Effects of exhaustive endurance exercise on pulmonary gas exchange and airway function in women

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Received 18 December 2000; accepted in final form 10 April 2001

Wetter, Thomas J., Claudette M. St. Croix, David F. Pegelow, David A. Sonetti, and Jerome A. Dempsey.

Effects of exhaustive endurance exercise on pulmonary gas exchange and airway function in women. J Appl Physiol 91: 847–858, 2001.—Seventeen fit women ran to exhaustion (14 ± 4 min) at a constant speed and grade, reaching 95 ± 3% of maximal O2 consumption. Pre- and postexercise lung function, including airway resistance [total respiratory resistance (Rrs)] across a range of oscillation frequencies, was measured, and, on a separate day, airway reactivity was assessed via methacholine challenge. Arterial O2 saturation decreased from 97.6 ± 0.5% at rest to 95.1 ± 1.9% at 1 min and to 92.5 ± 2.6% at exhaustion. Alveolar-arterial O2 difference (A-aDO2) widened to 27 ± 7 Torr after 1 min and was maintained at this level throughout exercise. Arterial PO2 (Pao2) fell to 80 ± 8 Torr at 1 min and then increased to 86 ± 9 Torr at exhaustion. This increase in Pao2 over the exercise duration occurred due to a hyperventilation-induced increase in alveolar PO2 in the presence of a constant A-aDO2. Arterial O2 saturation fell with time because of increasing temperature (+2.6 ± 0.5°C) and progressive metabolic acidosis (arterial pH: 7.39 ± 0.04 at 1 min to 7.26 ± 0.07 at exhaustion). Plasma histamine increased throughout exercise but was inversely correlated with the fall in Pao2 at end exercise. Neither pre- nor postexercise Rrs, frequency dependence of Rrs, nor diffusing capacity for CO correlated with the exercise A-aDO2 or Pao2. Although several subjects had a positive or borderline hyperresponsiveness to methacholine, this reactivity did not correlate with exercise-induced changes in Rrs or exercise-induced arterial hypoxemia. In conclusion, regardless of the degree of exercise-induced arterial hypoxemia at the onset of high-intensity exercise, prolonged exercise to exhaustion had no further deleterious effects on A-aDO2, and the degree of gas exchange impairment was not related to individual differences in small or large airway function or reactivity.

exercise-induced arterial hypoxemia; arterial blood gases; esophageal temperature; respiratory resistance; histamine

EXERCISE-INDUCED ARTERIAL hypoxemia (EIAH), defined as an inability to maintain resting levels of arterial O2 partial pressure (Pao2) and arterial O2 saturation (Sao2) of Hb, occurs in many trained subjects during incremental exercise tests to maximum (13, 18, 37). This condition is primarily due to an excessive alveo-to-arterial O2 difference (A-aDO2) and inadequate compensatory hyperventilation but also to increasing temperature and metabolic acidosis, which cause a rightward shift in the Hb-O2 dissociation curve (14). In susceptible individuals, during brief, high-intensity exercise, Pao2 falls in the first minute of exercise and stays relatively constant over the ensuing 2–4 min, whereas, at the same time, %Sao2 continues to fall as pH decreases (13, 21, 32). Furthermore, EIAH begins to occur even in submaximal exercise in some subjects and often worsens as work rate is further increased (13, 18, 40). During long-term, high-intensity exercise, these influences on pulmonary gas exchange might be altered. For example, in moderate-intensity [65% maximum O2 consumption (VO2 max)], prolonged exercise, ventilation-perfusion (V/Q) inequality was shown to increase with time, and although A-aDO2 did not widen much beyond resting levels and did not worsen over time in this study (20), this might not be the case in higher intensity endurance exercise. On the other hand, EIAH may be lessened in prolonged exercise because hyperventilation is progressive and arterial pH may remain near normal or actually shift in an alkaline direction over time (17).

Airway inflammation and narrowing, leading to abnormal ventilation distribution, could contribute to the widened A-aDO2 seen during incremental exercise. The condition of asthma is characterized by some degree of airflow inflammation, and high rates of ventilation result in a drying of airway mucosal cells and can lead to increases in bronchoconstrictor mediator release (8). Whereas asthmatic subjects typically respond to exercise with large and small airway constriction, perhaps in subjects with EIAH the large airways are protected from bronchoconstriction but smaller peripheral airways are not. Histamine is one inflammatory mediator that has been shown to increase during heavy exercise and that could cause bronchoconstriction at the level of the small airways and/or increase microvascular permeability (2). Both factors could contribute to gas exchange abnormalities. In addition, increases in peripheral airway resistance could constrain ventilation and...
contribute to the inadequate alveolar hyperventilation seen in subjects with EIAH. The differences in susceptibility to EIAH among fit subjects may also be related to differences in airway smooth muscle reactivity. To date, a role for exercise-induced changes in airway resistance has not been evident, as decreases in the maximal flow-volume loop after maximal exercise have not been demonstrated in subjects with EIAH (23). However, this does not rule out a significant role for increased airway reactivity, inflammation, and narrowing of the smaller airways in EIAH (26).

We were interested in the effects of prolonged, constant-speed, high-intensity exercise to exhaustion on EIAH and its components, as this type of exercise bout is more typical of a racelike situation than a progressive, incremental exercise test. We also wondered whether changes in large or small airway resistance or interindividually different in resting (preexercise) airway resistance or airway reactivity might be implicated as causes of an excessively widened A-aDO₂. We, therefore, characterized the development of EIAH and its components over the course of a ~ 15-min constant-speed treadmill exercise bout to exhaustion (mean of 93% ̇Vₒ₂ max) in fit women runners. We also compared pre- versus postexercise changes in lung function, including total respiratory resistance (Rrs) at 5–35 Hz and general airway reactivity to methacholine challenge, with the degree of gas exchange impairment. We hypothesized that EIAH, especially during prolonged, high-intensity exercise, would in part be due to enhanced airway reactivity and exercise-induced changes in airway caliber and resistance.

