Sex differences in the resistive and elastic work of breathing during exercise in endurance-trained athletes

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Submitted 5 February 2009; accepted in final form 5 May 2009

Guenette JA, Querido JS, Eves ND, Chua R, Sheel AW. Sex differences in the resistive and elastic work of breathing during exercise in endurance-trained athletes. Am J Physiol Regul Integr Comp Physiol 297: R166–R175, 2009. First published May 6, 2009; doi:10.1152/ajpregu.00078.2009.—It is not known whether the higher total work of breathing (WOB) in exercising women is higher due to differences in the resistive or elastic WOB. Accordingly, the purpose of this study was to determine which factors contribute to the higher total WOB during exercise in women. We performed a comprehensive analysis of previous data from 16 endurance-trained subjects (8 men and 8 women) that underwent a progressive cycle exercise test to exhaustion. Esophageal pressure, lung volumes, and ventilatory parameters were continuously monitored throughout exercise. Modified Campbell diagrams were used to partition the esophageal-pressure volume data into inspiratory and expiratory resistive and elastic components at 50, 75, 100 l/min and maximal ventilations and also at three standardized submaximal work rates (3.0, 3.5, and 4.0 W/kg). The total WOB was also compared between sexes at relative submaximal ventilations (25, 50, and 75% of maximal ventilation). The inspiratory resistive WOB at 50, 75, and 100 l/min was 67, 89, and 109% higher in women, respectively (P < 0.05). The expiratory resistive WOB was 131% higher in women at 75 l/min (P < 0.05) with no differences at 50 or 100 l/min. There were no significant sex differences in the inspiratory or expiratory elastic WOB across any absolute minute ventilation. However, the total WOB was 120, 60, 50, and 45% higher in men at 25, 50, 75, and 100% of maximal exercise ventilation, respectively (P < 0.05). This was due in large part to their much higher tidal volumes and thus higher inspiratory elastic WOB. When standardized for a given work rate to body mass ratio, the total WOB was significantly higher in women at 3.5 W/kg (239 ± 31 vs. 173 ± 12 l/min, P < 0.05) and 4 W/kg (387 ± 53 vs. 243 ± 36 l/min, P < 0.05), and this was due exclusively to a significantly higher inspiratory and expiratory resistive WOB rather than differences in the elastic WOB. The higher total WOB in women at absolute ventilations and for a given work rate to body mass ratio is due to a substantially higher resistive WOB, and this is likely due to smaller female airways relative to males and a breathing pattern that favors a higher breathing frequency.

There have been few attempts to systematically compare the work of breathing (WOB) between sexes (7, 9). We recently demonstrated that the WOB was higher in endurance-trained women at moderate to high levels of minute ventilation compared with trained males with no differences in the total WOB when comparisons were made at different percentages of maximal aerobic capacity (VO2max) (7). On average, women had a WOB that was approximately twice as high as men at ventilatory rates above 50 l/min. However, the analysis used in this previous study was limited in that it did not provide specific information regarding the individual components that make up the total WOB. The WOB can be subdivided into the work of the respiratory muscles to overcome the elasticity of the lung during inspiration, the work required to overcome airflow resistance during inspiration, the work of the expiratory muscles to overcome the elastic outward recoil of the chest wall, and the work required to overcome airflow resistance during expiration. It is currently unknown which of these factors contribute to the higher total WOB in women compared with men.

On the basis of mechanical grounds, we hypothesized that the resistive WOB would be higher in women because of their inherently smaller diameter airways (11, 13). However, this hypothesis may be an oversimplification because it is unknown whether women adopt a unique breathing pattern to minimize one WOB component at the expense of another. To this end, we reanalyzed data from our previous investigation (7) by partitioning the respiratory pressure-volume data into four distinct WOB components across a range of ventilations and also at 3 different body mass-corrected work rates achieved by all subjects. The WOB was compared at different mass-corrected work rates to determine whether the WOB is higher for a given level of external muscular work. Furthermore, we examined sex differences in breathing pattern to determine the effect of tidal volume and breathing frequency on the WOB.

METHODS

Subjects. Sixteen endurance trained athletes (8 men and 8 women) volunteered to participate in this study. Endurance-trained athletes were used instead of untrained individuals because they are capable of generating higher levels of minute ventilation compared with their untrained counterparts. This permits physiological comparisons across a wider range of values. Moreover, the mechanical work of breathing appears to be independent of fitness level (14). The subjects gave informed written consent and all experimental procedures received institutional ethical approval and conformed to the Declaration of Helsinki. All subjects were healthy nonsmokers and did not have any previous history of cardiopulmonary disease. Subjects with a forced expired volume in 1 s (FEV1.0) to forced vital capacity (FVC) ratio of <80% of predicted were excluded from the investigation.

