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Mechanics of Breathing during Exercise in Men and Women: Sex versus Body Size Differences?

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SHEEL, A.W. and J.A. GUENETTE. Mechanics of breathing during exercise in men and women: sex versus body size differences? *Exerc. Sport Sci. Rev.*, Vol. 36, No. 3, pp. 128–134, 2008. *Women have smaller airways and lung volumes and lower resting maximal expiratory flow rates relative to men. Female athletes develop expiratory flow limitation more frequently than male athletes, and they have greater increases in end-expiratory and end-inspiratory lung volume at maximal exercise. Women use a greater fraction of their ventilatory reserve and have a higher metabolic cost of breathing.* **Key Words:** dysanapsis, expiratory flow limitation, operational lung volumes, respiratory muscle, work of breathing

INTRODUCTION

Homeostasis of respiratory gases in the circulatory medium is reliant upon the coordinated changes that link tissue metabolism, alveolar ventilation, cardiac output, and peripheral blood flow. The pulmonary system in the young and healthy adult responds to dynamic exercise with remarkably precise regulation of alveolar ventilation that is matched to metabolic demand. Even during strenuous sea-level exercise, the arterial partial pressures of oxygen and carbon dioxide and arterial pH remain close to resting values, meaning that the neuromechanical control of alveolar ventilation is highly regulated. Exchange of air between the atmosphere and the alveoli is dependent, in part, upon the mechanical properties and interactions between the lung, the chest wall, including the abdomen, and the respiratory muscles that act upon them. The work of breathing can be divided into two categories: (i) elastic work, related to altering the shape of the anatomical structures involved, and (ii) resistive work, necessary to overcome the resistance to airflow in the airways. In general, the ventilatory response to exercise is thought to be governed by the principle of "minimal effort." This concept is supported in two ways. First, models describing the work of breathing indicate that the ventilatory patterns naturally observed during exercise are the least costly in terms of energy expenditure. Second, ventilation during exercise occurs within a range of lung volumes for which total lung compliance is greatest. This means that the amount of work performed on the lungs and chest wall to achieve a given tidal volume change is minimized compared with higher or lower lung volumes.

Despite the above, there are several lines of evidence, which show that the mechanical properties of the respiratory system, as it relates to exercise, are not without limits. Our research group, and others, has been exploring these limits and the ensuing physiological consequences. Our knowledge of the mechanics of respiration during exercise has been principally shaped by studies that have used male subjects. Only recently have we begun to understand that the respiratory responses to exercise in women may be different from that of men. This is based on anatomical differences in the respiratory system between men and women and documented differences in resting lung function. Our overall working hypothesis, and the focus of this review, is that these anatomically based differences become critically important to the integrated respiratory response to exercise in women. In this review, we present recent findings focusing on expiratory flow limitation (EFL), the regulation of lung volumes, and the work of breathing in exercising women. We also attempt to highlight what we view as questions that would benefit from additional research.

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DYSANAPSIS — REVISITED

The concept that individuals with large lungs do not necessarily have larger airways than do persons with small lungs was first described as "dysanapsis" in the 1970s (2) and 1980s (15). The term was used to reflect unequal growth and express the physiological variation in the geometry of the tracheobronchial tree and parenchyma due to different patterns of growth between men and women. Green *et al.* (2) commented that "dysanaptic" growth may seem unremarkable but may be physiologically important. More that 30 yr later, the concept continues to have considerable relevance as applied to our understanding of sex-based differences in pulmonary physiology. In this section, we briefly present the argument for dysanaptic growth and sex-based differences in resting pulmonary function.