We used women as our test subjects because 1) less exercise data, including blood-gas data, have been collected in women; 2) EIAH has been observed in some active women with a much lower absolute ̇Vₒ₂ max than in men with EIAH, and some of these women show significant EIAH even during submaximal exercise, possibly due to smaller relative lung and airway size (18, 27, 29); 3) there is some epidemiological evidence that women have greater general airway reactivity compared with men (35, 47).

METHODS

Subjects. Seventeen healthy women (nonsmoking) were recruited to participate in this study. Informed consent was obtained in writing from each subject, and all procedures were approved by the Institutional Review Board of the University of Wisconsin-Madison. All subjects were nonelite runners; however, most competed in local road races. Fourteen considered running their primary physical activity, two were cyclists, and one was a triathlete. Nine of the subjects were on oral contraceptives, and the other eight were tested during the follicular phase of their menstrual cycle. Based on a detailed questionnaire, all subjects were free from cardiopulmonary disease. Two subjects had used bronchodilators (last usage was >2 mo before the study); however, at the time of the study, none was taking medication with the exception of one subject taking allergy medication.

Resting pulmonary function tests. Vital capacity (VC), inspiratory capacity (IC), forced expiratory volume in 1 s (FEV₁), functional residual capacity, and total lung capacity (TLC) were determined as previously reported (28). Lung diffusing capacity for carbon monoxide (DLCO) and residual volume were determined by a single-breath, breath-holding technique (33). Briefly, seated subjects made a maximal inspiration from residual volume of a gas mixture containing 20.9% O₂, 0.5% Ne, 0.4% CO, balance N₂. The breath was held for 10 s and then expired. The first liter of expired gas was discarded, then ~50% of the VC was collected, and Ne and CO concentration was analyzed by gas chromatograph. Measurements were made in triplicate, separated by 5 min, and the average value was recorded. Closing volume was measured by using a standard single-breath N₂ washout procedure (42). Total Rrs was measured by using the forced oscillation technique (Jaeger, MS-IOS), and both room air (all subjects) and helium (11 subjects) were used as the inspired gas (9). Frequency dependence of resistance (Rrs, 5–25 Hz) was calculated as the change in Rrs from 5 to 25 Hz, and resonant frequency was the frequency at which reactance equaled zero. In 13 of the subjects, exhaled nitric oxide (NO) concentration was measured at a constant expiratory airflow rate, as previously described (45). These tests were all performed both before and after exercise.

Exercise protocols. Subjects breathed through a low-resistance, two-way valve (model 2400; Hans Rudolph, Kansas City, MO), and expired gases were sampled at the mouth and after a 8.64-liter mixing chamber via a Perkin-Elmer (Norwalk, CT) mass spectrometer (model 1100). Inspiratory and expiratory flow rates were measured separately by heated pneumotachographs (23). Signals were displayed on a chart recorder, sent through an analog-to-digital board, and sampled on a computer at 75 Hz. Subjects wore a heart rate monitor (Polar Electro, Kempele, Finland).

Initially, subjects completed an incremental ̇Vₒ₂ max exercise test on a treadmill. At a later date, a second treadmill test was conducted at a constant speed and a slight grade, which combined to elicit ~90–95% ̇Vₒ₂ max and could be sustained for ~15 min. DLCO tests were conducted on this day both pre- and ~30 min postexercise. This treadmill test served to familiarize the subjects with the exercise protocol to be conducted while drawing arterial blood. The exercise protocol on the day of blood collection (third exercise test) is depicted in Fig. 1. A 20-gauge arterial catheter (Arrow) was inserted percutaneously in the radial artery of the left arm under local 1% lidocaine anesthesia, and a Mon-a-therm nasopharyngeal temperature probe (Mallinckrodt Medical, St. Louis, MO) was placed intranasally in the lower one-third of the esophageal lumen. After preexercise lung function tests, resting arterial blood samples were collected while subjects breathed through the mouthpiece. After a brief warm-up, subjects ran for 3 min at 50 and 75% ̇Vₒ₂ max, and blood samples were collected during the final 30 s of each workload. The speed and grade of the treadmill were then increased over 30 s to the predetermined high-intensity (~90% ̇Vₒ₂ max) constant work rate (speed 8.0 ± 0.5 mph, grade 2.6 ± 0.8%). Subjects were instructed and encouraged to run as long as possible. Arterial blood was collected every 2 min beginning at minute 1 and also at exhaustion (minutes 1, 3, 5, . . . , final 30 s of exercise). After an ~30-min rest, during which time postexercise pulmonary function tests were performed, subjects again ran for 3 min at the same constant ~90% workload, after which time the grade was increased by 2–4% to bring the subjects to ̇Vₒ₂ max, and they ran until exhaustion (time at final workload = 95 ± 30 s).

On the day of blood collection, ambient temperature was 23 ± 1°C, barometric pressure was 732 ± 5 mmHg, and a 16-in. fan cooled subjects during the exercise bout.
Blood gas, body temperature, blood lactate, and plasma histamine measurements. Samples (3–5 ml) of arterial blood were drawn anerobically over 10–20 s during each trial for measurement of PO2, PCO2, and pH with a blood-gas analyzer calibrated with tonometered blood (ABL300, Radiometer), and sample of O2 saturation and Hb were measured with a CO-oximeter (OSM 3, Radiometer). Calculated SaO2 values (based on measured PaO2 and changes in body temperature and pH) were essentially identical to measured SaO2, [r = 0.96; where calculated SaO2 = 0.998 (CO-oximeter %SaO2) + 0.048]. Blood gases were corrected for body temperature changes during exercise. The alveolar O2 partial pressure (P[O2]) was estimated by using the ideal alveolar gas equation (34). Blood lactate concentration was analyzed by means of a Yellow Springs Instruments lactate analyzer (model 1500 (34). Blood lactate concentration was analyzed by means of a Yeo

Hematocrit was determined by microcentrifuge. Blood samples for histamine were drawn into tubes with EDTA and immediately placed on ice until centrifugation. Plasma was harvested and stored at 70°C until analysis with an enzyme immunoassay kit (Immunotech, Marseille, France).

