McClaran, Steven R., Craig A. Harms, David F. Pegelow, and Jerome A. Dempsey. Smaller lungs in women affect exercise hyperpnea. J. Appl. Physiol. 84(6): 1872–1881, 1998.—We subjected 29 healthy young women (age: 27 ± 1 yr) with a wide range of fitness levels [maximal oxygen uptake (VO₂max): 57 ± 6 ml·kg⁻¹·min⁻¹; 35–70 ml·kg⁻¹·min⁻¹] to a progressive treadmill running test. Our subjects had significantly smaller lung volumes and lower maximal expiratory flow rates, irrespective of fitness level, compared with predicted values for age- and height-matched men. The higher maximal workload in highly fit (VO₂max > 57 ml·kg⁻¹·min⁻¹, n = 14) vs. less-fit (VO₂max < 56 ml·kg⁻¹·min⁻¹, n = 15) women caused a higher maximal ventilation (VE) with increased tidal volume (VT) and breathing frequency (f₅) at comparable maximal VT/vital capacity (VC). More expiratory flow limitation (EFL; 22 ± 4% of VT) was also observed during heavy exercise in highly fit vs. less-fit women, causing higher end-expiratory and end-inspiratory lung volumes and greater usage of their maximum available ventilatory reserves. HeO₂ (79% He-21% O₂) vs. room air exercise trials were compared (with screens added to equalize external apparatus resistance). HeO₂ increased maximal expiratory flow rates (20–38%) throughout the range of VC, which significantly reduced EFL during heavy exercise. When EFL was reduced with HeO₂, VT, f₅, and VE (+16 ± 2 l/min) were significantly increased during maximal exercise. However, in the absence of EFL (during room air exercise), HeO₂ had no effect on VE. We conclude that smaller lung volumes and maximal flow rates for women in general, and especially highly fit women, caused increased prevalence of EFL during heavy exercise, a relative hyperinflation, an increased reliance on f₅, and a greater encroachment on the ventilatory “reserve.” Consequently, VT and VE are mechanically constrained during maximal exercise in many fit women because the demand for high expiratory flow rates encroaches on the airways’ maximum flow-volume envelope.

There are important gender differences in resting pulmonary function (5) that might have an effect on the integrated ventilatory response and respiratory muscle work during exercise. Adult women consistently have smaller lung volumes and lower maximal expiratory flow rates even when corrected for standing height relative to men (5). Sitting height or differences in trunk length for the same standing height account for some, but not all, gender differences in lung volumes and maximal expiratory flow rates in teenagers and young adults (31). Mead (28) suggests that gender differences in pulmonary function can be explained by smaller-diameter airways relative to lung size, and these differences probably become significant relatively late in the growth period of the lung. Thurlbeck (33) found that mature men have a larger lung size brought about by a greater number of alveoli relative to that in mature women.

A substantial reserve exists for increases in ventilation in the young to middle-aged normal, healthy untrained man, even at maximal exercise (10, 14, 17). However, the endurance-trained man with a higher maximal oxygen uptake (VO₂max) and CO₂ production, producing a high ventilatory demand, begins to approach the mechanical limits for inspiratory and expiratory pressure and flow development (10, 20). As the tidal exercise flow-volume loop reaches the boundary of the maximal ventilatory loop and the tidal breath becomes progressively more flow limited, endurance-trained men begin to increase their end-expiratory lung volume (EELV), causing a less optimal length of the inspiratory muscles for pressure generation (20). In addition, end-inspiratory lung volume (EILV) begins to approach total lung capacity (TLC) because of the rise in EELV and the large tidal volume (VT). Recently, it was determined that the decline in pulmonary function with normal aging caused the older habitually trained adult to also show significant expiratory flow limitation, relative hyperinflation, increased work of breathing and, in some cases, a mechanical limit to ventilation at maximal exercise (19, 27). Thus the effects of mechanical constraints of the lung on volumes and maximal expiratory flow rates become very important to control of breathing during exercise in both the endurance-trained male athlete and the habitually trained older adult during high-intensity exercise.