There is direct anatomical evidence to show that the pattern of airway-parenchymal growth for boys is different from that of girls. Postmortem lungs obtained from boys (n = 36) and girls (n = 20) (6 wk to 14 yr) showed that boys have larger lungs than girls starting at approximately 2 yr (22). Even when lung volume was corrected for differences in body length, it seems that, with increasing age, boys continue to have larger lungs per unit of stature. If there is perfectly proportional growth of the airways and lung parenchyma, then the ratio of airway area to lung volume should be constant and independent of lung volume. A deviation from this would reflect unequal growth or dysanapsis. This relationship was assessed by Mead (15) who determined the association between airway size (estimated from maximal expiratory flow/static recoil pressure at 50% vital capacity) and lung size (vital capacity) in women (20–36 yr), men (23–48 yr), and boys (13–18 yr). They found that adult men have airways that are approximately 17% larger in diameter than are the airways of women. From their analyses, it was shown that women and boys have airways that are smaller relative to lung size than men, and the apparent sex-based differences occur late in the growth period. Additional support for airway parenchymal dysanapsis comes from cross-sectional studies that have made estimates of tracheal area (13). Martin *et al.* (13) used acoustic reflectance to determine tracheal cross-sectional area in young (20–35 yr) healthy men (n = 26) and women (n = 28). By design, subjects were of varying stature with the intent to create subgroups with overlapping heights and lung volumes. When matched for total lung capacity, the tracheal cross-sectional area was 40% less in women compared with that in men (Fig. 1). As such, even after controlling for lung volume it seems that men, on average, have significantly larger tracheal areas, and there is an apparent effect of biological sex on lung structure.

Given the aforementioned disparity in pulmonary structure, differences in resting pulmonary function are predictable. Indeed, it is well known that women typically have smaller lung volumes and maximal expiratory flow rates (Fig. 1) even when corrected for standing height (as a surrogate for chest volume) relative to men (13). Although we have made the case for sex-based differences in pulmonary structure and resting pulmonary function, the question germane to this review is the following: do these

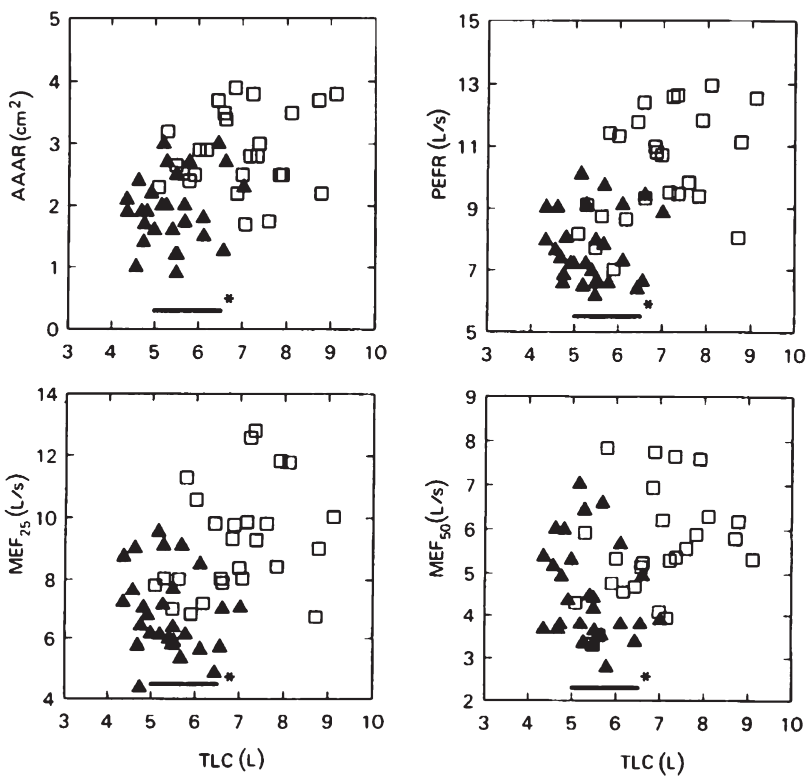

Figure 1. Evidence of dysanapsis. Indexes of airway size versus total lung capacity (TLC) in female (▲) and male subjects (□). *Indicates overlap range of TLC. When matched for TLC, tracheal area as measured by airway area acoustic reflectance (AAAR) was 40% greater in male subjects. Peak expiratory flow rates (PEFR) and maximal expiratory flow after 25% (MEF_{25}) and 50% (MEF_{50}) of vital capacity were 23% and 11% greater in male subjects than in female subjects, respectively. (Reprinted from Martin, T.R., R.G. Castile, J.J. Fredberg, M.E. Wohl, and J. Mead. Airway size is related to sex but not lung size in normal adults. *J. Appl. Physiol.* 63:2042–2047, 1987. Copyright © 1987 The American Physiological Society. Used with permission.)

differences have any consequence to the integrated pulmonary response of the exercising woman?