Methacholine challenge test. A methacholine challenge test (MCT) was done to test for an association between general airway reactivity to a bronchoconstrictor agent and exercise-induced changes in airway function or the development of EIAH or a widened A-aDO2. This test was done on a separate day in 16 of the subjects following American Thoracic Society guidelines (3). A DeVilbiss nebulizer (model 646) and Rosenthal dosimeter were used to administer methacholine chloride (Provocholine, Methapharm). A five-breath dosimeter protocol was used, and doses of saline that were 0.0625, 0.25, 1, 4, 16, and 32 mg/ml of methacholine were administered. Output of the nebulizer was 0.009 ml/breath with a 0.6-s activation. Subjects breathed in to TLC and held each breath for ~5 s. The time interval between doses was kept at 5 min. At baseline and between each dose, measures of Rrs were made first, as this method has been shown to be a more sensitive test compared with FEV1 to measure changes in bronchial tone (36, 43) and avoids a lung volume history, which might reverse a bronchoconstriction effect. This was followed by the conventional FEV1 measure and then IC measurement as an indication of the functional significance of the bronchoconstriction (i.e., changes in end-expiratory lung volume). Exhaled NO was measured last. If and when a >20% fall (from the saline dose) in FEV1 occurred, the FEV1 maneuver was repeated one to two times. If the FEV1 fell more than 20%, the dosing protocol was stopped, a bronchodilator (albuterol) administered, and tests repeated to ensure recovery from bronchoconstriction.

Statistical analysis. Subjects were divided into two groups based on the PaO2 maintained during the high-intensity prolonged exercise bout to exhaustion (the mean PaO2 value of minute 1 through the end value was calculated for each individual) and labeled according to low PaO2 (~80 Torr; Lo-PaO2, n = 8) and high PaO2 (~100 Torr; Hi-PaO2, n = 8). This categorization is similar to the >10-Torr fall in PaO2 from resting values used previously during an incremental maximal exercise test (18) but is less influenced by hyper- or hypoventilation at rest. Seven of eight subjects in Lo-PaO2 and none in Hi-PaO2 had a mean PaO2 decrease of >10 Torr from rest during the exercise bout. Repeated-measures two-way ANOVA was used to compare mean values for each group across time. If a main effect (group or time) or interaction (group × time) was observed, Tukey’s post hoc analysis was used to determine where the differences existed. For analysis of data conducted at different exercise intensities, intensity replaced time as the factor. Linear regression was used to establish correlations. Significance was set at P < 0.05. Data are presented as means ± SD.

RESULTS

General data. Subjects’ physical and resting lung function characteristics are shown in Table 1. VO2 max

Table 1. Subject characteristics and resting pulmonary function

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>Height, cm</th>
<th>Weight, kg</th>
<th>VO2max, ml·kg⁻¹·min⁻¹</th>
<th>TLC, liters</th>
<th>VC, liters</th>
<th>FRC, liters</th>
<th>FEV1, liters</th>
<th>MVV15, l/min</th>
<th>Rrs 5 Hz, cmH2O·l⁻¹·s⁻¹</th>
<th>[Hb], g/dl</th>
<th>DLCO, ml·min⁻¹·mmHg⁻¹</th>
<th>% Predicted</th>
</tr>
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<tbody>
<tr>
<td>27 ± 7</td>
<td>166 ± 7</td>
<td>55 ± 6</td>
<td>50 ± 4</td>
<td>5.4 ± 0.5</td>
<td>3.9 ± 0.4</td>
<td>3.2 ± 0.3</td>
<td>122 ± 23</td>
<td>9.8 ± 1.0</td>
<td>13.4 ± 1.2</td>
<td>280 ± 3.4</td>
<td>91 ± 11</td>
<td></td>
</tr>
<tr>
<td>19–44</td>
<td>152–178</td>
<td>46–68</td>
<td>44–56</td>
<td>4.5–6.1</td>
<td>3.3–4.7</td>
<td>2.6–4.0</td>
<td>95–173</td>
<td>2.8–8.7</td>
<td>11.3–15.1</td>
<td>22.2–34.2</td>
<td>11 ± 9</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>134 ± 15*</td>
<td>102 ± 10</td>
<td>101 ± 11</td>
<td>102 ± 11</td>
<td>128 ± 25*</td>
<td>91 ± 11*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n = 17. VO2max, maximal oxygen consumption; TLC, total lung capacity; VC, vital capacity; FRC, functional residual capacity; FEV1, forced expiratory volume in 1 s; MVV15, maximal voluntary ventilation in 15 s; Rrs 5 Hz, total respiratory resistance at a frequency of 5 Hz; [Hb], hemoglobin concentration; DLCO, diffusing capacity for CO (not adjusted to a constant Hb value). Adjusted to Hb = 14.6 mg/dl, DLCO would be 29.2 ± 3.1 ml·min⁻¹·mmHg⁻¹. Prediction equations are from Knudson et al. (24) for DLCO; Drinkwater et al. (15) for VO2max; Crape et al. (12) for TLC, VC, and FRC; Knudson et al. (25) for FEV1; and Baldwin et al. (6) for MVV.

*Predicted value significantly different than obtained value (P < 0.05).
was ~30% above predicted values, whereas DL\textsubscript{CO} was ~9% lower ($P = 0.003$) than predicted. Maximal voluntary ventilation in 15 s was also ~30% above predicted using a prediction equation based on age and body surface area (BSA); however, with the use of another common predictor (FEV\textsubscript{1} × 40), this fell to 95 ± 15% of predicted.