We asked whether the smaller lung volumes and lower maximal expiratory flow rates in women relative to men would alter the degree of expiratory flow limitation and thereby affect the ventilatory response to exercise. We also questioned whether the increased ventilatory demands of a higher maximal workload in a highly fit woman would cause a different ventilatory response to exercise relative to that of a less-fit woman. Last, we used HeO₂ breathing (79% He-21% O₂) to increase the size of the maximal flow-volume envelope to examine the effects of reducing the mechanical constraints to airflow on the ventilatory response to exercise in women.

METHODS

Twenty-nine female subjects, age 18–42 yr, were recruited to participate in the study. All except four of the subjects ran at least three times per week and averaged 32.5 miles/wk as a group (Table 1). All subjects’ pulmonary function tests were within the normal predicted range (Table 2), and none had any history of cardiovascular or lung disease. None of the subjects was a smoker. All procedures were approved by the Human Subjects Committee Institutional Board of the University of Wisconsin-Madison. Informed consent was obtained in writing from each subject before testing.
inspiratory and expiratory tubing during the HeO2 trial to similar to that for room air. Mesh screens were added to the collecting in a calibrated tissot.

Flow, Volume, and Gas Measurements

All measurements have been described previously (27). Inspired and expired flow rates were measured separately by a pneumotachographs (model 3800, Hans Rudolph). Volume calibration was performed for each inspiratory gas with various steady-state flows and verified by determining functional residual capacity (FRC), and forced expiratory volume in 1 s were determined in a Collins body plethysmograph (22) by using Boyle’s law. Residual volume (RV) was determined by using an inert gas with a single 10-s breath-hold dilution test (8).

The HeO2 gas was warmed and humidified in a manner similar to that for room air. Mesh screens were added to the inspiratory and expiratory tubing during the HeO2 trial to attain identical external apparatus resistance with the ambient room air (79% N2-21% O2) trial at flow rates from 0.5 to 9.0 l/s. Apparatus resistance was 0.80, 0.99, and 1.49 cmH2O·l−1·s with room air and 0.90, 1.00, and 1.50 cmH2O·l−1·s with HeO2 gas at flow rates of 3.1, 5.8, and 8.5 l/s, respectively. Thus with the added external resistance the He effect was limited only to reducing the subjects’ internal airway resistance.

Inspiried and expired gases were sampled at the mouth and in a mixing chamber via a mass spectrometer (model 1100, Perkin-Elmer), an Applied Electrochemistry model S-3A oxygen analyzer, and a Beckman Medical model LB-2 gas analyzer for measurement of CO2. All signals were sent through an analog-to-digital board (Techmar Labmaster; Scientific Solutions, Solon, OH) and sampled on a computer (PC Tailor 486 DX/250) at 75 Hz.

Resting Pulmonary Function Tests

Resting pulmonary function tests and exercise measurements were performed at the John Rankin Laboratory of Pulmonary Medicine. Vital capacity (VC), inspiratory capacity (IC), and forced expiratory volume in 1 s were determined by using a Collins 13.5-liter water-sealed spirometer (Warren E. Collins, Braintree, MA). Resting thoracic gas volume for the determination of functional residual capacity (FRC) was determined in a Collins body plethysmograph (22) by using Boyle’s law. Residual volume (RV) was determined by using an inert gas with a single 10-s breath-hold dilution test (8).

Measurement of Arterial Blood Gases, Lactate, pH, and Potassium

Before the room air trial, subjects had a 20-gauge indwelling plastic catheter placed in the radial or brachial artery under local 1% lidocaine anesthesia. Multiple arterial blood samples (3 ml) were drawn during rest and the last 30 s of each workload for measurement of PCO2, pH, and potassium. Blood gases and pH were analyzed by using electrodes (Radiometer ABL2; OSM 3) calibrated with tonometered blood of known PO2 and PCO2. Arterial blood gases were corrected for temperature changes during exercise as measured from a thermocouple (Mona-a-Therm 6500) placed intranasally into the lower one-third of the esophagus. Blood lactate concentration was analyzed by a YSI lactate analyzer (model 1500 Sport) calibrated with reference standards spanning the appropriate range of values (0–30 mmol/l). Plasma potassium was analyzed by an AVL electrolyte analyzer (series 9100). Progesterone was determined by radioimmunoassay (Endocrine Sciences, Tarzana, CA).