EXPIRATORY FLOW LIMITATION

In healthy young (18–40 yr) men, there is a large reserve for increasing ventilation even at maximal exercise. However, in some highly trained male endurance athletes, the mechanical limits for inspiratory and expiratory pressure development and flow generation can be reached during exercise. The high O_2 consumption and CO_2 production, and the associated ventilatory demands of heavy exercise, results in large increases in both tidal volume and breathing frequency. Expiratory flow limitation occurs during exercise when maximal expiratory flow is achieved during tidal breathing. The presence of EFL may cause reflex inhibition of the hyperventilatory response and/or an alteration in breathing pattern. These responses may cause significant increases in the work and O_2 cost of breathing.

There is now good evidence to show that some endurance-trained male subjects develop EFL during strenuous exercise (10). The smaller diameter airways and lung volumes in women result in lower peak expiratory flow rates and vital capacities. These factors mean that women have a smaller maximal flow-volume loop and thus a much smaller capacity to generate ventilation during exercise relative to their male counterparts. A smaller maximum flow-volume loop may predispose women to developing EFL even despite the fact that they achieve lower levels of ventilation during exercise. Figure 2 summarizes these concepts in a theoretical response to progressive exercise in age- and height-matched men and women. Tidal flow-volume loops are plotted relative to the maximal flow-volume loop. The forced vital capacity (FVC) and peak expiratory flow values are based on established prediction equations. In this comparison, the female subject has a smaller maximal flow-volume loop and lower maximal flow rates. With increasing exercising intensity, the female tidal flow-volume loop increases to the point of intersecting the boundary of the maximal flow-volume loop. This is in contrast to an age- and height-matched male subject where no EFL is present. These concepts are supported by the work of McClaran *et al.* (14) who were the first to demonstrate that women develop significant EFL during heavy exercise because of their smaller lungs and lower maximal expiratory flow rates.

The few studies that have assessed EFL in women have used a technique whereby tidal flow-volume loops are positioned within the maximal flow-volume loop according to end-expiratory lung volume. Expiratory flow limitation is considered present if the tidal breath meets or exceeds the expiratory boundary of the maximal flow-volume loop as shown in Figure 2. This technique provides an excellent visual representation of flow limitation and the operational lung volumes during exercise, but some have suggested that quantifying EFL using this technique may overestimate or even falsely detect the presence of EFL (11). An alternative method is to apply a negative expiratory pressure at the mouth and compare the flow-volume curve during the ensuing expiration with that of the preceding control breath. If application of the negative pressure does not cause an increase in flow, then the subject is considered flow limited. This technique alleviates some of the limitations associated with more traditional approaches. Work from our laboratory (3) used the negative expiratory pressure method to measure EFL in a group of highly trained female endurance athletes (Fig. 3). We found that 9 of 10 women experienced significant EFL during maximal cycle exercise, a finding that is consistent with the work of McClaran *et al.* (14), who found EFL in 86% of their fit women during treadmill running to exhaustion. An important observation was that the female subject with the largest FVC (134% of predicted) was the lone female to not experience EFL (Fig. 3, subject 3). It would