A GROWING NUMBER OF INVESTIGATIONS aimed at characterizing the healthy female respiratory response to exercise have reported sex-based differences in pulmonary gas exchange (8, 18) and respiratory mechanics (7, 12). These studies show that young adult women free from respiratory disease may be more susceptible to pulmonary limitations during exercise, which is likely associated with women having smaller lungs and airways relative to size-matched males (13, 23).
Experimental overview. Subjects participated in two testing sessions separated by a minimum of 48 h. All women were tested during the early follicular phase (days 3 to 8) of the menstrual cycle as determined via a self-reported menstrual history questionnaire. On the first day, subjects performed general spirometry to assess lung function and an incremental cycle test to exhaustion to determine $V_{O2\max}$. They also received extensive practice on how to perform inspiratory capacity maneuvers at rest and during exercise. The second day served as the primary testing day, which included 10 min of seated quiet breathing followed by an incremental cycle test to exhaustion using the identical exercise protocol as used on day 1.

**Pulmonary function.** FVC, FEV$_{1.0}$, FEV$_{1.0}$/FVC, and peak expiratory flow were obtained using routine spirometry according to standardized procedures and expressed using prediction equations (1).

**Maximal cycle exercise.** Subjects performed an incremental test to exhaustion on a cycle ergometer using a step protocol. Men and women began cycling at 200 W and 100 W, respectively, with the work rate increasing by 30 W every 3 min. Ventilatory and mixed expired metabolic parameters were assessed using a customized metabolic cart consisting of a calibrated pneumotachograph (model 3813; Hans Rudolph, Kansas City, MO) and calibrated CO$_2$ and O$_2$ analyzers (Models CD-3A and Model S-3-A/I, respectively; Applied Electrochemistry, Pittsburgh, PA).

Flow, volume, and pressure. Inpiratory and expiratory flow was measured using a heated and calibrated pneumotachograph (model 3813, Hans Rudolph, Kansas City, MO) attached to a mouthpiece. Inspiratory and expiratory volume was obtained through numerical integration of the flow signal. Esophageal pressure ($P_{eso}$) was obtained by placing a 10-cm-long latex balloon (no. 47–9005; Ackrad Laboratories, Cranford, NJ) ~45 cm down from the nostril (15) after application of a local anesthetic. All air was removed from the balloon by having subjects perform a Valsalva maneuver. The balloon was then inflated with 1 ml of air as per manufacturer specifications. $P_{eso}$ was measured using a calibrated piezoelectric pressure transducer ($\pm 100$ cmH$_2$O; Raytech Instruments, Vancouver, BC, Canada).

End expiratory lung volume. End-expiratory lung volume (EELV) was determined by having subjects perform inspiratory capacity (IC) maneuvers at rest and during exercise as previously described (7). Two to three IC maneuvers were obtained near the middle and end of each 3-min exercise bout and additional IC maneuvers were performed immediately prior to exhaustion. EELV was calculated as the difference between FVC and the IC volume. FVC was used to calculate EELV rather than total lung capacity because it was not possible to measure residual lung volume in our subjects. FVC maneuvers were performed before and immediately after exercise with the largest FVC value being used for the analysis.

Work of breathing. The muscular WOB was determined using modified Campbell diagrams as described by Roussos and Campbell (19) and using the technique of Yan et al. (25). Flow, volume, and pressures from several breaths (~5–20) corresponding to ~50, 75, and 100 l/min and 25, 50, 75, and 100% of maximal ventilation were selected for each subject and ensemble averaged using a customized software program (Bibo, LabVIEW software V6.1; National Instruments, Austin, TX). The same procedure was performed to compare the WOB at 3.0, 3.5, and 4.0 W/kg. These ventilatory rates and workloads were selected because nearly all male and female subjects were successfully able to reach these values. Additional Campbell diagrams were also generated for each stage of exercise to determine the relationship between average inspiratory flow and the inspiratory resistive WOB. An example of the modified Campbell diagram in a representative male subject at ~75% of maximal minute ventilation (i.e., 115 l/min) is shown in Fig. 1. A line was drawn connecting the points of zero flow (i.e., EELV and EILV) representing the dynamic compliance of the lung. The compliance of the chest wall was derived using previously published data (3) based on both age and sex as done by others (2, 4, 21, 25). The chest wall compliance line was positioned through functional residual capacity (EELV at rest) and extended to EELV and EILV. The muscular WOB was then partitioned into four separate components. The area inside of the $P_{eso}$-loop to the left of the lung compliance line (oblique hatching) represents the work needed to overcome airflow resistance during inspiration (i.e., inspiratory resistive work). The area enclosed by the lung compliance and chest wall compliance lines (horizontal hatching) represents the work needed to overcome lung elasticity (i.e., inspiratory elastic work). The area to the right of the chest wall compliance line (stippling) represents the active muscular work needed to overcome airflow resistance during expiration (i.e., expiratory resistive work). Lastly, the area between the lung and chest wall compliance lines below functional residual capacity (vertical hatching) represents the work needed to overcome the outward elastic recoil of the chest wall to maintain EELV below functional residual capacity (i.e., expiratory elastic work). The sum of all four areas shown in Fig. 1 represents the total WOB. All WOB values were multiplied by breathing frequency, representing a unit of power (i.e., J/min). However, as conventionally used, we will refer to this throughout the manuscript as the WOB rather than the power of breathing.