Determination of Inspiratory Flow Limitation

Each subject performed a minimum of 3–5 voluntary maximal flow-volume loop (MFVL) maneuvers during the room air and HeO2 trials before and immediately after exercise, with the largest loop being used for comparison with tidal breathing. A maximal IC measurement was obtained during the last 20 s of each 2.5-min workload. A mean of 10–20 tidal breaths taken at the end of each workload was averaged (by using a computer averaging program) to provide a representative tidal flow-volume loop for that workload.

### Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SE</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>27.2 ± 1.4</td>
<td>(18–42)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>165.3 ± 1.3</td>
<td>(155–179)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>59.0 ± 1.3</td>
<td>(46–69)</td>
</tr>
<tr>
<td>V̇O₂max, ml·kg−1·min−1</td>
<td>54.6 ± 1.4</td>
<td>(34–72)</td>
</tr>
<tr>
<td>V̇O₂max, %predicted†</td>
<td>146.4 ± 4.8</td>
<td>(85–203)</td>
</tr>
<tr>
<td>Running, miles/wk</td>
<td>32.5 ± 3.8</td>
<td>(0–90)</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 29 women. †Predicted values are based on gender and age (24).

### Table 2. Resting lung volumes and flow rates (%Predicted)

<table>
<thead>
<tr>
<th>Lung Volumes</th>
<th>Mean ± SE</th>
<th>Women*</th>
<th>Men*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC, liters</td>
<td>5.54 ± 0.15†‡</td>
<td>106 ± 3</td>
<td>94 ± 2</td>
</tr>
<tr>
<td>VC, liters</td>
<td>4.06 ± 0.11†‡</td>
<td>106 ± 3</td>
<td>88 ± 2</td>
</tr>
<tr>
<td>IC, liters</td>
<td>2.57 ± 0.12†‡</td>
<td>109 ± 4</td>
<td>81 ± 3</td>
</tr>
<tr>
<td>RV, liters</td>
<td>1.57 ± 0.06†‡</td>
<td>114 ± 4</td>
<td>124 ± 5</td>
</tr>
<tr>
<td>FRC, liters</td>
<td>2.92 ± 0.11†‡</td>
<td>102 ± 4</td>
<td>107 ± 4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Flow rates</th>
<th>Mean ± SE</th>
<th>Women*</th>
<th>Men*</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1, liters</td>
<td>3.35 ± 0.10†</td>
<td>106 ± 3</td>
<td>87 ± 3</td>
</tr>
<tr>
<td>FEV1/VC, %</td>
<td>85.2 ± 1.10‡</td>
<td>99 ± 3</td>
<td>96 ± 3</td>
</tr>
<tr>
<td>Peak flow, l/s</td>
<td>7.84 ± 0.14‡</td>
<td>98 ± 2</td>
<td>77 ± 4</td>
</tr>
<tr>
<td>MEF50, l/s</td>
<td>4.35 ± 0.10‡</td>
<td>103 ± 3</td>
<td>91 ± 2</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 29 subjects. TLC, total lung capacity; VC, vital capacity; IC, inspiratory capacity; RV, residual volume; FRC, functional residual capacity; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; peak flow, maximal expiratory flow; MEF50, maximal expiratory flow after exhalation of 50% of VC. *Predicted values are based on gender, age, and height (9, 25). †Significantly different from predicted values for women (P < 0.05). ‡Significantly different from predicted values for men (P < 0.05).
The EELV was determined by subtracting the maximal IC for each workload from the TLC as measured at rest (19). EELV was calculated as the sum of EELV plus VT. Flow limitation for each workload was computed as the percentage of the expiratory tidal flow-volume loop for each workload that intersected the expiratory boundary of the MFVL.