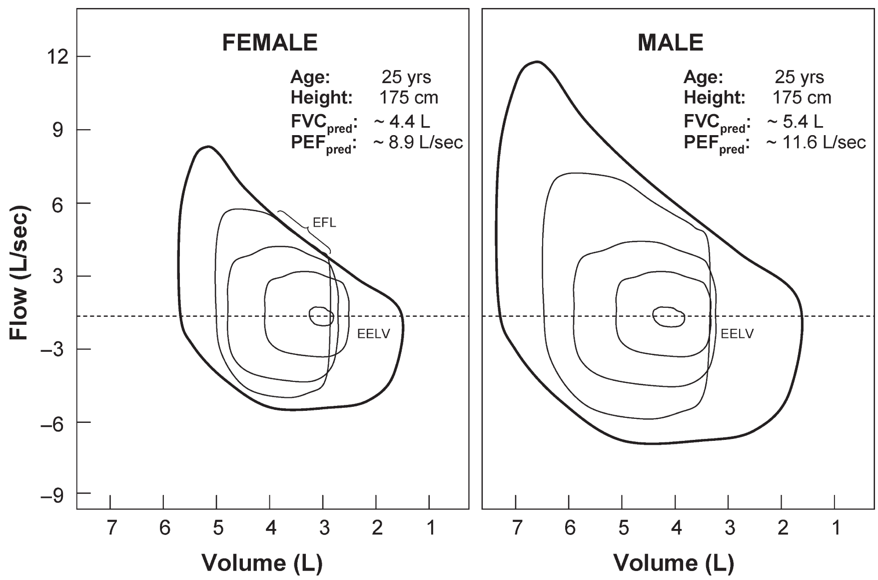

Figure 2. Theoretical response to progressive exercise in age- and height-matched men and women. Based on predictive equations, women have a smaller forced vital capacity (FVC) and peak expiratory flow rate (PEF). The figure shows increasing tidal volumes and the presence of flow limitation in women when the expiratory tidal flow-volume loop intersects the volitional maximal flow-volume loop. At maximal exercise, there is a greater increase in end-expiratory lung volume (EELV) in women relative to men. This leftward shift in EELV back toward resting values is indicative of dynamic hyperinflation.

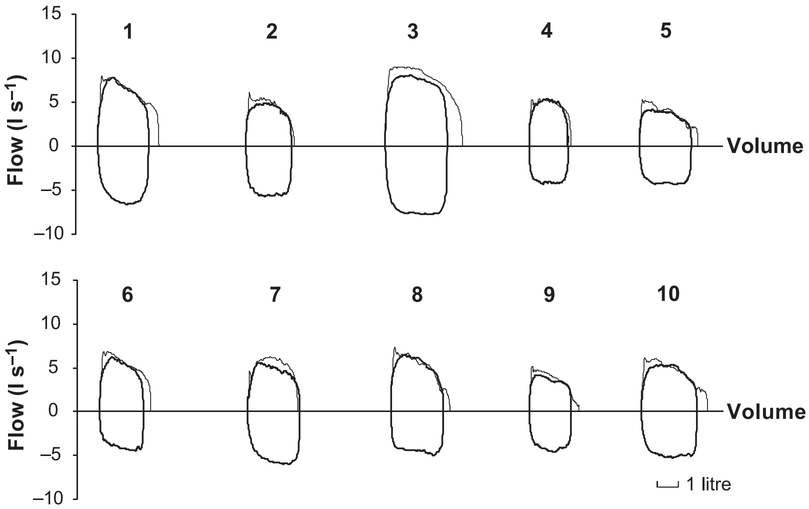

Figure 3. Expiratory flow limitation in women as assessed with the negative expiratory pressure technique. *Dark lines* represent the control breath, and *thin lines* represent the negative expiratory pressure breath. Expiratory flow limitation was considered present when there was an overlap between the negative expiratory pressure breath and preceding control expiration. Expiratory flow limitation was shown to occur in 9 of the 10 female subjects during near-maximal exercise. Subject 3 was the only female subject that did not develop expiratory flow limitation, and she had the largest lungs (134% of predicted). (Data from Guenette, J.A., J.D. Witt, D.C. McKenzie, J.D. Road, and A.W. Sheel. Respiratory mechanics during exercise in endurance-trained men and women. *J. Physiol*. 581:1309–1322, 2007. Copyright © 2007 Blackwell Publishing. Used with permission.)

therefore be predicted that the amount of respiratory work performed would be lower in this individual and other women with larger-than-average lungs (discussed below).