**Prolonged exercise data.** Individual and group mean data collected at rest and during the high-intensity exercise bout to exhaustion are presented in Figs. 2–4. Blood-gas data revealed a rapid fall in PaO\textsubscript{2}, a widening of A-aDO\textsubscript{2}, and a progressive decline in arterial P\textsubscript{CO\textsubscript{2}} (P\textsubscript{ACO\textsubscript{2}}) on initiation of exercise. Throughout the duration of exercise, PaO\textsubscript{2} increased slightly as PaO\textsubscript{2} rose (107 ± 3 Torr at minute 1 to 112 ± 3 Torr at exhaustion), and P\textsubscript{ACO\textsubscript{2}} fell and A-aDO\textsubscript{2} remained relatively unchanged over the duration of the exercise. Overall mean SaO\textsubscript{2} declined by 2.5 ± 1.9% at minute 1 and fell further throughout exercise to a nadir of 92.5 ± 2.6% at exhaustion (range 86.2–95.6%). In subjects with lower mean PaO\textsubscript{2} values (Lo-P\textsubscript{O\textsubscript{2}}), differences in SaO\textsubscript{2}, P\textsubscript{AO\textsubscript{2}}, and A-aDO\textsubscript{2} from Hi-P\textsubscript{O\textsubscript{2}} were apparent early in the exercise bout (by 1–3 min), but the patterns of change over time were similar, although subjects in Lo-P\textsubscript{O\textsubscript{2}} had a reduced rise in PaO\textsubscript{2} from minute 1 to exhaustion. Although mean P\textsubscript{ACO\textsubscript{2}} did not differ between groups, the decrease over time was greater in Hi-P\textsubscript{O\textsubscript{2}} as was the increase in minute ventilation/O\textsubscript{2} consumption (V\textsubscript{O\textsubscript{2}}).

A-aDO\textsubscript{2} explained 93% of the variance in PaO\textsubscript{2} ($P < 0.001$), whereas the correlation with P\textsubscript{ACO\textsubscript{2}} was also significant ($P = 0.017$) but explained less (33%) of the variance (Fig. 5, A and B). The major differences in arterial oxygenation and gas exchange that occurred among subjects at the point of exhaustion were already present near the onset of high-intensity endurance exercise. A-aDO\textsubscript{2} and PaO\textsubscript{2} were not significantly correlated to V\textsubscript{O\textsubscript{2}}\textsubscript{max} ($r = 0.02, P = 0.93$) in this group of runners with a narrow range of V\textsubscript{O\textsubscript{2}}\textsubscript{max} values (44–56 ml·kg\textsuperscript{-1}·min\textsuperscript{-1}).

Metabolic and heart rate data were similar between Lo-P\textsubscript{O\textsubscript{2}} and Hi-P\textsubscript{O\textsubscript{2}}, both in terms of absolute values and changes over exercise time (Figs. 3 and 4). V\textsubscript{O\textsubscript{2}} increased throughout the first 7 min of exercise, peaked at 95 ± 3% of V\textsubscript{O\textsubscript{2}}\textsubscript{max}, and then remained stable until exhaustion (range 87–99% of V\textsubscript{O\textsubscript{2}}\textsubscript{max}). V\textsubscript{O\textsubscript{2}} did not differ between groups. CO\textsubscript{2} production also increased from 2.46 ± 0.35 l/min at minute 1 to 2.93 ± 0.42 l/min at exhaustion. Heart rate increased from 60 ± 12 beats/min at rest to 171 ± 15 beats/min at minute 1 and 189 ± 12 beats/min at exhaustion. The increase in minute ventilation over time was due predominantly to increased breathing frequency as tidal volume reached a maximum of 51 ± 8% of VC (range 33–71%) during minute 7 before decreasing slightly over the remaining time to exhaustion.

Over the time of the exercise bout, pH fell progressively due to a steady but highly variable 2–8 mmol/l.
Fig. 3. O₂ consumption (\( \dot{V}O_2; A \)), minute ventilation (\( \dot{V}E; B \)), and breathing frequency (bf; C) at rest and during the \(-90\% V_{O2\max}\) exercise bout to exhaustion. Lines and symbols are as defined in Fig. 2 legend. Values are means ± SD. *Significant difference between groups (\( P < 0.05 \)). Time effect was significant (\( P < 0.001 \)) for all variables.

Fig. 4. Arterial pH (\( pH_a; A \)), arterial lactate (lactate\(_a; B \)), and esophageal body temperature (temp\(_{es}; C \)) at rest and during the \(-90\% V_{O2\max}\) exercise bout to exhaustion. Lines and symbols are as defined in Fig. 2 legend. Values are means ± SD. Time effect was significant (\( P < 0.001 \)) for all variables.
rise in blood lactate, which was partially compensated by the steady fall in PaCO2. Esophageal temperature was 36.9 ± 0.3°C at rest, increased to 37.3 ± 0.4°C after the warm-up period, and then increased to 37.7 ± 0.4°C at minute 1 and 39.5 ± 0.4°C at exhaustion (range 39.0–40.3°C). The pattern of temperature increase with exercise duration was similar among subjects; however, the range of absolute values was ±1.3°C at all exercise time points.

The amount of hemoconcentration from rest to exhaustion was 1.4 ± 0.2 g/dl with the majority (1.0 ± 0.2 g/dl) occurring by minute 1 (no difference between Hi-PO2 and Lo-PO2). As a result of this and the decrease in %SaO2, arterial O2 content increased from 17.4 ± 1.5 and 18.0 ± 1.6 g/dl at rest to 18.0 ± 1.2 and 19.2 ± 1.5 g/dl at exhaustion in Lo-PO2 and Hi-PO2, respectively.