Estimation of Maximal Ventilation Available During Exercise

Maximal ventilation available during exercise was estimated by using two methods. 1) The maximal voluntary ventilation (MVV) was calculated as 12 s of volitional maximal ventilatory effort extrapolated (multiplied by 5) to 1 min. 2) Maximal ventilatory capacity (VEcap) was calculated for each subject on the basis of the relationship between the MFVL and the tidal exercise flow-volume loop at maximum exercise (21). By using the VT and EELV at maximum exercise, maximal respiratory frequency (fmax) was obtained as if the subject had breathed exclusively along the inspiratory and expiratory boundaries of the MFVL during the tidal breath. After the maximal VT (VTmax) was divided into small increments (average: 20–40 ml), minimum expiratory time was determined by dividing each volume increment by the maximal expiratory flow within each volume segment and these times were then summed over the expiratory phase of the VT. In a similar manner, by using the same volume increments and the maximal inspiratory flow, minimum inspiratory time was calculated

\[
\dot{V}_E\text{cap} = f_{\text{max}}(60/\text{minimum Ti} + \text{minimum Te})
\]

where Ti and Te are inspiratory and expiratory time, respectively.

Prediction Equations

We selected prediction equations for resting lung function from cross-sectional studies that reflected the background of our subject population, namely, those that included both male and female subjects who were nonsmokers, Caucasian, and primarily US residents (9, 25).

Statistical Analysis

We used paired t-tests with Bonferroni correction for multiple comparisons of pairs of mean values for actual vs. predicted pulmonary function variables and for room air vs. HeO2 breathing at specific work rates. Unpaired t-tests were used to compare mean values between highly vs. normally fit groups.

RESULTS

Resting Pulmonary Function Tests

The group mean values of the resting lung volumes and maximal flow rates are shown in Table 2. Mean TLC, VC, IC, and RV were 6–16% larger (P < 0.05) than predicted values for age- and height-matched women, with no significant differences in FRC and in all values of maximal expiratory flow rates. Compared with predicted values for men of comparable age and height, TLC, VC, IC, and all maximal expiratory flow rates were significantly smaller, whereas RV and FRC were significantly larger.

Ventilatory and Lung Volume Response to Progressive Exercise

The ventilatory responses from rest through maximal exercise are shown in Figs. 1 and 2. During the progression from rest to moderate through heavier exercise, VT showed a progressive increase, as did breathing frequency. From heavy through maximal exercise, VT plateaued with the increased breathing frequency accounting for all of the increase in minute ventilation (VE). VT/VC increased gradually through heavy exercise and leveled off at 50–52% during heavy through maximal exercise. There was a significant linear relationship (r = 0.88) between VC and VTmax described by the following equation: VTmax (liters) = 0.527VC – 0.05. Dead space volume/VT dropped significantly from rest to moderate exercise, with a small further decrease through maximal exercise. Alveolar ventilation increased progressively from rest to moderate through maximal exercise. The arterial blood potassium, pH, lactate, and PCO2 (PaCO2) values during progressive exercise are shown in Fig. 3, A and B. There was a gradual increase in potassium from rest to moderate through maximal exercise.
exercise. Levels of arterial blood pH and lactate were unchanged from rest to mild and moderate exercise, followed by a progressive metabolic lactacidosis during heavy and maximal exercise. Group mean PaCO2 dropped significantly from rest to mild exercise (19 subjects showed an immediate significant drop (2.3.6 ± 0.3 Torr) and 10 exhibited an isocapnic response (2.0.2 ± 0.15 Torr). At maximal exercise, all 29 subjects showed a significant hyperventilatory response (PaCO2: 2.3.0 to 2.9.0 Torr from rest).