REGULATION OF LUNG VOLUMES DURING EXERCISE

End-expiratory lung volume (EELV) decreases early during exercise and remains below resting values during moderate intensity exercise. During heavier workloads, EELV may increase toward, or above, resting values, whereas end-inspiratory lung volume (EILV) continues to increase to facilitate an increase in tidal volume. End-inspiratory lung volume commonly approaches 85% of total lung capacity as subjects approach near-maximal exercise intensities. Decreasing EELV occurs, in part, to optimize diaphragm length and, in turn, lower or minimize the inspiratory work of breathing. However, the presence of EFL during exercise may trigger a reflex response whereby EELV actually increases to avoid dynamic compression of the airways (19). This relative hyperinflation of the lungs allows subjects to increase expiratory flow rates because they are breathing at a larger lung volume. This breathing pattern comes at the expense of an increase in the elastic work of breathing because lung compliance is reduced as lung volume increases. Thus, hyperinflation may induce respiratory muscle fatigue because the muscles are contracting from a shorter length. This means that the muscular force required to ventilate the lungs during heavy exercise is closer to the maximal capacity of the respiratory muscles to generate force.

We recently examined EFL and its accompanying hyperinflation in highly trained men and women. During submaximal exercise, we observed nearly identical changes in both EILV and EELV (Fig. 4). However, as the subjects approached maximal exercise, there were significant sex differences. For example, women increased EELV back toward resting values, indicating that they were beginning to hyperinflate their lungs in response to EFL. When expressed relative to FVC, women had significantly higher EELV compared with men at maximal exercise. This is consistent with the absence of EFL during moderate exercise intensities and the presence of EFL during maximal exercise. McClaran *et al.* (14) examined the effect of EFL on the regulation of lung volumes in a group of women by having subjects breathe a helium inspirate to increase the size of the maximum flow-volume loop and therefore eliminate EFL. When EFL was absent, subjects were able to maintain a lower EELV, which implies an important interrelationship between the presence of ventilatory constraint and the regulation of lung volumes during exercise. Figure 4 also

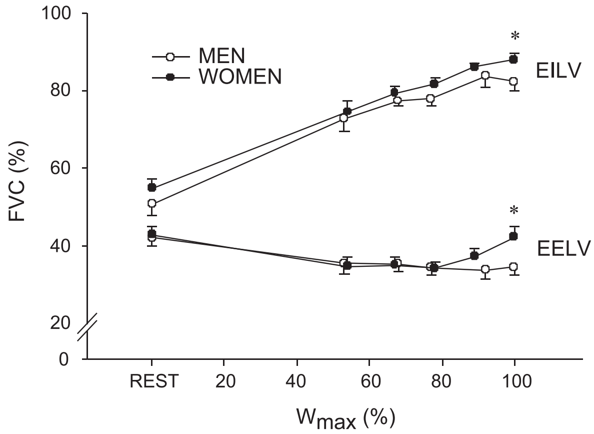

Figure 4. Regulation of lung volumes in men and women during progressive exercise to exhaustion. Shown are end-inspiratory lung volume (EILV) and end-expiratory lung volume (EELV) expressed as % FVC at rest and during progressive exercise to maximal workload (W_{max}) in men and women. Values are means ± SE. *Significantly different from men ($P < 0.05$). (Reprinted from Guenette, J.A., J.D. Witt, D.C. McKenzie, J.D. Road, and A.W. Sheel. Respiratory mechanics during exercise in endurance-trained men and women. *J. Physiol*. 581:1309–1322, 2007. Copyright © 2007 Blackwell Publishing. Used with permission.)

demonstrates that the relative EILV is significantly higher at maximal exercise in women compared with that in men. An increase in EILV is necessary for these women to maintain their exercising tidal volume. Moreover, the EILV measured in these women was approaching 90% of their FVC, indicating that there would be a substantially increased elastic load on the inspiratory muscles relative to their male counterparts whose EILV was only 82% of FVC. Based on the higher relative values for EILV and EELV in women, it would be predicted that the work of breathing would also be higher in women compared with that in men.