Data processing. All raw data were recorded continuously at 200 Hz using a 16-channel data acquisition system (PowerLab/16SP model ML 795, AD Instruments, Colorado Springs, CO) and stored on a computer for subsequent analysis (Chart v5.3, AD Instruments).

Statistical analysis. Descriptive characteristics were compared between sexes using unpaired t-tests. Preplanned comparisons were used to compare men and women for the various WOB components and the ventilatory parameters at the target ventilations and work rates using unpaired t-tests. Linear regression analysis using Pearson correlations was performed to test for associations between specific WOB components and pulmonary function parameters. The α level was set at 0.05 for all statistical comparisons. Values are presented throughout the manuscript as means ± SD with the exception of Figs. 2, 4, 5, 6, and 7, where values are reported as means ± SE.
RESULTS

Subject characteristics. The subjects used in the present investigation completed a study that has been previously published (7). The present study has 8 males and 8 females, while our previous manuscript reported data on 8 males and 10 females. Two females were excluded from the present analysis because they did not have Peso data \((n = 1)\) or were unable to correctly perform IC maneuvers \((n = 1)\). Males and females were not different for age \((25.9 \pm 4.9 \text{ vs. } 24.9 \pm 3.1 \text{ yr, respectively})\), but men were taller \((183.9 \pm 6.6 \text{ vs. } 168.8 \pm 4.0 \text{ cm, } P < 0.0001)\), heavier \((76.6 \pm 9.8 \text{ vs. } 64.3 \pm 3.6 \text{ kg, } P < 0.01)\) and had a higher VO_{\text{max}} \((69.5 \pm 7.8 \text{ vs. } 59.2 \pm 4.7 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}, P < 0.01)\). Table 1 summarizes the pulmonary function data for the present study. As expected, women had smaller FVC, FEV\(_{1.0}\), and peak expiratory flows compared with men. All subjects were within normal values for all pulmonary function measures except peak expiratory flows, which were typically >120% of predicted. There were no significant sex differences in percent predicted values for any pulmonary function parameters.

Work of breathing vs. absolute minute ventilation. Figure 2 shows the total WOB \((A)\) and the constituent components of the WOB \((B–E)\) at comparable absolute ventilations and at maximal ventilation in men and women. The total WOB was significantly higher in women at 75 and 100 l/min but not at 50 l/min. The total WOB at 50, 75, and 100 l/min was 23, 33, and 48% higher in women, respectively, but was 45% higher in men at maximal ventilations. The inspiratory resistive WOB was 67, 89, and 109% higher in women at 50, 75, and 100 l/min, respectively \((P < 0.05)\), while the expiratory resistive WOB was only significantly higher in women at 75 l/min. The expiratory resistive WOB was 131% higher in women. There was no significant difference in the elastic WOB during inspiration or expiration at any absolute ventilation. However, the inspiratory elastic WOB was 42% higher in men at maximal ventilations \((P = 0.05)\). Figure 3 shows Campbell diagrams for an individual male and female subject matched for minute ventilation, tidal volume, and breathing frequency. This figure demonstrates the significantly higher pressures needed to maintain the same ventilatory loads resulting in a much higher inspiratory and expiratory resistive work, with little difference in elastic work.

Work of breathing vs. relative submaximal minute ventilation. The total WOB plotted against percentages of maximal minute ventilation is shown in Fig. 4. Men had a significantly higher total WOB for any given percentage of maximal ventilation compared with women. The total WOB was 120, 60, and 50% higher in men at 25, 50, and 75% of maximal minute ventilations, respectively. While each component of the WOB was higher in men for a given percentage of minute ventilation, the largest (and statistically significant) differences were seen with the inspiratory elastic WOB (data not shown). The absolute ventilations in men vs. women corresponding to 25, 50, and 75% of maximal ventilations were 48.4 ± 6.5 vs. 32.8 ± 7.0 l/min, 90.3 ± 14.7 vs. 62.9 ± 12.2 l/min, and 134.9 ± 22.1 vs. 94.9 ± 18.4 l/min, respectively. Thus, the absolute ventilations were, on average, 31% higher in men when comparing sexes at the aforementioned relative minute ventilations. The tidal volumes were 75, 37, and 36% higher in men at 25, 50, and 75% of maximal minute ventilations \((P < 0.05)\), respectively with little to no difference in breathing frequency.