Fitness Effects on Resting Lung Function, Ventilation, and Expiratory Flow Limitation During Exercise

Figure 4 shows individual values for VO2max plotted against %predicted VC and %predicted maximal expiratory flow at 50% of VC (MEF50) for all 29 subjects. There was no significant correlation between %predicted VO2max and predicted values for any resting lung volumes or expiratory flow rates. To determine whether there were fitness effects on ventilation and lung volumes at maximal exercise, we divided the 29 subjects into highly fit (VO2max > 57 ml·kg⁻¹·min⁻¹, n = 14) and less-fit (VO2max < 56 ml·kg⁻¹·min⁻¹, n = 15) groups for comparison (Table 3). There were no significant differences between groups in age, height, weight, resting lung volumes, or maximal expiratory flow rates. Highly fit women had a significantly higher maximal ventilation (VEmax), accounted for by both a higher VT and breathing frequency (P < 0.05) at maximal exercise compared with less-fit women. Highly fit women also had significantly higher VEmax/VEcap, EELV/TLC, and EILV/TLC compared with less-fit women.

Ensemble-averaged tidal flow-volume loops for rest through maximal exercise in highly fit and less-fit women are shown in Fig. 5. Expiratory flow limitation was minimal or nonexistent in all subjects through moderate-intensity exercise. Less-fit women showed minimal expiratory flow limitation during maximal exercise, but the significantly higher VEmax in highly fit women was enough to produce considerable flow limitation during high-intensity exercise. During heavy and maximal exercise, 12 of 14 in the highest-fitness group had significant expiratory flow limitation, whereas only 4 of 15 showed flow limitation in the less-fit group.

Effect of the Available Maximal Flow-Volume Envelope on Exercise Ventilation and Lung Volumes

To determine whether expiratory flow limitation in women affected their ventilatory response and lung volumes during exercise, we used HeO2 breathing in 22 subjects to increase the size of the MFVL and, in turn, reduce the amount of expiratory flow limitation during exercise. The averaged MFVL with the ensemble-averaged rest and tidal exercise loops placed within the MFVL for the room air and HeO2 trials are shown in Fig. 6. HeO2 increased maximal volitional expiratory flow rates at 75, 50, and 25% of VC by 2.5, 1.7, and...
0.6 l/s, respectively, compared with room air. At maximal exercise, mean expiratory flow limitation was significantly reduced (from 26 ± 5 to 5 ± 3% of VT) during HeO2 compared with room air breathing. Coincident with the reduction in expiratory flow limitation with HeO2 vs. room air, subjects also showed a significantly lower EELV and EILV at maximal exercise and a significant increase in Ve, VT, and breathing frequency (P < 0.05).

Figure 7 compares the ventilatory response in the room air vs. HeO2 trials at the same workloads during progressive exercise in the 15 subjects who showed significant expiratory flow limitation (range 19–78% of VT) at one or more work rates during the room air trial. Ve was not significantly different (P > 0.60) at comparable workloads between the room air vs. HeO2 trials when subjects showed no expiratory flow limitation during the room air trial. However, HeO2 significantly increased breathing frequency, VT, and Ve (compared with room air) (P < 0.01) only at workloads where significant expiratory flow limitation occurred during the room air trials. At these workloads, expiratory flow limitation averaged 38% of VT during room air breathing and 7% of VT during HeO2 breathing.

DISCUSSION
The purpose of this study was to determine whether the ventilatory response to heavy exercise in women is constrained by their smaller lung volumes and reduced capability of their airways for flow rate. The major findings in this study were that 1) the higher exercise capability and therefore ventilatory response in the highly trained women led to increased expiratory flow limitation and greater utilization of ventilatory reserve compared with less-trained women and 2) significant expiratory flow limitation in women constrained the ventilatory response during high-intensity exercise. The data obtained in our study, compared with published data in men, suggest that the relatively smaller lung volumes and lower maximal expiratory flow rates in women caused them to utilize a greater percentage of their ventilatory reserve during exercise.