HIGH WORK OF BREATHING

The work of breathing is higher during dynamic exercise compared with that during rest because both breathing frequency and tidal volume are increased. With mild to moderate exercise, the predominant response is that tidal volume expands into both inspiratory and expiratory reserve volumes, with small increases in breathing frequency. During heavier work, once tidal volume reaches 50%–60% of vital capacity, there is a plateau in tidal volume, and further increases in minute ventilation are accomplished by elevations in breathing frequency. It should be emphasized that there is often considerable interindividual variation in this respiratory pattern. Elastic work increases substantially as tidal volume increases relative to rest. Beyond the level of exercise where tidal volume reaches a plateau, elastic work will theoretically decrease with increasing breathing frequency because more of the elastic energy that is stored in the chest wall and/or lung during inspiration or expiration is recovered in the succeeding part of the breathing cycle. However, resistive work increases significantly with flow rate. Resistance to airflow, particularly during EFL, increases the work of expiration to a similar extent as inspiration during exercise. The increased resistive work associated with flow rate, the increased elastic work associated with increased tidal volume, and the increased breathing frequency collectively result in an increase in the total work of breathing. If EFL and hyperinflation occur during exercise, these will cause further increases in the work of breathing, namely, increased elastic work during inspiration and augmented resistive work during expiration.

Figure 5 shows the mean relationship between the work of breathing and ventilation in men and women (3). At rest and during low intensity exercise, the work of breathing is the same between men and women. With increasing exercise intensity and the accompanying rise in minute ventilation, the work of breathing in women significantly increases out of proportion to men. When minute ventilation ($\dot{V}E$) exceeds 90 $L{\cdot}min^{-1}$, the work of breathing in women is approximately twice that of men. Therefore, the work and presumably the O_2 cost of moving a given volume of air in and out of the lungs are substantially higher in women. It should also be noted that both curves in Figure 5 have been extrapolated to 200 $L{\cdot}min^{-1}$ for theoretical purposes only. To further compare men and women, we (3) described the relationship between the work of breathing and minute ventilation using the following equation as described by

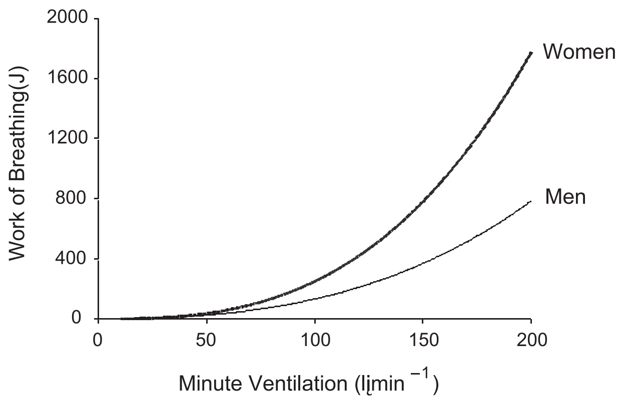

Figure 5. Work of breathing in men and women. Each curve represents a mean curve relating the work of breathing versus minute ventilation. Each curve has been extrapolated to 200 $L{\cdot}min^{-1}$ for theoretical purposes. The work of breathing is essentially the same at rest and during very low levels of ventilation. As ventilation increases with increasing intensity, the work of breathing in women significantly increases out of proportion relative to men. (Reprinted from Guenette, J.A., J.D. Witt, D.C. McKenzie, J.D. Road, and A.W. Sheel. Respiratory mechanics during exercise in endurance-trained men and women. *J. Physiol.* 581:1309–1322, 2007. Copyright © 2007 Blackwell Publishing. Used with permission.)