Work of breathing vs. external muscular work. Figure 5 shows the total WOB \((A)\), inspiratory resistive WOB \((B)\), and expiratory resistive WOB \((C)\) vs. work rate (corrected for body mass) in men and women. Figure 5A demonstrates that the total WOB was significantly higher in women at ~3.5 W/kg \((239 ± 31 \text{ vs. } 173 ± 12 \text{ J/min, } P < 0.05)\) and 4.0 W/kg \((387 ± 53 \text{ vs. } 243 ± 36 \text{ J/min, } P < 0.05)\). The inspiratory resistive WOB was higher in women at ~3.0 W/kg \((56 ± 8 \text{ vs. } 41 ± 4 \text{ J/min, } P = 0.05)\), 3.5 W/kg \((93 ± 15 \text{ vs. } 56 ± 5 \text{ J/min, } P < 0.05)\) and 4.0 W/kg \((162 ± 24 \text{ vs. } 81 ± 2 \text{ J/min, } P < 0.05)\). The expiratory resistive WOB was higher in women at ~3.5 W/kg \((44 ± 11 \text{ vs. } 20 ± 3 \text{ J/min, } P < 0.05)\) and 4.0 W/kg \((67 ± 16 \text{ vs. } 35 ± 8 \text{ J/min, } P = 0.05)\). There were no significant differences in the inspiratory or expiratory elastic components at any work rate.

Breathing pattern. Figure 6 shows the breathing frequency \((A)\) and tidal volume \((B)\) response to exercise. It can be seen that men achieved a maximal minute ventilation that was considerably higher than women \((180.2 ± 28.7 \text{ vs. } 126.2 ± 24.2 \text{ l/min, respectively})\). Generally, women breathed with a significantly higher breathing frequency and lower tidal volume to achieve the same absolute minute ventilation as men. Breathing frequency was significantly different between sexes at 75 and 100 l/min while tidal volume was attenuated in women at all ventilations above 50 l/min. Figure 7 shows the effect of tidal volume \((A)\) and breathing frequency \((B)\) on the inspiratory elastic WOB at the four ventilatory points (i.e., 50, 75, 100 l/min and maximal ventilation). For any given tidal volume, the inspiratory elastic WOB is considerably higher in women. However, the inspiratory elastic WOB is lower in women for any given breathing frequency. Although these are physiologically significant observations, specific statistical procedures could not be performed on the data presented in Fig. 7.

Lung size vs. work of breathing. Figure 8 summarizes the relationships between different components of the WOB and FVC with all subjects pooled together. The WOB values shown in this figure are from a minute ventilation corresponding to 100 l/min. We chose to report data at 100 l/min for the regression analysis for three reasons. First, we wanted to report data at the highest range of absolute ventilations when the work and metabolic cost of breathing are highest. Second, this ventilation tended to show the largest sex-based difference in the total WOB and inspiratory resistive WOB. Finally, all subjects achieved 100 l/min of ventilation during exercise. FVC was used as a surrogate of total lung capacity (less

Table 1. Pulmonary function data

<table>
<thead>
<tr>
<th></th>
<th>Men ((n = 8))</th>
<th>Women ((n = 8))</th>
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<tbody>
<tr>
<td>FVC, liters</td>
<td>6.0 ± 0.3 (4.5–7.2)</td>
<td>4.5 ± 0.2 (3.8–5.4)*</td>
</tr>
<tr>
<td>FVC, %predicted</td>
<td>105 ± 5 (84–125)</td>
<td>108 ± 5 (92–134)</td>
</tr>
<tr>
<td>FEV(_{1.0}), liters</td>
<td>5.1 ± 0.4 (3.5–6.4)</td>
<td>3.8 ± 0.2 (3.0–4.5)*</td>
</tr>
<tr>
<td>FEV(_{1.0}), %predicted</td>
<td>106 ± 5 (80–133)</td>
<td>106 ± 5 (80–131)</td>
</tr>
<tr>
<td>PEF, l/s</td>
<td>12.6 ± 0.5 (10.4–14.8)</td>
<td>8.1 ± 0.4 (6.5–10.0)*</td>
</tr>
<tr>
<td>PEF, %predicted</td>
<td>124 ± 4 (109–138)</td>
<td>118 ± 7 (91–148)</td>
</tr>
<tr>
<td>FEV(_{1.0})/FVC, %</td>
<td>85.3 ± 1.5 (78.3–88.6)</td>
<td>84.6 ± 2.1 (74.3–92.4)</td>
</tr>
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FVC, forced vital capacity; FEV\(_{1.0}\), forced expired volume in 1 s; PEF, peak expiratory flow. *Significantly different from men \((P < 0.01)\). Ranges are presented in parentheses.
residual volume) to determine the relationship between lung size and the WOB. FVC was significantly and linearly related to the total WOB, the inspiratory resistive WOB, and the expiratory resistive WOB. When partitioned into individual groups, the correlation coefficients relating FVC to the total WOB, the inspiratory resistive WOB, and expiratory resistive WOB in women was 0.92 (P < 0.001), 0.78 (P = 0.02), and 0.73 (P = 0.04), whereas the men were 0.46 (P = 0.25), 0.27 (P = 0.52), and 0.75 (P = 0.03), respectively.