Gender Comparisons of Resting Lung Function and the Ventilatory Response to Exercise

Prediction equations for lung function show a significant gender difference in adults (see review of lung function in Ref. 5). Height-matched men have larger-diameter airways (28), with larger lung volumes and diffusion surfaces (33) compared with women. Our
findings support this generalization because our young female subjects had significantly smaller lung volumes and lower maximum expiratory flow rates compared with predicted values for men at the same age and standing height (Table 2). Some of these gender differences in resting lung function are partially explained by differences in sitting height, which may serve as a surrogate for chest volume (31).

Typically, men demonstrate a large increase in VT and breathing frequency from mild to moderate exercise, followed by a plateau in VT from heavy to maximal exercise. We observed a similar response in women (Fig. 1). In addition, when the VT\textsubscript{max} was equalized for VC (Table 3), the values for our female subjects were consistent with previously reported values in trained men (20) and with those of untrained men and women (23) (VT\textsubscript{max}/VC ~ 50%). Given this consistent ratio of VT\textsubscript{max} to VC for both men and women, combined with the lower VC values in height-matched women (Table 2), we would therefore speculate that women would have a lower VT\textsubscript{max} compared with men.

Because women are generally shorter than men, and because both gender and height are important determinants of lung volumes and expiratory flow rates (5), we would suggest two important differences in the ventilatory response to exercise in women compared with men. 1) Given the similar VT\textsubscript{max}/VC in both men and women, the smaller VC in women would also cause a plateau at a lower VT\textsubscript{max}. Thus a woman would presumably need to rely on a higher breathing frequency at any given VE compared with a man during high-intensity exercise. 2) A woman would also have lower maximal expiratory flow rates (5), creating a smaller maximal flow-volume envelope. Thus a woman would be expected to show significant expiratory flow limitation sooner (i.e., at a lower VE) or at a comparable VE\textsubscript{max}, and more of the VT would be flow limited. In addition, the increase in expiratory flow limitation in a woman would increase EELV and EILV compared with a man.

We utilized both VE\textsubscript{cap} and MVV to estimate maximal available ventilation and observed VE\textsubscript{max}/VE\textsubscript{cap} and VE\textsubscript{max}/MVV in women, which often exceeded 80% at a VE of 110–120 l/min (Table 3). This suggests that at any comparable ventilation during exercise, highly fit women would use a substantially greater portion of their ventilatory reserve compared with that reported for men (20). Eventually, a highly fit man approaches a similar percentage of ventilatory capacity (VE\textsubscript{max}/VE\textsubscript{cap} > 80%) but not until he reaches much greater levels of VO\textsubscript{2} and VE than does a woman (20). Therefore,
both gender per se and height have an effect on lung volumes and maximal flow rates, and each is an important determinant of the ventilatory response to heavy exercise and of the proportion of maximal available ventilation utilized.

Effect of Fitness on Flow Limitation and Lung Volumes During Exercise

The similar lung volumes and maximal expiratory flow rates among our subjects with a wide range in \( VO_2_{max} \) values (Fig. 4) are in agreement with studies demonstrating that neither fitness nor habitual running and/or training has an effect on pulmonary function (20, 26, 29, 30). However, there is good evidence that very young male and female swimmers (2, 4) and competitive adult male and female swimmers (3, 7) have larger lungs compared with the normal population.

We observed minimal amounts of expiratory flow limitation in the less-fit women at maximal exercise (\( V_\dot{E}\max = 104 \text{ l/min} \)) and, after the initial fall in EELV during moderate exercise, EELV remained below resting FRC (Fig. 5A) throughout exercise. Presumably, the lower EELV maintained a more optimal length of the inspiratory muscles for pressure generation (17). In contrast, the higher \( V_\dot{E}\max \) (\( \approx 113 \text{ l/min} \)) in the highly fit women was sufficient to cause significant expiratory flow limitation, which in turn caused EELV to approach and exceed resting FRC during heavy and maximal exercise (Fig. 5B). Trained men also raise their EELV when they experience significant expiratory flow limitation, but because of their relatively larger MFVL they do not generally experience this until ventilation exceeds 120 l/min (20). Therefore, the combination of an increased ventilatory demand and a higher EELV from the greater prevalence of expiratory flow limitation in a highly fit woman would presumably cause EILV to approach 90% of TLC. It has been suggested that with trained young men (20), and especially with trained older adults (19), the increase in elastic work incurred when more of the tidal breath occurs at high lung volumes would preclude reaching an EILV > 90% of TLC. Therefore, a small flow-volume envelope and significant expiratory flow limitation caused a very high EILV during heavy exercise in the highly fit women, and, to minimize elastic work, further increases in \( \dot{V}r \) do not appear to be an available option. Thus increasing breathing frequency (compared with men) would seem to be the only strategy available to a highly fit woman to attain the necessary ventilation to meet the metabolic needs of high-intensity exercise.

