow for the entire duration of the expiration. \dot{V}_E , minute ventilation; V_T , tidal volume; F_b , breathing frequency; NEP, negative expiratory pressure; $\Delta EELV$, change in end-expiratory lung volume.

the thoracic gas compression artefact of the maximum flow–volume loop may lead to a false detection or overestimation of expiratory flow limitation (Ingram & Schilder, 1966). In addition, differences in the volume and time history that precede tidal expiration and forced expiratory manoeuvres may result in a false detection of expiratory flow limitation (D'Angelo *et al.* 1993, 1994; Koulouris *et al.* 1997b). Since the volume and time history of a spontaneous tidal breath is different from that of an FVC manoeuvre, it is possible that the traditional method may be problematic, even when correction has been made for thoracic gas compression (Koulouris, 2002). The negative expiratory pressure technique is advantageous in that it does not require the correction for gas compression and the time history is the same between the control and negative expiratory pressure breaths. Using the negative expiratory pressure method, Mota *et al.* (1999) demonstrated that only 1 out of 9 male cyclists developed expiratory flow limitation at maximal exercise which is considerably lower than that previously reported in men (Johnson *et al.* 1992). Given these findings, it

remains possible that expiratory flow limitation may have previously been overestimated in women during exercise.

McClaran *et al.* (1998) measured expiratory flow limitation in a group of fit ($\dot{V}_{O_{2max}} = 62.9 \text{ ml kg}^{-1} \text{ min}^{-1}$) and less fit ($\dot{V}_{O_{2max}} = 48.1 \text{ ml kg}^{-1} \text{ min}^{-1}$) women and found evidence of expiratory flow limitation in 12 of the 14 (86%) fit women and 4 of the 15 (27%) less fit women. Using a similar technique, Walls *et al.* (2002) found expiratory flow limitation in 7 out of 8 (88%) recreationally active women ($\dot{V}_{O_{2max}} = 46.8 \text{ ml kg}^{-1} \text{ min}^{-1}$). Both studies examining expiratory flow limitation in women have utilized the traditional approach, and given the findings of Mota *et al.* (1999) in men with the negative expiratory pressure technique, it is possible that they overestimated expiratory flow limitation in women. However, the results from the present study are in excellent agreement with previous expiratory flow limitation studies in women, despite the fact that we used a technique that is less likely to incorrectly characterize subjects as being flow limited.