Plasma histamine was significantly increased from rest to minute 3 and further increased at end exercise (137 ± 96% above resting values). Values ranged between 2 and 8 nmol/l at exhaustion, and all returned toward resting levels during recovery (Fig. 6). The mean PaO2 maintained during exercise was positively correlated to end-exercise histamine level (Fig. 5C), and this relationship was of borderline significance (P = 0.051) when the changes in PaO2 and histamine from rest to end exercise were correlated (Fig. 5D).

**Causes of O2 desaturation during exercise.** For the Lo-PO2 group, we partitioned the amount of the total fall in SaO2 from rest at 3 min (4.7 ± 1.8%) and at exhaustion (6.7 ± 2.7%) due to the effects of PaO2, pH, and temperature. For the initial (rest to minute 3) fall in SaO2, the 21 ± 8 Torr drop in PaO2 was the most significant factor, accounting for 65 ± 7% of the decrease in SaO2. From 3 min to end exercise, the contri-
cise at 100% of $\dot{V}O_2\text{ max}$ in Lo-P $O_2$ and Hi-P $O_2$ groups.

6 $\text{mean } SaO_2, P\text{a}O_2, A-aDO_2, P\text{a}CO_2, \text{pH, and esophageal temperature at 3 min of exercise at 50, 75, and 90}^6$

11% of the $Hb-O_2$ desaturation from resting values was caused by the combination of metabolic acidosis (decrease of 0.14

11% $\text{pH accounted for the entire remaining decrease in } SaO_2$

11% due to increasing temperature and decreasing pH accounted for the entire remaining decrease in $SaO_2$ that occurred over time. At the end point of prolonged exercise, $54 \pm 11\%$ of the $Hb-O_2$ desaturation from resting values was caused by the combination of metabolic acidosis (decrease of $0.14 \pm 0.08 \text{ pH units}$) and a $2.5 \pm 0.5^\circ\text{C}$ rise in temperature, and the remainder ($46 \pm 11\%$) was due to a $17 \pm 9 \text{Torr}$ decrease in $Pao_2$.

Effects of exercise intensity on $EIAH$. Figure 7 shows mean $SaO_2, Pao_2, A-aDO_2, Paco_2, \text{pH, and esophageal temperature at 3 min of exercise at 50, 75, and 90}^6$ $VO_2\text{ max and during a shorter bout (95 \pm 30 s) of exercise at 100\% of } VO_2\text{ max in Lo-Po2 and Hi-Po2 groups (categorized based on } Pao_2 \text{ during 90\% prolonged exercise).}$

The most notable findings were that, by $75\%$ of $VO_2\text{ max}$, $Paco_2$ was already significantly lower and $A-aDO_2$ wider in those subjects who showed the most $EIAH$ during prolonged exercise (i.e., Lo-Po2 group).

Changes in lung function after exercise and correlation to $EIAH$. Pre- and postexercise lung function tests are shown in Table 2. Preexercise $Rrs$ varied considerably among subjects ($2\text{–}9 \text{cmH}_2O^{-1}\text{.l}^{-1}\text{.s}$), and individual changes in $Rrs$ after exercise were highly variable. $Rrs$ at all frequencies fell in four subjects and was unchanged (changes of $\leq 1 \text{cmH}_2O^{-1}\text{.l}^{-1}\text{.s}$) in the others. The higher the preexercise $Rrs$, the greater the fall in $Rrs$ after exercise ($r = 0.42, P = 0.096$) and low $Pao_2$ ($r = -0.41; P = 0.105$). It was not related to differences in $Paco_2$.

The frequency dependence of $Rrs$ was also not affected by exercise and did not correlate with exercise blood-gas variables. Substituting helium for room air caused $Rrs$ to fall by $17 \text{Torr decrease in PaO}_2$. The slope of the $N_2$ washout was inversely correlated to exercise $SaO_2$ ($r = -0.485; P = 0.036$) and low $Pao_2$ ($r = -0.53, P = 0.002$), but this was primarily due to large decreases in two subjects with high preexercise $Rrs$ values. Neither pre- nor postexercise $Rrs$ was correlated with the exercise $A-aDO_2$, $Paco_2$; however, there was a trend for an increase in $Rrs$ after exercise to be related to a wide $A-aDO_2$ ($r = 0.42; P = 0.096$) and low $Pao_2$ ($r = -0.41; P = 0.105$). It was not related to differences in $Paco_2$.

Baseline $FEV_1$ (%predicted) was correlated to nadir exercise $SaO_2$ ($r = 0.567; P = 0.018$) and to $Pao_2$ ($r = 0.589; P = 0.002$). The slope of the $N_2$ washout was inversely correlated to exercise $SaO_2$ ($r = -0.736; P = 0.002$) and positively with $A-aDO_2$ ($r = 0.550; P = 0.034$). VC (%predicted) was negatively associated with $A-aDO_2$ ($r = 0.485, P = 0.048$), and forced VC (%predicted) with $PaO_2$ ($r = 0.511; P = 0.036$). No other resting lung function measures correlated with the degree of hypoxemia.