Consequences of Expiratory Flow Limitation to Ventilatory Response

The purpose in comparing the He\( \dot{O}_2 \) vs. room air trials was to determine the effects of increasing the size of the MFVL, thereby reducing expiratory flow limitation, on lung volumes and ventilation. We noted previously that EELV begins to rise in our subjects at the
onset of significant flow limitation. However, with the reduction in expiratory flow limitation with HeO2 breathing, our subjects maintained a lower EELV (Fig. 5) and, despite a higher Vt, had a lower EELV. Furthermore, the lower EELV in the HeO2 vs. room air trials, occurring only when HeO2 breathing significantly reduced flow limitation, provides additional evidence that expiratory flow limitation is the cause of the increase in EELV during heavy exercise.

We believe this is the first study to use room air vs. HeO2 trials to directly determine the effects of flow limitation on the magnitude of the ventilatory response during high-intensity exercise in either men or women. Other studies have noted a higher ventilatory response during exercise with HeO2 vs. room air, but none had data on flow limitation that could be used to explain the differences. At comparable workloads, our subjects had a higher VE only when expiratory flow limitation was reduced with HeO2 vs. room air (Fig. 7), and VE was unaffected by HeO2 at workloads that did not produce expiratory flow limitation during the room air trial (Figs. 7 and 8). Brice and Welch (6) also observed an unchanged VE during moderate exercise when comparing room air vs. HeO2 and a consistently higher VE with HeO2 breathing during heavy exercise, but they did not determine expiratory flow limitation. They speculated that the HeO2 effect on ventilation did not occur during moderate exercise because both room air and HeO2 flows were essentially laminar, and it was only during high-intensity exercise that the more laminar flows with HeO2 breathing significantly decreased airway resistance. However, the similar VE (room air vs. HeO2) in our subjects without flow limitation, even during heavy exercise and at high flow rates (Figs. 7 and 8), would suggest that VE is increased with HeO2 only when flow limitation is reduced. Thus we have consistent evidence that even relatively small amounts of expiratory flow limitation have an inhibitory effect on the magnitude of the ventilatory response during exercise. In contrast, Hussain et al. (18) observed an increased ventilatory response with HeO2 breathing even during moderate exercise when flow limitation was highly unlikely. However, these investigators were also reducing the external apparatus resistance during HeO2 compared with room air breathing, which might explain the HeO2 effect on ventilation at the lower exercise workloads. We added external resistance during the HeO2 trial to attain identical external apparatus resistance to the room air trial. Importantly, we were then able to narrow the scope of the HeO2 effect to address only changes in internal airflow resistance and expiratory flow limitation on the ventilatory response.

Our results showing a marked effect of HeO2 on the ventilatory response during heavy exercise contrast with those using a proportional assist ventilator (PAV) to "unload" the inspiratory muscles. Gallagher and Younes (13) and Younes (34) observed no effect on exercise ventilation even when the load on respiratory muscles was substantially reduced via PAV; these authors speculated that the higher VE previously shown with HeO2 breathing occurs because the He replacement of N2 (in the inspirate) is a stimulus to breathing. However, our data obtained both within and among subjects strongly suggest that reducing flow limitation is required for an HeO2 effect on exercise VE. In contrast, "unloading" with the PAV has no effect on the size of the maximal flow-volume envelope and thus would only help to determine whether the pressure generated by the respiratory muscles might constrain ventilation. In contrast, HeO2 provides only a minimal pressure unloading effect on inspiratory muscles but has a substantial effect on the maximal flow-volume envelope. Accordingly, if the use of HeO2 primarily evaluates the effect of expiratory flow limitation on ventilation, then our findings imply that flow limitation exerted a significant constraint on the ventilatory response to heavy and maximal exercise in fit women.