Flow vs. work of breathing. The inspiratory resistive WOB was plotted against the corresponding average inspiratory flow throughout all exercise intensities in each individual subject as shown in Fig. 9A. All of the raw data points from Fig. 9A were fitted with a second-order polynomial (mean r² for all subjects = 0.99 ± 0.01) to produce a mean curve for all men and women as shown in Fig. 9B. Fig. 9, A and B show that the inspiratory resistive WOB was higher in women for any given flow rate above ~2 l/s, and the magnitude of this difference increased disproportionally in women with increasing flow. Figure 9B also shows the response of an individual female subject with FVC and peak expiratory flows that were 134 and 148% above predicted values, respectively.

**DISCUSSION**

Our present understanding of the WOB during exercise is primarily based on studies conducted in males but a recent study by our group demonstrated significant differences in the total WOB between men and women for a given absolute minute ventilation (7). The present study adds to the previous literature by systematically measuring the elastic and resistive WOB in exercising women. The novel findings from this study are four-fold. First, the inspiratory resistive WOB was higher in women for any given absolute minute ventilation while the expiratory resistive WOB was higher in women at only 75 l/min. There were no sex differences in the inspiratory or expiratory elastic WOB across any absolute minute ventilation. However, the total WOB was actually higher in men when compared across relative percentages of maximal ventilations, due to their higher absolute tidal volumes and thus higher minute ventilations. Second, the total WOB and the inspiratory and expiratory resistive WOB were higher in women when performing the same relative external muscular work. Third, the WOB was inversely related to lung size and presumably airway size. Lastly, the inspiratory resistive WOB was consid-
Fig. 3. Modified Campbell diagrams from an individual male and female subject matched approximately for absolute minute ventilation [100 vs. 101 l/min (STPD)] tidal volume (2.1 vs. 2.2 liters), breathing frequency (52 vs. 49 breaths/min), age (24 vs. 25 years), and mass (64.6 vs. 64.2 kg), respectively. The male was slightly taller than the female subject (181 vs. 167 cm, respectively). Oblique hatching represents the inspiratory resistive work of breathing (Ir). Horizontal hatching represents the inspiratory elastic work of breathing (Ie). Stippling represents the expiratory resistive work of breathing (Er). Vertical hatching represents the expiratory elastic work of breathing (Ee). Cf, dynamic lung compliance; Ccw, chest wall compliance. Upward arrow represents inspiration and downward arrow represents expiration. Small open circles represent zero flow points.

Fig. 4. Total work of breathing vs. relative percentages of maximal minute ventilation in men (○) and women (●). Values are expressed as means ± SE. *Significantly different between groups (P < 0.05).

erably higher for a given level of inspiratory flow compared
with men, demonstrating the importance of airway size in
determining the mechanical cost of breathing. We interpret our
findings to mean that the higher total WOB observed in
exercising women at absolute ventilations is due to a higher
resistive WOB, which can be attributed to relatively smaller
lungs and airways.

Resistive work of breathing vs. minute ventilation. In our
previous work (7), we plotted the total WOB against a range of
ventilatory rates and fit the data points to the following equa-
tion as originally described by others (10, 17): WOB = aV̇E³ +
bV̇E². The term bV̇E² describes 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 aV̇E³ represents the work done in overcoming
the resistance to turbulent flow. We found that the constant a
was significantly higher in women meaning that the higher
total WOB in women is associated with the additional resistive
work due to turbulent airflow. Although this is an instructive
analysis, it does not permit a quantitative measure of the
individual factors that make up the total WOB at specific time
or physiological points. By using a more extensive approach,
we have now partitioned the total WOB into its individual
components at specific values of minute ventilation and at
standardized work rates. During progressive exercise, we
found that both inspiratory and expiratory resistive work were
significantly higher in women over a range of ventilatory rates
(Fig. 2, B and C). Interestingly, we observed significant dif-
fferences in inspiratory resistive work at low levels of minute
ventilation (50 l/min), and the magnitude of difference in-
creased as ventilation increased up to 100 l/min. Figure 3
provides a compelling example of the high pressures that are
needed in a female subject to achieve the same minute venti-
lation as a male subject. It is important to note that the male
and female subject shown in Fig. 3 have been matched for both
breathing frequency, tidal volume, age, and body mass. Despite
the fact that both subjects are breathing at the same volume and
rate, the inspiratory and expiratory resistive work components
are considerably higher in the female subject.