### Table 2. Pre- and postexercise lung function

<table>
<thead>
<tr>
<th>Preexercise</th>
<th>Postexercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Rrs$, air, at 5 Hz, cmH$_2$O·l$^{-1}$·s$^{-1}$</td>
<td>4.86 ± 1.64</td>
</tr>
<tr>
<td>$\Delta Rrs$, air, 5-25 Hz, cmH$_2$O·l$^{-1}$·s$^{-1}$</td>
<td>0.75 ± 0.93</td>
</tr>
<tr>
<td>$Rrs$, helium, at 5 Hz, cmH$_2$O·l$^{-1}$·s$^{-1}$</td>
<td>4.01 ± 1.48</td>
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<tr>
<td>$\Delta Rrs$, helium, 5-25 Hz, cmH$_2$O·l$^{-1}$·s$^{-1}$</td>
<td>1.02 ± 0.48</td>
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<tr>
<td>Resonant frequency, Hz</td>
<td>12.6 ± 5.3</td>
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<tr>
<td>$DlCO$, ml·min$^{-1}$·mmHg$^{-1}$</td>
<td>28.3 ± 3.8</td>
</tr>
<tr>
<td>FRC, liters</td>
<td>2.77 ± 0.53</td>
</tr>
<tr>
<td>RV, liters</td>
<td>1.70 ± 0.28</td>
</tr>
<tr>
<td>$N_2$ slope, %N$_2$/liter</td>
<td>1.25 ± 0.53</td>
</tr>
<tr>
<td>Closing volume, liters</td>
<td>0.24 ± 0.13</td>
</tr>
<tr>
<td>$[[NO]_{CF}$, ppb</td>
<td>19 ± 10</td>
</tr>
<tr>
<td>$FEV_1$, liters</td>
<td>3.38 ± 0.38</td>
</tr>
<tr>
<td>$FVC$, liters</td>
<td>4.16 ± 0.39</td>
</tr>
</tbody>
</table>

Values are means ± SD; $n = 17$, unless otherwise indicated. $Rrs$ ($n = 17$ for air, $n = 11$ for helium); $\Delta$, change; $FVC$, forced vital capacity; $RV$, residual volume; $N_2$ slope, nitrogen washout slope ($n = 15$); $[[NO]_{CF}$, exhaled breath nitric oxide concentration measured at a constant expiratory flow rate ($n = 11$). $^a$Significantly different from pre-exercise value ($P < 0.05$).
Airway reactivity to methacholine. Individual values for FEV₁, Rrs, and IC during the MCT are presented in Fig. 8. With the use of the clinical definition of the concentration of methacholine causing a 20% fall in FEV₁ (PC₂₀), 2 of 16 subjects would be classified as having a positive MCT (PC₂₀ < 4 mg/ml), and three additional subjects would be considered to have borderline bronchial hyperresponsiveness (PC₂₀ = 4–16 mg/ml). The rest had normal bronchial responsiveness (PC₂₀ > 16 mg/ml). We also calculated 95% confidence intervals for both Rrs and FEV₁ values in each subject based on repeated baseline measurements conducted on the various test days (n = 4–12 values). We then determined the dose of methacholine that caused a significant change in Rrs or FEV₁ (i.e., one that exceeded the 95% confidence interval). Seven subjects had a measurable change in Rrs before (at a lower dose) FEV₁ changed; in four, Rrs and FEV₁ changed at the same dose; and in five, FEV₁ changed at a lower dose. Rrs of 5–25 Hz changed in response to the MCT in a similar manner across subjects as did Rrs at 5 Hz. A fall in IC was related to the increase in Rrs. IC decreased from 2.41 ± 0.51 liters at baseline to 2.12 ± 0.46 liters after the final methacholine dose; it also decreased to a greater extent in those subjects who had a positive or borderline response to the methacholine (decrease of 23 ± 11% from baseline to final dose compared with a decrease of 8 ± 7% in the subjects with a normal response). Constant-flow expiratory NO concentration did not change in response to any dose of methacholine.

Response to methacholine did not predict EIAH. There was no relationship between the percent decline in FEV₁ or increase in Rrs at 5 Hz during the MCT and exercise PaO₂ or A-aD O₂ (r ≤ 0.1, P > 0.6). In addition, exercise-induced changes in Rrs and FEV₁ were not related to bronchial hyperresponsiveness to methacholine in our group of subjects. Five subjects had a >1 cmH₂O-l⁻¹-s increase in Rrs at a methacholine dose of 4 mg/ml; in these same subjects, the change in Rrs pre- to postexercise was a fall of between 0.3 and 2.0 cmH₂O-l⁻¹-s.

DISCUSSION

The purpose of this study was to determine the time course of SaO₂ and gas exchange during prolonged, constant work rate, high-intensity running exercise to exhaustion and to evaluate baseline and changes in pre- to postexercise lung function, including airway resistance, in relation to EIAH. At the first minute of exercise, PaO₂ fell 14 Torr from rest and A-aD O₂ widened to 27 Torr; at the same time, PaCO₂ was nearly unchanged from rest. After the initial fall, PaO₂ rose slightly as PaO₂ increased with the onset of hyperventilation, and there was no further worsening of pulmonary gas exchange (as evidenced by a constant A-aD O₂) over the exercise time. SaO₂ continued to fall throughout the exercise bout, indicating the importance of a time-related decrease in pH and increasing temperature at any given PaO₂. Changes in large or small
airway function with exercise and airway responsiveness to methacholine were not related to the development or degree of EIAH or gas exchange impairment. This lack of correlation existed despite the fact that several subjects had high baseline airway resistance and/or bronchial hyperresponsiveness to methacholine.

Comparison with previous “prolonged” constant-workload studies. Many studies have examined EIAH by using an incremental exercise protocol or very short-term heavy exercise; however, there have been relatively few studies that have examined the time course of EIAH or gas exchange during a constant-workload exercise bout lasting >5 min, and none of these has been conducted with female subjects. The studies that have been done were conducted at lower intensities and over a longer exercise time than the present study (17, 20, 46, 48). In each of these studies, arterial desaturation was generally absent as PaO₂ did not fall >5 Torr on initiation of exercise and typically rose slightly across the exercise time, whereas A-aDO₂ ranged between 10 and 25 Torr, and in only one of the studies (48) did it worsen over time. Interestingly, most of the subjects in the Dempsey et al. study (13) who showed no EIAH during long-term, moderate-intensity exercise did desaturate significantly during short-term maximal exercise. In the present study, high-intensity, prolonged exercise elicited significant gas exchange impairment and EIAH in approximately one-half of the subjects.