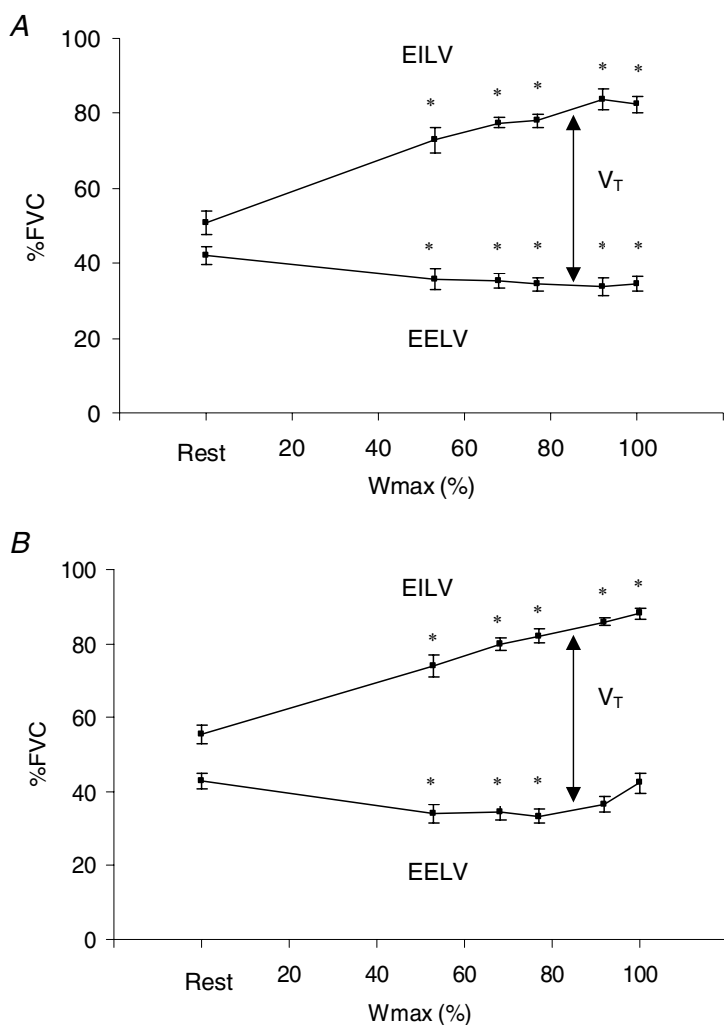


Figure 3

Subdivision of lung volumes, expressed as percentage forced vital capacity (FVC) at rest and during progressive exercise to maximal workload (W_{max}) in men (A) and women (B). EILV, end-inspiratory lung volume; EELV, end-expiratory lung volume; V_T , tidal volume. Values are means \pm S.E.M. *Significantly different from rest ($P < 0.05$).

Table 3. Mean values of constants *a* and *b* from eqn (1)

	Men (<i>n</i> = 8)	Women (<i>n</i> = 9)
<i>a</i> (J min ⁻¹)/(l min ⁻¹) ³ (× 10 ⁻⁵)	6.4 ± 4.1 (2.5–14.0)	19.0 ± 14.4* (7.0–54.8)
<i>b</i> (J min ⁻¹)/(l min ⁻¹) ² (× 10 ⁻³)	6.8 ± 3.2 (2.0–10.3)	6.4 ± 7.4 (–5.2–14.9)

Constant *a* represents the work done in overcoming the resistance to turbulent flow. Constant *b* represents the work done in overcoming viscous resistance (see text). Values are means ± s.d. with ranges in parentheses. *Significantly different from men (*P* < 0.05).

To this point, we have presented our findings as suggesting that athletes either do or do not develop expiratory flow limitation at maximal exercise. Indeed, this is a commonly used representation of expiratory flow limitation during exercise (McClaran *et al.* 1998; Mota *et al.* 1999; Walls *et al.* 2002). However, we favour the concept that expiratory flow limitation is not an all-or-none phenomenon but rather it is a physiological situation

where compensatory ‘strategies’ are available. For example, seven (6 female and 1 male) subjects in this study developed expiratory flow limitation during the final workload but were later assessed as being non-flow-limited according to the negative expiratory pressure test. Figure 2 illustrates a typical example of this where there was a general trend for subjects to slightly decrease V_T and increase F_b such that total \dot{V}_E did not change. This tachypnoeic breathing pattern probably occurred because increasing V_T would have been too difficult due to the expiratory flow limitation and the increasing elastic load on inspiration. When the tidal flow–volume loops are aligned, it can be seen that end-expiratory lung volume shifts, resulting in the avoidance of expiratory flow limitation. Importantly, it should be noted that the magnitude of the negative expiratory pressure was identical in both tests. It should also be noted that there may have been a bronchodilatory response which enabled some subjects to overcome expiratory flow limitation. Our finding that some subjects exhibit expiratory flow limitation and then do not, could partially explain the discrepancy between the work of Mota *et al.* (1999) and Johnson *et al.* (1992).