Consequences of Flow Limitation to Ventilatory Work and Gas Exchange

The increased expiratory flow limitation and relative hyperinflation during heavy exercise in women likely resulted in an increased work and O2 cost of hyperpnea from a combination of factors. First, the smaller VC, resulting in a lower \( V_{t_{\text{max}}} \) and therefore a higher breathing frequency in women, would increase the amount of dead space ventilation. Thus an even higher ventilation is necessary to obtain a similar alveolar ventilation as in men, which would result in a less efficient exercise hyperpnea. Second, a higher breathing frequency with a shortened expiratory time causes higher expiratory flow rates that increase the likelihood and the amount of expiratory flow limitation. Aaron et al. (1) noted that subjects with significant expiratory flow limitation had the highest O2 cost per liter of VE, presumably because of the increase in expiratory resistance and turbulent airflow with more of the tidal breath in a compressed, smaller-diameter airway. Third, the higher EELV caused by the expiratory flow limitation would shorten the initial length of the inspiratory muscles. Accordingly, Johnson et al. (20) reported that the hyperinflation caused by the increases in flow limitation had a significant effect on the fraction of total inspiratory muscle capacity utilized and also caused a significant fall in dynamic compliance at an EEE/TLC of 86%. The highly fit women, with an EEE/TLC of 90% during heavy exercise, would likely have an equal or greater fall in dynamic compliance, and thus an increased elastic load on the inspiratory muscles over a greater portion of the tidal breath. Overall, the less efficient hyperpnea and the higher respiratory muscle O2 requirement in a woman compared with a man would be expected to increase respiratory muscle competition for blood flow and VO2, thereby possibly compromising perfusion to the exercising limb locomotor muscles (15).

Despite the presumed higher work of breathing and associated respiratory muscle O2 cost with hyperinflation caused by the high expiratory flow limitation in a woman during heavy exercise, all of our subjects showed...
a hyperventilatory response that was adequate for CO₂ elimination (Paco₂ < 38 Torr; Fig. 3B). In addition, there was no correlation among our subjects between the amount of expiratory flow limitation and the magnitude of their hyperventilatory response (data not shown). However, we also found a high prevalence of exercise-induced arterial hypoxemia (EIAH) during heavy exercise in our female subjects, which correlated closely with an excessively widened alveolar-arterial O₂ difference (16). From the alveolar air equation, we calculated that given the excessively widened alveolar-arterial O₂ difference, ventilation at VO₂max would have to be over 50 l/min higher to offset the EIAH in our female subjects. This additional ventilation required would exceed both estimates of ventilatory capacity (MVV and V̇Ecap) in our female subjects. However, we cannot be sure that, even if the mechanical constraints on flow limitation were removed, subjects would “choose” to increase ventilation sufficiently to offset the EIAH. For example, the increase in ventilation with HeO₂ at VO₂max (~16 l/min) (Fig. 6) is only about one-third of that required to completely offset the arterial hypoxemia. Accordingly, Dempsey et al. (12) observed in highly fit men that HeO₂ breathing significantly, but not completely, attenuated the EIAH during high-intensity exercise. Overall then, the smaller lung volumes and lower maximal flow rates that create expiratory flow limitation in a fit, exercising woman appear to result in ventilation at V̇O₂max that would exceed both estimates of ventilatory capacity (MVV and V̇Ecap) in our female subjects. However, we cannot be sure that, even if the mechanical constraints on flow limitation were removed, subjects would “choose” to increase ventilation sufficiently to offset the EIAH.

REFERENCES