Elastic work of breathing vs. minute ventilation. The elastic
work required to increase and decrease the volume of the lung
is related to the elastic forces that develop in the tissues of
the lung and chest wall. Unique to this study, we found that there
were no sex differences in the elastic WOB at any absolute
ventilation. However, with further examination, it can be seen
in Fig. 7A that the inspiratory elastic WOB is substantially
higher in women for a given tidal volume. This can be
attributed to the fact that women are breathing at a higher
percentage of their total lung capacity for a given level of
ventilation, which reduces the compliance of the lungs. Per-
haps more important is the observation that women adopt a
higher breathing frequency for a given minute ventilation,
which acts to reduce the inspiratory elastic WOB (Fig. 7B).
This type of breathing pattern comes at the expense of an
increased resistive WOB. This is an important observation if
one is to consider how breathing patterns are regulated in
humans in an effort to minimize the total WOB. The “principle
of minimum effort” was first used to describe that for a given
alveolar ventilation, there is a breathing frequency that is
optimal (17). This pattern is adopted because if the breathing
frequency is too low, then large amounts of elastic work are
required, whereas if the breathing frequency is too high, then
respiratory muscle work is expended to ventilate dead space
(i.e., wasted ventilation). During exercise the diaphragm gen-

Fig. 2. Total work of breathing vs. relative percentages of maximal minute ventilation in men (○) and women (●). Values are expressed as means ± SE. *Significantly different between groups (P < 0.05).
This suggests that under spontaneously breathing conditions, the diaphragm tension or O₂ cost is what is being minimized during exercise. On the basis of the present study, it appears that women use a higher breathing frequency to minimize the elastic WOB, which comes at the expense of a higher resistive WOB.

Total work of breathing vs. minute ventilation. The total WOB was higher in women at any absolute ventilation comparison above 50 l/min, which is consistent with our previous findings using a different analysis technique (7). In our previous work, we also compared the total WOB between men and women at different percentages of VO₂max and found that the total WOB was modestly higher in men at VO₂max, but there was no statistically significant difference (7). However, in the present study, we have shown that the total WOB is significantly higher in men when compared at maximal ventilations (Fig. 2) and also at submaximal relative percentages of maximal ventilation (Fig. 4). We attribute this discrepant finding to the fact that the modified Campbell diagram technique takes into account the compliance of the chest wall, which allows us to calculate the additional part of the inspiratory elastic WOB, which extends beyond the area directly within the pressure-volume loop (see Fig. 1). Indeed, it can be seen in Fig. 2 that the only component to approach statistical significance at maximal ventilations was the inspiratory elastic WOB (P = 0.05). The primary driving force for the higher total WOB at submaximal relative ventilations was also the inspiratory elastic WOB (data not shown). This is due to the fact that for a given relative percentage of maximal ventilation, the tidal volume is considerably higher in men with little to no differ-

Fig. 5. Total work (A), inspiratory resistive work (B), and expiratory resistive work of breathing (C) vs. work rate in men (○) and women (●). Values are expressed as means ± SE. *Significantly different between groups (P < 0.05); †P = 0.05.

This suggests that under spontaneously breathing conditions, the diaphragm tension or O₂ cost is what is being minimized during exercise. On the basis of the present study, it appears that women use a higher breathing frequency to minimize the elastic WOB, which comes at the expense of a higher resistive WOB.

Total work of breathing vs. minute ventilation. The total WOB was higher in women at any absolute ventilation com-

Fig. 6. Breathing frequency (A) and tidal volume (B) vs. minute ventilation in men (○) and women (●). The last data point represents maximal minute ventilation. Values are expressed as means ± SE. *Significantly different between groups (P < 0.05).
ence in breathing frequency. This will substantially increase the inspiratory elastic WOB and thus the total WOB when comparisons are made at relative intensities. We have purposely limited the majority of our analysis and interpretation in this study and in our previous work (7) to absolute ventilations to determine whether the mechanical cost of moving a given amount of air in and out of the lungs is different between sexes. Examining the mechanics of breathing between sexes at relative ventilations is a difficult comparison because men are utilizing a much higher tidal volume and thus have higher minute ventilations than women. For example, the men in this study were breathing 54 l/min higher than women at maximal exercise. Despite the fact that maximal ventilations were 43% larger in our male subjects, it is interesting to note that there were no significant differences in the resistive WOB components. This lends further support to the finding that women have a substantially higher resistive WOB than men.