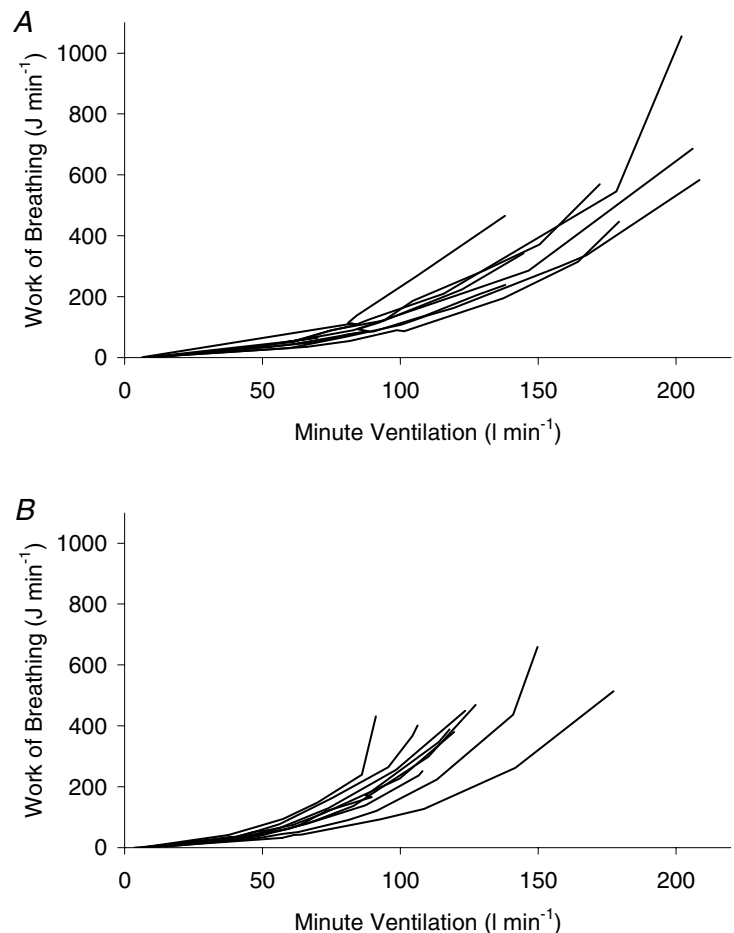


Figure 4
Individual responses of the work of breathing versus minute ventilation in men (A) and women (B).

Operational lung volumes

It is well known that end-expiratory lung volume decreases during exercise in men (Lind & Hesser, 1984; Sharratt *et al.* 1987; Henke *et al.* 1988b; Johnson *et al.* 1992; Mota *et al.* 1999) and this was also observed in the present study. Henke *et al.* (1988a) suggest that mechanical feedback from the lung and chest wall cause active expiration and reductions in functional residual capacity. Decreasing end-expiratory lung volume may then optimize diaphragm length and in turn lower or minimize the inspiratory work of breathing. Inspiratory work of breathing is reduced by recovering some of the work done by the expiratory muscles during the previous expiration (Collett & Engel, 1986; Road *et al.* 1986; Henke *et al.* 1991; Johnson *et al.* 1991). Although men and women demonstrated similar changes in end-expiratory lung volume throughout the majority of submaximal exercise, there were significant differences as subjects approached maximal exercise (Fig. 3B). The women in this study increased end-expiratory lung volume such that it was no longer significantly below resting values. In fact, when normalized to FVC, the women in this study had a significantly higher end-expiratory lung volume compared to men at maximal exercise. This is in contrast to a recent study which found no differences in operational lung volumes between men and women when normalized to FVC (Vogiatzis *et al.* 2005). The difference between these studies is probably a function of subject fitness levels. Vogiatzis *et al.* (2005) used untrained subjects with women only achieving a maximal \dot{V}_E of 69 l min^{-1} whereas subjects in the present study ventilated at a much higher rate (120 l min^{-1}). These untrained women did not increase end-expiratory lung volume at maximal exercise because their ventilatory load was probably insufficient to elicit expiratory flow limitation. Therefore, we would

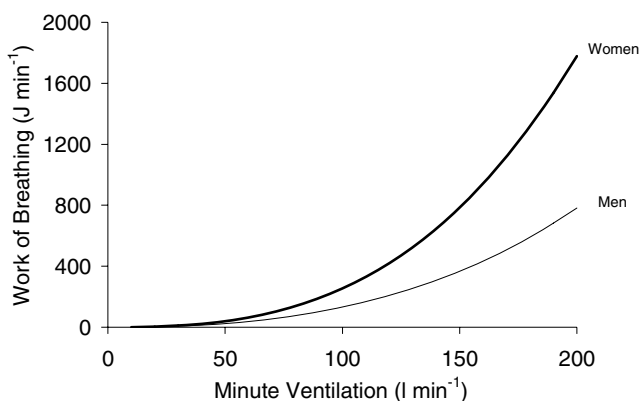


Figure 5 Mean curves relating the work of breathing to minute ventilation in men (thin line) and women (thick line). Both curves are based on mean values of constants a and b from eqn (1). Each curve has been extrapolated to 200 l min^{-1} .