Otis *et al.* (18): Work of breathing = $a\dot{V}E^3 + b\dot{V}E^2$. 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 constant a and b was then determined for each individual subject. Constant a was significantly higher in women, which we interpret to mean that the higher work of breathing in women is associated with the additional work needed to overcome the resistance to turbulent airflow. 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 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 with the men, and this may be one of many major reasons for their higher work of breathing. We observed interindividual variability for constants a and b, which may be related to the differences in lung volumes or airway size. 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 FVC and constant a ($r = -0.54$; $P < 0.05$). Perhaps more importantly was the finding that constant a was significantly correlated with peak expiratory flow rates in women ($r = -0.76$; $P < 0.05$) and when all subjects were pooled together ($r = -0.68$; $P < 0.05$). Peak expiratory flow rates may serve as an indirect indicator of airway size, which may explain, in part, the increased work done in overcoming the resistance to turbulent airflow in women relative to men. Future studies, which measure the work of breathing in exercising women, could provide further insight into this question by creating modified Campbell diagrams, which yield elastic and resistive work during both inspiration and expiration.

SEX VERSUS BODY SIZE DIFFERENCES?

In general, women tend to be smaller than men, and it is difficult to separate the issue of sex versus size differences with respect to lung/airway structure and mechanics. To support the argument that there are sex-based differences, there must be clear differences that occur irrespective of size. Conversely, differences in morphological features without consideration of sex would argue for absolute size-based differences. Based on the available data, a definitive answer to this question is not yet possible. Additional well-designed studies that consider the important and likely independent influences of body size, lung size, and fitness are necessary. However, as a start-point, we favor the concept that it is absolute lung structure rather than sex *per se* that influences the mechanics of respiration during exercise. To argue this perspective, we are, admittedly, forced to rely upon few experimental data points and largely indirect evidence. In our study (3), the female subject with the largest lung volume and flow rate had the lowest work of breathing relative to other women (Fig. 6, dashed line), and she was the only female subject to not demonstrate EFL or relative hyperinflation, despite achieving a level of minute ventilation in excess of 170 L·min^{-1} at maximal exercise (Fig. 3, subject 3). The level of ventilation observed in this female subject is extraordinary. This particular subject was only 166 cm tall, with an FVC of 5.4 L, whereas the group mean height for men was 184 cm, with an average FVC and minute ventilation of 5.6 L and 161 L·min^{-1}, respectively. Interestingly, the work of breathing this subject generated during exercise fits the mean values for men across all ranges of ventilation. This exception provides additional insight into our primary argument. Specifically, if we operate with the premise that the anatomical evidence of sex-based dysanapsis is indeed correct, the "normal" or "typical" pulmonary structure and resting pulmonary function in women results in a high work of breathing during exercise.

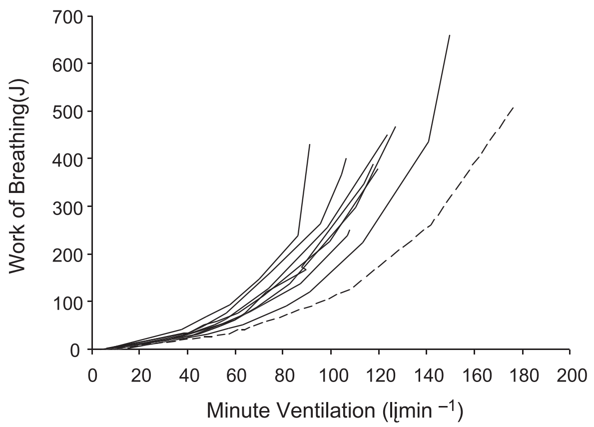

Figure 6 . Individual responses of the work of breathing versus minute ventilation in women. The *dashed line* represents the female subject with the largest lungs who had the lowest work of breathing for any given minute ventilation. (Reprinted from Guenette, J.A., J.D. Witt, D.C. McKenzie, J.D. Road, and A.W. Sheel. Respiratory mechanics during exercise in endurance-trained men and women. *J. Physiol.* 581:1309–1322, 2007. Copyright © 2007 Blackwell Publishing. Used with permission.)