Work of breathing vs. external muscular work. Fig. 5 shows the WOB required to perform the same relative external work on the cycle ergometer. Rather than using absolute work rate (i.e., power) in Watts, we have normalized the work rate by expressing it in Watts per kilogram body mass, which provides a physiologically relevant comparison because it minimizes the potential confounding effect of body size differences. Moreover, it allows us to compare the physiological cost of breathing between sexes for a given standardized external work load. Even when normalized for body mass, the total WOB is higher at 3.5 and 4.0 W/kg with the inspiratory and expiratory resistive WOB components accounting for the vast majority of this difference (Fig. 5). At 3.5 and 4.0 W/kg, the inspiratory resistive WOB was 67 and 100% higher, respectively in women, while the expiratory resistive WOB was 123 and 89% higher in women, respectively. It is important to note that these comparisons do not take into account lean body mass since
presumably the smallest airways had the highest resistive WOB. Therefore, those with the smallest lungs and values than men, which were inversely related to a higher (see Fig. 8). As would be expected, women had lower FVC associations between the resistive WOB at 100 l/min and FVC mass and therefore do not attempt to overstate these findings. This limitation in our study without a measurement of lean body WOB values. However, we cannot directly assess the impact of certain account for some of the differences observed in our maximum output relative to their male counterparts. This will certainly account for some of the differences observed in our WOB values. However, we cannot directly assess the impact of this limitation in our study without a measurement of lean body mass and therefore do not attempt to overstate these findings.

Sex vs. size differences. We observed statistically significant associations between the resistive WOB at 100 l/min and FVC (see Fig. 8). As would be expected, women had lower FVC values than men, which were inversely related to a higher resistive WOB. Therefore, those with the smallest lungs and presumably the smallest airways had the highest resistive WOB. We do not have a direct measurement of airway size in our subjects but similar correlation coefficients were also observed when relating the resistive WOB components against peak expiratory flows, which may serve as a crude surrogate for airway size. We are cognizant of the limits of correlative evidence and therefore do not attempt to overstate these findings. However, in an effort to provide a more mechanistic understanding of the higher resistive WOB in women, particularly on inspiration, we performed additional analyses as shown in Fig. 9. In this analysis, Fig. 9A shows the inspiratory resistive WOB for a given level of inspiratory flow in individual subjects while Fig. 9B represents the group average. These data show that for a given level of flow, the resistive WOB is higher in women, and the magnitude of this difference increases disproportionally with increasing flow. Fig. 9B includes one female subject superimposed with the mean curves. This subject had unusually large lungs and peak expiratory flows (>130% predicted). In fact, her FVC and peak expiratory flows were relatively close to the group mean values for men. Interestingly, her inspiratory resistive WOB response for a given level of flow was nearly identical to the average curve for the male subjects. These observations in conjunction with correlative evidence points to an anatomical basis (i.e., smaller lungs and airways) for the WOB differences that we observed during exercise. Additional physiological and performance-based consequences of these anatomical differences in lung and airway size have been reviewed elsewhere (20).

Our sex-based comparisons were made between men and women of significantly different statures. It could be argued that our findings simply reflect size differences rather than a true male-female difference in lung and airway size. However, there is reason to suggest that our findings would be similar between men and women of comparable sizes (i.e., men and women matched for total lung capacity). We make this claim based on two lines of anatomical evidence. First, in healthy young men and women matched for total lung capacity, women have significantly smaller tracheal areas (2.79 vs. 1.99 cm²) as assessed by acoustic reflectance (11). As such, the reduced female tracheal area would result in a higher WOB for a given level of minute ventilation. Air flow is determined, in part, by Poiseuille’s law, and the factors governing it are internal diameter, length, gas viscosity, and airflow pressure, where the radius is raised to the fourth power. As such, even a small difference in airway radius is magnified and would have an effect on airflow resistance and the accompanying WOB. Second, the relationship between airway size (estimated from maximal expiratory flow/static recoil pressure at 50% vital capacity), and lung size (vital capacity) shows that adult men have airways that are 17% larger than those of women (13). This has been termed “dysanapsis” to reflect the dissociation between airway size and lung parenchymal size (5). Given the brief summary presented above, coupled with the findings of the present study, it appears that the higher resistive WOB seen in women is due to inherently smaller airways.

Methodological considerations. Our measures of the work done by the respiratory muscles do not take into account the distorting forces of the chest wall observed at high levels of minute ventilation. Volume displacement of the rib cage and abdomen can be independent of one another (19). Phrased differently, this means that all of the respiratory muscles do not necessarily shorten during inspiration nor do all of the muscles
of expiration shorten during expiration. We recognize this as a critique of the modified Campbell approach and that our measure of the WOB may be underestimates. However, it is unlikely that this systematic underestimation applied to all subjects equally would have had any substantive effect on our overall conclusion that women have a higher WOB during exercise owing to a greater resistive WOB. This is supported by optoelectronic plethysmography measures, which suggest that men and women utilize muscles of the rib cage compartment and those of the abdomen to the same extent (24).