Table 4. Correlation analysis of spirometry data with constant a

Variable vs. constant a	All ($n = 17$)	Men ($n = 8$)	Women ($n = 9$)
FVC	-0.54*	NS	NS
FEV _{1.0}	-0.59*	NS	-0.69*
FEV _{1.0} /FVC	-0.49*	NS	-0.62
PEF	-0.68*	NS	-0.76*

Definitions of abbreviations: FVC, forced vital capacity; FEV_{1.0}, forced expiratory volume in 1 s; FEV_{1.0}/FVC, forced expiratory volume in 1 s/forced vital capacity; PEF, peak expiratory flow. NS, non-significant correlation ($P > 0.05$). *Statistically significant correlation ($P < 0.05$).

argue that our results at submaximal exercise are in good agreement with the findings of Vogiatzis *et al.* (2005) and the difference at maximal exercise between these studies is probably due to the presence or absence of expiratory flow limitation.

Increases in end-expiratory lung volume have previously been shown to increase in men that are capable of achieving very high levels of muscular work and the increases are often associated with the presence of expiratory flow limitation (Olafsson & Hyatt, 1969; Grimby *et al.* 1971; Johnson *et al.* 1992). Increasing end-expiratory lung volume permits utilization of the higher flow rates available at larger lung volumes. Pellegrino *et al.* (1993a) investigated the effect of expiratory flow limitation on end-expiratory lung volume by imposing an expiratory threshold load in male subjects. They concluded that the increase in end-expiratory lung volume during exercise is associated with expiratory flow limitation and that compression

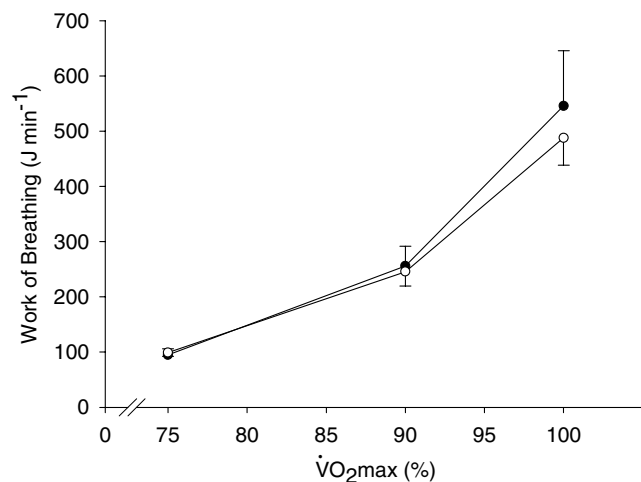


Figure 6 Work of breathing at various percentages of maximal oxygen consumption ($\dot{V}_{O_2\max}$) in men (●) and women (○). Values are means \pm S.E.M.

of airways downstream from the flow-limited segment may elicit a reflex mechanism that influences breathing pattern by prematurely terminating expiration. McClaran *et al.* (1998) also examined the effect of expiratory flow limitation on end-expiratory lung volume in a group of women by having subjects breathe a helium inspirate (79% He, 21% O₂) in order to increase the size of the maximum flow–volume loop and thus eliminate expiratory flow limitation. Reducing expiratory flow limitation caused subjects to maintain a lower end-expiratory lung volume. Furthermore, the lower end-expiratory lung volume occurred only when HeO₂ caused a significant reduction of expiratory flow limitation. These findings are consistent with ours and those of Pellegrino *et al.* (1993a) implying an interrelationship between expiratory flow limitation and the increase in end-expiratory lung volume associated with heavy exercise.

This study has also shown that relative end-inspiratory lung volume is significantly higher at maximal exercise in women compared to men. Given the higher end-expiratory lung volume in women, it is not surprising then that end-inspiratory lung volume is also higher as this occurs in order to preserve the exercise V_T . The end-inspiratory lung volumes in these women are approaching levels that may be considered a marker of ventilatory constraint and an index of increased ventilatory work (Belman *et al.* 1996). The higher end-inspiratory lung volume would likely increase the elastic load on the inspiratory muscles over a greater portion of the tidal breath relative to men.

