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

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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).

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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 $V_{\text{O}2\text{max}}$. 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. Inspiratory 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 ($P_{\text{es}}$) 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. $P_{\text{es}}$ 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 3813, Cranford, NJ) 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 $P_{\text{es}}$-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., W/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 r-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 r-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 a priori 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 $P_{eso}$ data ($n = 1$) or were unable to correctly perform IC maneuvers ($n = 1$). Males and females were not different for age (25.9 ± 4.9 vs. 24.9 ± 3.1 yr, respectively), but men were taller (183.9 ± 6.6 vs. 168.8 ± 4.0 cm, $P < 0.0001$), heavier (76.6 ± 9.8 vs. 64.3 ± 3.6 kg, $P < 0.01$) and had a higher $\dot{V}O_{2\text{max}}$ (69.5 ± 11.0 vs. 59.2 ± 4.7 ml·kg$^{-1}$·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, 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 at 75 l/min 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 to 100% of predicted. There were no significant differences in percent predicted values for any pulmonary function parameters.

WORK OF BREATHING IN MEN AND WOMEN

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 ± 6 (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>
<tr>
<td>FEV1.0/FVC, %predicted</td>
<td>101 ± 2 (92–106)</td>
<td>98 ± 2 (86–109)</td>
</tr>
</tbody>
</table>

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 r^2 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-
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 equation as originally described by others (10, 17): \( \text{WOB} = aV_{\dot{E}}^3 + bV_{\dot{E}}^2 \). The term \( bV_{\dot{E}}^2 \) 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 \( aV_{\dot{E}}^3 \) 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 differences in inspiratory resistive work at low levels of minute ventilation (50 l/min), and the magnitude of difference increased 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 ventilation 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. Perhaps 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 generates most of the inspiratory driving force and appears to remain within the favorable part of its length-tension curve (6).
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 V₀₂max and found that the total WOB was modestly higher in men at V₀₂max, 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. workload in men (○) and women (●). Values are expressed as means ± SE. *Significantly different between groups (P < 0.05); †P = 0.05.](http://ajpregu.physiology.org/)

![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).](http://ajpregu.physiology.org/)
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

![Graph A](image_url)

**Fig. 7.** Inspiratory elastic work of breathing vs. tidal volume (A) and breathing frequency (B) at the four ventilatory points (i.e., 50, 75, 100 l/min and maximal ventilation) in men (○) and women (●). Values are expressed as means ± SE.

![Graph B](image_url)

**Fig. 8.** Regression analysis of the total work (A), inspiratory resistive work (B), and expiratory resistive work (C) vs. forced vital capacity (FVC) in men (○) and women (●). Work of breathing values are obtained at a minute ventilation of 100 l/min.
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 mass. Therefore, it is important to acknowledge that this interpretation has its limitations because the female participants are still working at a slightly higher percentage of their maximum output relative to their male counterparts. Therefore, it is important to acknowledge that this interpretation has its limitations because the female participants are still working at a slightly higher percentage of their 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

Fig. 9. Inspiratory resistive work of breathing vs. average inspiratory flow in individual male (thin lines) and female (thick lines) subjects (A). B: mean inspiratory resistive work of breathing vs. average inspiratory flow in women (thick line) and men (thin line) and an individual female subject (dashed line) with larger than average FVC and peak expiratory flow values.
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 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.

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