The compliance of the chest wall is required to determine the various WOB components using the modified Campbell diagram method. It is typically very difficult to reliably measure the compliance of the chest wall because naive subjects have a difficult time completely relaxing their respiratory muscles. Therefore, we based our chest wall compliance values on previously published data taking into account both age and sex (3), as done by others (2, 4, 21, 25). There are limitations with this approach that warrant discussion. For example, the chest wall compliance values we used were obtained in healthy volunteers with normal static lung volumes and FEV$_{1.0}$ values, and it is assumed that the values were measured in untrained individuals. Therefore, we are making the assumption that the compliance of the chest wall is similar between trained and untrained subjects. To our knowledge, there are no studies that have studied the effect of fitness on the compliance of the chest wall. Although there are inherent limitations in using “normative” data and applying it to elite athletes, we do not think that this has had an effect on our main conclusions regarding sex differences in the WOB. We base this assumption on several factors. First, according to Estenne et al. (3), there are no sex differences in the compliance of the chest wall (at least in untrained individuals). Our men and women were of similar relative fitness levels, so it is reasonable to assume that this lack of a sex difference should persist along the fitness continuum, and any potential errors in our chest wall compliance values would likely be a systematic error across all subjects. Secondly, the vital capacity values in our men (6.0 ± 1.0 l) and women (4.5 ± 0.5 l) were nearly identical to the age-matched men (6.0 ± 0.9 l) and women (4.3 ± 0.4 l) from whom we derived are chest wall compliance values. Finally, we have calculated that even a ±10% change in the compliance of the chest wall would only affect the elastic components by approximately ±3–5%, the inspiratory resistive WOB by less than ±0.5%, and the expiratory resistive WOB by ±1.5–3%.

The elastic WOB measurements that we and others (21, 25) have made may be underestimations because the calculations are based on tidal volume measured at the mouth, which ignores gas compression (16). Gas compression is typically negligible in healthy individuals at rest or during exercise. However, under conditions where expiratory flow limitation is present, this could increase the magnitude of underestimation. We did observe expiratory flow limitation in many of our female and male subjects (7) during high levels of exercise, but we do not believe that this had a major influence on our findings or overall interpretation of the present study, particularly at submaximal workloads. Specifically, we observed no demonstrable difference between men and women in the elastic WOB at low levels of ventilation (50 l/min) when expiratory flow limitation is not present. This absence held true at higher levels of ventilation, suggesting that any underestimation was most likely consistent across all ventilatory rates. Thus, any underestimation due to gas compression likely had a negligible influence on our findings and conclusion that the elastic WOB is similar between men and women for a given level of ventilation. The current study design does not allow us to determine the direct role of expiratory flow limitation and the corresponding changes in operational lung volumes between sexes because flow limitation was typically observed at maximal to near-maximal intensities. As such, it would be difficult to isolate the effects of expiratory flow limitation on our WOB values in men and women because any potential differences would be masked by the fact that men have much higher tidal volumes and thus ventilations at maximal exercise. A novel study design would be required to assess sex-based differences in expiratory flow limitation and the direct corresponding effect on the WOB.

**Perspectives and Significance**

This study is the first to systematically assess the mechanisms of a higher WOB in women during dynamic exercise. Describing sex differences in breathing mechanics poses a significant challenge because of the inherent difficulties in comparing men and women due to known differences in body size and an incomplete understanding of the most appropriate allometric scaling factor to use. In the present study, we have made a number of unique physiological comparisons. First, comparing the WOB for a given level of ventilation allowed us to quantify the additional cost of breathing necessary to move a fixed amount of air through smaller lungs and airways in women. Second, comparing men and women at different percentages of maximal ventilations allowed us to determine the cost of breathing for a given relative intensity. Third, comparing sexes at a standardized size-corrected work rate enabled us to determine whether there are differences in the WOB for a given level of external muscular work. The data from this study suggest that the higher overall WOB in women during dynamic exercise is due to a substantially greater resistive work during inspiration and expiration with no differences in the elastic WOB. However, much of these differences are reversed when comparisons are made at relative intensities. We conclude that sex-based differences in lung and airway size result in the higher work and thus O$_2$ cost of breathing in women during exercise for a given absolute level of ventilation or exercise intensity.

**ACKNOWLEDGMENTS**

We thank our subjects for their enthusiastic participation. This study was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC) and the British Columbia Lung Association.

**GRANTS**

J. A. Guenette was supported by graduate scholarships from NSERC, the Michael Smith Foundation for Health Research (MSFHR), and the Sir James Lougheed Award of Distinction. J. S. Querido was supported by graduate scholarships from NSERC and the MSFHR. A. W. Sheel was supported by a Scholar Award from the MSFHR and a New Investigator award from the Canadian Institutes of Health Research.

**REFERENCES**