Relative contributions of PaO₂, pH, and temperature to the fall in SaO₂. The fall in PaO₂ that occurred in the rest-to-exercise transition accounted for the majority of the decreased SaO₂ early in the exercise bout. However, in most subjects, PaO₂ then rose slightly over the course of exercise, and the further fall in SaO₂ was completely due to decreasing pH and increasing temperature and the resultant rightward shift of the Hb-O₂ dissociation curve.

Individual variations in temperature, pH, and PaO₂ can greatly affect SaO₂. Esophageal temperature increased to ≥39°C in all subjects and in two reached ≥40.0°C at exhaustion. This temperature increase is higher than what is typically seen during an incremental exercise test (38.2°C in Ref. 18) and is likely the result of a greater amount of time spent near maximal effort. Changes in the pH of arterial blood were more varied, falling only slightly in some and to <7.20 in several others. What is the effect of differences in pH and temperature in subjects with similar PaO₂ and A-aDO₂ values on SaO₂? Two subjects maintained an A-aDO₂ of ~28 Torr and a PaO₂ of ~80 Torr, but their pH fell to ≤7.20 and body temperature rose to 40°C. In these subjects, SaO₂ decreased to ≤90% at exhaustion. In contrast, two other subjects with a wider A-aDO₂ (~34 Torr) and a lower PaO₂ (~77 Torr), but whose pH remained >7.33 and temperature rose to only 39.5°C, had an SaO₂ at end exercise of 93–94%. Thus, whereas PaO₂ remains the primary determinant of SaO₂, the influence of individual differences in changes in pH and body temperature during exercise and the importance of changes in these variables over exercise time should not be overlooked. The effects of pH on desaturation in rows during high-intensity exercise have been stressed previously (32).

Correlation of EIAH with resting lung function. Our resting spirometry values were within normal ranges. DLCO was slightly below predicted values based on equations by Knudson et al. (24) and also by Crapo and Morris (11). The absolute values for DLCO and for DLCO/V̇A of our female subjects were nearly identical to those found in similar groups of fit female subjects (18, 19).

Hopkins et al. (20) found that the development of V̇A/Q̇ inequality during exercise (as measured by the log SD of Q distribution during the multiple inert-gas elimination technique) was significantly correlated with the ratio of TLC to BSA (TLC/BSA) and hypothesized that perhaps people with a smaller relative lung size would have smaller airways and blood vessels and that this could accentuate any regional inhomogeneities in the distribution of air and blood flow (20). We found no relationship between A-aDO₂ and TLC/BSA (r = 0.166; P = 0.525), nor was a relationship found in the study by Harms et al. (18), which included 29 female subjects with a wide range of EIAH at V̇O₂ max. Despite this, in the present study, several other measures of lung size or function (VC, FVC, and FEV₁) were weakly (r < 0.6; see RESULTS), but significantly, correlated with the A-aDO₂ or PaO₂ during exercise. Therefore, it is unclear what, if any, role lung size has in explaining EIAH in healthy subjects. We emphasize that a lack of correlation between lung size and EIAH does not contradict the positive correlation reported of lung size to exercise V̇A/Q̇ uniformity, because overall mean V̇A/Q̇ rises substantially during exercise, thereby negating much of the effect of V̇A/Q̇ nonuniformity on arterial oxygenation.

Airways and EIAH. Our rationale for studying the role of small airway reactivity and small airway resistance in EIAH was threefold. First, we reasoned that V̇A/Q̇ maldistribution was a potential contributor to the widened A-aDO₂ in persons with EIAH because, in both fit men (13, 41) and especially in female subjects (18), an excessive A-aDO₂ was already obvious, even in mild-to-moderate-intensity exercise. These changes are unlikely to be attributable to diffusion limitation at these lower metabolic requirements; however, we wish to emphasize that diffusion limitation is a very likely contributor to EIAH and excessive A-aDO₂ during high-intensity and maximal exercise intensities (41). Second, a recent study using pharmacological blockade also pointed to airway inflammation as a potential cause of the widened A-aDO₂ in EIAH, at least in older, fit subjects (38). Thus airway resistance changes may be involved. However, in normal subjects, tests of large airway resistance, namely the expiratory flow-volume loop or FEV₁, show no effect of maximum exercise; in fact bronchodilation is most often observed both during and after exercise (8), even in the presence of severe EIAH (23). Therefore, we reasoned that small or peripheral airway diameters might be compromised with...
heavy exercise, thereby creating a maldistribution of mechanical time constants and of inspired ventilation (26). Finally, we also suspected that even relatively small increases in airway resistance may be especially important in women who, in general, have smaller airway diameters and lung volumes relative to men of similar age and stature (4, 29). This hypothesis was tested by using the forced oscillation technique to measure Rrs under physiological conditions with tidal breathing. The frequency dependence of Rrs (5–25 Hz) has been shown to be sensitive to selective increases in small airway resistance and to correlate highly with frequency dependence of compliance, especially when He-O2 is used as an inspirate (9). Change in the phase III of the single-breath N2 test was also used to document any exercise-induced changes in the distribution of inspired gas (10). On the other hand, there are several limitations to these methods. These tests were conducted postexercise, and, therefore, any changes apparent during exercise may have resolved in the recovering, resting subjects.

Our findings did reveal several subjects with abnormally elevated baseline Rrs and/or frequency dependence of Rrs, steep slopes of the phase III single-breath N2 test, and abnormal airway reactivity. Nonetheless, the findings were also consistent in demonstrating that exhaustive, prolonged exercise per se had no measurable deleterious effect on large or small airway function in any subject, nor was the absolute level of airway resistance or airway reactivity a significant determinant of the exercise-induced widening of the A-aDO2 or of EIAH.