Abnormalities in pulmonary gas exchange during heavy exercise have been reported in aerobically trained men and animals (*e.g.*, horses and dogs). Few studies have examined impaired gas exchange in women, and the prevalence remains unclear. However, there is some evidence to suggest that women, by virtue of relatively smaller lungs, may be more susceptible to arterial hypoxemia during exercise than men (5,20). The question of sex versus size, with respect to gas exchange during exercise, has been addressed by Olfert *et al.* (17) who compared fit young men and women who were matched for age, height, lung volumes, and maximal O_2 consumption. No exercise-induced abnormalities were observed in these women. They concluded that aerobic fitness level and lung size are likely more important than biological sex for the occurrence of pulmonary gas exchange impairment during exercise. This is relevant to the present discussion because mechanical constraints, specifically EFL, can affect gas exchange (14). The study by Olfert *et al.* (17) highlights that women with relatively large lungs do not experience impaired gas exchange and presumably EFL during exercise.

UNRESOLVED QUESTIONS

Respiratory Muscle Fatigue

The diaphragm, as the primary muscle of inspiration, is highly resistant to fatigue. However, respiratory muscle fatigue has been shown to occur in healthy male subjects during strenuous exercise (9). *Fatigue* has been defined as a loss in the capacity of a muscle to generate force and/or the velocity of contraction in response to a load and is accompanied by recovery during rest (16). For fatigue to occur, the diaphragm must sustain extremely high levels of force output (13), and during heavy endurance exercise, the magnitude of fatigue and the likelihood of its occurrence increase as the relative intensity exceeds 85% of maximal O_2 consumption. An often underappreciated component of respiration during strenuous exercise is the important contribution of the expiratory muscles. Taylor *et al.* (21) have shown that there is also significant fatigue of the abdominal muscles after heavy exercise. The presence or absence of inspiratory or expiratory muscle fatigue has not been systematically assessed in female subjects. With limb muscles, it seems that female subjects generally exhibit greater relative fatigue resistance than male subjects (8). It is not known if this apparent difference is also present in the muscles of respiration.

Consequences of a High Work of Breathing

An important consequence of high levels of respiratory muscle work is the vasoconstriction and reduction in blood flow to working locomotor muscles, accompanied by changes in norepinephrine spillover (1). These effects were demonstrated by mechanically loading or unloading the respiratory muscles at maximum exercise (4). Changes in leg blood flow were observed that indicate a competitive relationship between locomotor and respiratory muscles for a limited cardiac output. Does the high work of breathing in women elicit a greater competition for a finite cardiac output during heavy exercise? We now know that specific respiratory muscle training has the ability to attenuate the respiratory muscle metaboreflex in men (23), but we do not know if training the respiratory muscles alters this reflex differently in women.

Exercise Performance

Does respiratory muscle fatigue or a high work of breathing have a measurable effect on exercise performance? This was addressed by subjecting highly trained male cyclists to exercise performance trials, consisting of cycling to exhaustion, beginning at 90% of maximal O_2 consumption, under control conditions and during respiratory muscle loading or unloading (6). Unloading increased endurance time by 14%, and respiratory muscle loading reduced performance time by 15%. By manipulating the very high work of breathing in women, might these exercise performance effects be magnified?

CONCLUSIONS

Collectively, we interpreted our findings and those of others to mean that sex-based differences in pulmonary structure and function have important consequences to the development of flow, volume, and pressure during dynamic exercise. There is reason to suggest that the pulmonary system of endurance-trained female subjects may be at a disadvantage compared with their male counterparts during intense exercise. This is supported by three sets of evidence. First, there is a tendency for women to develop EFL more frequently than men. Second, women have higher relative increases in EELV and EILV during exercise. Third, women have a higher work of breathing across a wide range of ventilations during exercise compared with men. We attribute the underlying mechanism for the above to be related to the smaller lungs and presumably the smaller diameter airways in women. As a cautionary point, we emphasize that our interpretations are based on few studies and a limited number of subjects, and our understanding of female pulmonary responses to exercise remains incomplete. As Haverkamp and Dempsey (7) commented, only recently has there been an appreciable understanding that the respiratory responses to exercise in the so-called forgotten sex may indeed be different from that of men. To fully address questions of sex- or size-based differences, future studies must consider the importance of matching subjects for age, body and lung size, and aerobic capacity.

Acknowledgments

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