Work of breathing

The relationship between work of breathing and \dot{V}_E during exercise has been examined in several studies (Milic-Emili *et al.* 1962; Coast *et al.* 1993; Cibella *et al.* 1999). However, all of the above-mentioned studies were exclusively conducted with male subjects. Since women generally have smaller vital capacities compared to height-matched men, it would be expected that women would have an increased elastic work of breathing. It would also be expected that the dimensions of the airways would be smaller or fewer in number. When coupled with a smaller vital capacity, the resistance to flow would consequently be higher (Otis, 1954). As expected, the men were able to achieve a higher \dot{V}_E and V_T compared to women at maximal exercise. Figure 5 shows the mean relationship between the work of breathing and \dot{V}_E in men and women. It can be seen that the work of breathing is essentially the same at rest and during very low levels of exercise \dot{V}_E (i.e. < 60 l min⁻¹). However, as \dot{V}_E increases beyond this point, the work of breathing in women significantly increases out of proportion to men. In fact, the work of breathing in women is approximately twice that of men at ventilations beyond 90 l min⁻¹. Thus,

the physiological cost of moving a given amount of air in and out of the lungs is substantially higher in women. The present results are in good agreement with Topin *et al.* (2003) who suggest a higher O₂ cost of breathing in women.

The method of analysis in the present study is similar to those used by other researchers that have compared the work of breathing between two groups (Milic-Emili *et al.* 1962; Cibella *et al.* 1999). Constant a was significantly higher in women which may be an indication that the higher work of breathing in women is associated with the additional work needed to overcome the resistance to turbulent flow. This may explain why the magnitude of the difference between men and women increased out of proportion with increasing levels of \dot{V}_E . Based on mechanical grounds, it would be expected that subjects with larger lung volumes would have lower pulmonary resistance (Briscoe & Dubois, 1958) and thus a lower work of breathing for a given level of \dot{V}_E . The women in this study had significantly smaller lungs compared to the men and this may be one of many major reasons for their higher work of breathing. We observed inter-individual variability for constants a and b which may be related to the differences in lung volumes (see Table 3 for range). Consistent with the concept of differences in lung volumes was the observation that when men and women were pooled together, there was a significant, albeit modest, correlation between lung volume and constant a (Table 4). Moreover, the female with the largest lungs (subject 3) had the lowest work of breathing relative to other women and she did not demonstrate expiratory flow limitation.

Although we did not measure airway diameter, the increased resistive work in women is probably dependent on their inherently smaller diameter airways (Mead, 1980). It was noted that constant a was significantly correlated with FEV_{1.0} and peak expiratory flow in women and also when all subjects were pooled together. Since the shape of the maximum flow–volume loop is determined, in part, by the diameter of the airways, it seems likely that the relatively strong and significant negative correlations between constant a and the FEV_{1.0} and peak expiratory flow is an indication that airway diameter is partially responsible for the higher work of breathing in women. Although differences in lung volume and airway diameter are explanations for the present findings we make this claim cautiously as it is based on correlative rather than causative evidence.

In this study we have shown that women are more likely to have expiratory flow limitation, hyperinflation and increased work of breathing. When expressed at the same level of absolute minute ventilation women have higher work of breathing (Fig. 5). When expressed at a relative intensity men and women appear to have a similar work of breathing (Fig. 6). We interpret our collective findings to mean that at a given workload expiratory flow limitation is more common in women because their ventilations are

higher and equally or more importantly their maximum flow–volume envelopes are smaller. Comparing the work of breathing at equal relative intensities brings the work of breathing data together because the ventilations are substantially different between men and women at a given absolute work rate. Men and women have a similar work of breathing at 100% $\dot{V}_{O_{2max}}$ and yet women have a minute ventilation that is substantially lower (~25%) than their male counterparts. Therefore, a similar work of breathing at 100% $\dot{V}_{O_{2max}}$ between men and women suggests that the physiological cost of breathing is higher in women.