We consider these mostly negative data concerning the relationships of airway resistance to EIAH as follows. For the high baseline Rrs subjects, it is feasible that these airway resistances were simply not sufficiently elevated to cause enough maldistribution of mechanical time constants to effect distribution of ventilation. Alternatively, moderate-to-heavy-intensity exercise with augmented tidal volumes will promote bronchodilation because of the tethering effects of the increased traction created by parenchymal attachments to the airway (44). Indeed, this lung-to-airway mechanical interaction at high tidal volume has also recently been shown to reduce the force generation by activated airway smooth muscle (16), and exercise-induced bronchodilation also occurs conversely secondary to a changing neurochemical control of bronchiolar smooth muscle (8). Furthermore, increases in inspiratory flow rate have been shown to elicit a more uniform topographical distribution of ventilation (5), and this influence may have been sufficient during heavy exercise, when peak flow rates increase 10 times or more and tidal volume is four to five times higher than at rest, to overcome these interindividual differences in Rrs. Certainly, the lack of exercise-induced increases in frequency dependence of Rrs may also reflect our inability with an indirect measurement to detect differences in the “silent zone” of the lung periphery until a very large number of these peripheral airways are compromised (9, 26).

MCT. Five of sixteen subjects had a positive MCT or were classified with borderline hyperresponsiveness. These responses to methacholine, whether measured in terms of Rrs or FEV1, did not correlate with changes in Rrs or FEV1 that occurred pre- to postexercise. In addition, the bronchoconstriction associated with the MCT did not correlate with the amount of hypoxemia present during exercise. As none of our subjects had any significant amount of bronchoconstriction (measured either with Rrs or FEV1) after exercise, this lack of correlation is not surprising. The finding that subjects with hyperreactive airways did not respond to exercise in a similar manner as they did to methacholine has also been reported by others (1) and may reflect the fact that even exhaustive exercise (at least in the nonasthmatic subject) does not involve sufficient bronchoprovocation via release of inflammatory mediators to cause measurable changes in central or peripheral airway diameter.

Histamine and EIAH. Histamine is an inflammatory mediator that can induce airway bronchoconstriction via effects on smooth muscle but also is known to increase vascular permeability (7). Plasma histamine has also been found to be significantly higher in athletes compared with sedentary controls at the end of a maximal exercise bout (2). Furthermore, a significant correlation between histamine release (%H = plasma histamine as a percentage of whole blood histamine) and the degree of hypoxemia implicates a possible role for this inflammatory mediator in the exercise-induced fall in PaO2 (2, 31). Because histamine in the circulation likely reflects basophil release to a much greater extent than lung mast cell release, is complicated by a very short half-life, and is possibly released during centrifugation, it is unclear whether histamine is causal or only indirectly related to EIAH (7, 22, 30, 39).

In our subjects, mean plasma histamine concentration increased with time over the course of the constant work rate exercise bout, and the absolute concentration and change from rest was similar (2) or slightly higher (31) at exhaustion to values found in athletes at the end of an incremental maximal exercise test. In contrast to previous studies, subjects in the present study with the greatest amount of hypoxemia tended to have a lower, not higher, plasma histamine concentration (see Fig. 5, C and D). A confounding factor may be differences in subject selection; all subjects in the present study were athletes of comparable fitness levels, whereas Anselme et al. (2) compared highly trained athletes with sedentary subjects. Thus the corresponding work rates (and potentially other factors such as time of exercise, body temperature, pH, etc.) at maximal exercise were different between those two groups. Both previous studies did find significant correlations with the change in %H from rest to maximal exercise and the drop in PaO2 in their highly trained athletes. The meaning of %H is unclear as changes in %H from rest to maximal exercise are primarily due to changes in plasma histamine because whole blood histamine remains relatively unchanged (31) or increases during exercise (2). Furthermore, %H remained un-
changed across exercise intensities of 50–100% of \( V_{O2 \text{max}} \) (31). Given this, it is unclear why %H correlates with EIAH. Perhaps %H is simply a marker for “leaky basophils,” which in turn is correlated with an increased permeability of the pulmonary vasculature. The association between a reduction in %H and a reduction in the widening of the A-aDO2 and fall in PaO2 during exercise with the administration of nedocromil sodium provides indirect evidence for at least a partial causative role for histamine in EIAH (38); however, other possibilities exist. Because nedocromil sodium acts as a general mast cell stabilizer, it does not only block histamine release. Reduction of other potential inflammatory mediators (e.g., leukotrienes or prostaglandins) could have been responsible for the improvement in EIAH.

Finally, the findings of the present study show a rapid widening of the A-aDO2 immediately on onset of high-intensity exercise, with no further widening over the remaining exercise time to exhaustion. These data cast doubt on an inflammatory mechanism for EIAH simply because of the speed and stability of the occurrence of EIAH. Certainly, the role of histamine or other inflammatory mediators in EIAH remains in question, at least those mediators whose release would be influenced by increased flow and shear rates in both the airways and the pulmonary vasculature.

In summary, we demonstrated that continuing, high-intensity exercise, beyond the initial few minutes, has little further effect on gas exchange and that a continued fall in \( S_aO_2 \) is due to the combined effects of decreasing pH and increasing body temperature. We also confirmed that subjects with the greatest degree of EIAH during high-intensity exercise begin to show significant gas exchange abnormalities even during moderate-intensity exercise. We found that several of these fit subjects had high baseline airway resistance and hyperreactive airway responses to bronchoprovocation; however, airway resistance or its frequency dependence was not increased by prolonged, high-intensity exercise, nor was EIAH correlated with airway resistance or its reactivity. The reason why gas exchange impairment during exercise occurs in some subjects remains unanswered; whatever the cause, it becomes apparent early during high-intensity exercise and does not worsen over time.

We thank our subjects for enthusiastic participation in this study. Special thanks to Matt O’Brien for technical assistance with methacholine dosing, Dr. Keith Meyer for medical assistance, and Zhuzai Xiang for analysis of histamine samples. Support for this project was provided by National Heart, Lung, and Blood Institute (NHLBI) Grant RO1 HL-15469 and jointly by the US Departments of Veterans Affairs and Defense. T. J. Wetter was supported by a NHLBI training grant.

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