Critique of methods

The negative expiratory pressure technique has been validated in mechanically ventilated patients (Valta *et al.* 1994) and in resting patients with chronic obstructive pulmonary disease (Koulouris *et al.* 1995). It has been used during exercise in competitive cyclists (Mota *et al.* 1999) and in healthy untrained individuals and patients with chronic obstructive pulmonary disease (Koulouris *et al.* 1997a). Koulouris *et al.* (1997a) suggest that the negative expiratory pressure technique is more reliable for assessing expiratory flow limitation during exercise compared to conventional methods. However, some have questioned the validity of this technique during exercise because the negative expiratory pressure may induce reflex inhibition of expiratory muscle activity which leads to a decrease in expiratory driving pressure (de Bisschop *et al.* 2006). These authors suggest that expiratory flow limitation is dependent on the magnitude of the negative pressure. For example, they found evidence of expiratory flow limitation when a 5 hPa (~5.1 cmH₂O) negative pressure was used but not when the negative pressure was increased to 9 hPa (~9.2 cmH₂O). We used a negative pressure of approximately -10 cmH₂O which should be sufficient to avoid any false detection of expiratory flow limitation (Mota *et al.* 1999). Figure 2 illustrates that a subject can be flow limited or not flow limited irrespective of the negative pressure used.

The measurement of end-expiratory lung volume was determined using inspiratory capacity manoeuvres. End-expiratory lung volume may be altered by performing inspiratory capacity manoeuvres which could happen as subjects prepare to perform the manoeuvre or transiently after the manoeuvre is performed (Johnson *et al.* 1999). To account for any alterations in end-expiratory lung volume, several breaths were monitored prior to the inspiratory capacity manoeuvre so that the necessary corrections could be made. Subjects were also given extensive practice during the familiarization day and also during the experimental testing day. Since inspiratory capacity manoeuvres are dependent on subject motivation, it is possible that subjects will not fully inspire to total lung capacity when

performing the manoeuvre. To account for this potential limitation, continuous measurements of oesophageal pressure were made so that maximal inspiratory pressure during the inspiratory capacity manoeuvres could be monitored. If the maximal inspiratory pressure obtained during exercise was similar to that obtained repeatedly at total lung capacity at rest, there can be confidence that total lung capacity was reached during the manoeuvres (Younes & Kivinen, 1984; Babb *et al.* 1991; Johnson *et al.* 1995). If subjects failed to achieve the pre-exercise target pressures, they were required to repeat the inspiratory capacity manoeuvre during exercise. Therefore, it is unlikely that the inspiratory capacity was underestimated at any point during exercise.

In estimating the forces involved in breathing there are inherent assumptions that merit discussion. Our estimation of the work of breathing does not take into account the flow-resistive work done on tissues of the thorax and abdomen. Although this is considered to make up a relatively small portion of the total work of breathing, particularly during increasing levels of \dot{V}_E (Agostoni, 1961), we acknowledge that our work of breathing values may in fact underestimate the total mechanical work of breathing. Within the calculation of the work of breathing, several factors have previously been considered negligible. As Otis *et al.* (1950) described, the respiratory system is almost continuously accelerating and decelerating and the work to overcome inertia probably contributes to the overall work of breathing. The kinetic energy imparted to the air may also be a relevant factor. However, the often used equation to determine the work of breathing (see eqn (1)) does not include these potential influences as they have been typically considered minor. It is possible that with high levels of ventilation during exercise these typically neglected influences may be of greater importance. To our knowledge quantifiable estimates of inertia and kinetic energy are not available. However, given the magnitude of difference we observed between men and women for the work of breathing it is unlikely that our overall conclusion and interpretation would be different by including these additional influences.

Conclusions

The results from this study indicate that the pulmonary system of endurance-trained females may be at a disadvantage compared to their male counterparts during intense exercise. We demonstrated that female athletes tend to develop expiratory flow limitation more frequently than male athletes. It was also observed that women have higher relative increases in end-expiratory lung volume and end-inspiratory lung volume at maximal exercise. Finally, women tend to have a higher work of breathing across a wide range of ventilations during exercise compared to men. Many of the differences

observed in this study are due to the smaller lungs and presumably the smaller diameter airways in women. Several studies have reported that women may be susceptible to pulmonary system limitations during exercise including exercise-induced arterial hypoxaemia (Harms *et al.* 1998; Richards *et al.* 2004) and expiratory flow limitation (McClaran *et al.* 1998). These studies, in combination with the present findings, suggest that the female pulmonary system may be at a disadvantage compared to their male counterparts during intense exercise. However, our understanding of female pulmonary responses to exercise remains incomplete. In order to fully address questions of sex-based differences future studies must consider the importance of matching subjects for age, body and lung size, and aerobic capacity.

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