Effects of prior exercise on exercise-induced arterial hypoxemia in young women

CLAUDETTE M. ST. CROIX, CRAIG A. HARMS, STEVEN R. MCCCLARAN, GLENN A. NICKELE, DAVID F. PEGELOW, WILLIAM B. NELSON, AND JEROME A. DEMPSEY

John Rankin Laboratory of Pulmonary Medicine, Department of Preventive Medicine, University of Wisconsin, Madison, Wisconsin 53705

AN EXCESSIVE WIDENING of the alveolar-arterial O₂ difference (A-aDO₂), which leads to exercise-induced arterial hypoxemia (EIAH), occurs during severe exercise in many highly fit humans (7, 25) and in the Thoroughbred horse (2, 31). This failure of homeostasis may occur as a result of functionally based mechanisms that are present only during the exercise period, such as a transient maldistribution of alveolar ventilation-to-pulmonary capillary flow ratio (VA/Qc) and/or alveolar-capillary diffusion disequilibrium. For example, a mismatch of increased cardiac output with expansion of the pulmonary capillary vasculature might cause diffusion disequilibrium during exercise via a markedly reduced red blood cell transit time in the lung (7, 15). On the other hand, recent evidence points to structural changes at the alveolar-capillary interface induced by heavy exercise. Such structurally based mechanisms for EIAH may have long-lasting effects.

EIAH and pulmonary hemorrhage have been shown to occur in Thoroughbred racehorses during severe exercise, presumably as a result of stress failure of the blood-gas barrier; these results are achieved via high pulmonary capillary transmural pressures (31). In humans, lung diffusion capacity for carbon monoxide (DLCO) is reduced for up to 1 h after strenuous exercise (4, 9, 17), and VA/Qc inequalities have been shown to persist during the postexercise period after ventilation and cardiac output have returned to baseline values (26). EIAH has been associated with an increase in histamine release (1), which may be related to an inflammatory reaction at the pulmonary capillary level, potentially contributing to a mild interstitial edema. In addition, the inhibition of histamine release has been associated with an improvement in gas exchange (23). Recent reports of higher concentrations of red blood cells and protein in bronchoalveolar lavage fluid after brief intense exercise in athletes (14) do not necessarily imply abnormalities in gas exchange but do support the hypothesis that mechanical stress is the mechanism for altered blood-gas barrier function in the human.

Given the indirect evidence for alveolar capillary damage in the human, we hypothesized that subsequent exercise after heavy exercise, especially in those subjects with EIAH, would increase the severity of the EIAH and perhaps even cause significant EIAH in those subjects who did not initially experience it. We previously documented a high incidence of EIAH in active females during progressive exercise to maximal O₂ consumption (VO₂max); the EIAH was caused primarily by an excessively widened A-aDO₂, with a lack of sufficient compensatory hyperventilation (11). The description of these responses and the analysis of the potential mechanisms can be found in the previous paper (11). These female subjects, particularly those in habitual training, were especially appropriate to test our current hypothesis because they displayed such a wide A-aDO₂ and an exceptionally high prevalence of EIAH.

METHODS

Details of our methods are provided in the recent paper by Harms et al. (11), and in the present paper we summarize only the essential techniques and protocols.

Subjects. Of the 29 women who participated in the previous study (11), 28 completed the present study. All subjects were nonsmokers, ages 18–42 yr (mean, 27.2 ± 6.4 yr), with resting pulmonary function within normal limits (total lung capacity, vital capacity, and forced expiratory volume per 1 s were 106 ± 3% predicted). Resting DLCO averaged 26.4 ± 4.5
ml·min⁻¹·Torr⁻¹. Taking into account any differences in Hb or hematocrit between our subjects and the population in which the reference equations were developed, the DlCO for our subjects was 88 ± 16% of that predicted according to Crapo and Morris (6) and 86 ± 15% of that predicted according to Knudson et al. (16). None of the subjects was anemic (Hb, 12.8–15.5 g/dl), and all subjects were free of any history or symptoms of cardiopulmonary disease, including exercise-induced asthma. In additional studies (19), all subjects showed a normal increase in their maximal flow-volume envelope immediately after exercise. There was a wide variation in fitness levels (VO₂max 31–70 ml·kg⁻¹·min⁻¹; 82–202% of value predicted on the basis of gender and age). Twenty-four of the subjects were runners (including 13 former collegiate runners and 1 former Olympian), and all competed regularly in middle- and long-distance races. Twenty of the subjects ran at least 3 times/wk, averaging 36.3 ml/wk (range, 5–90 ml/wk). Four subjects were sedentary. 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 tests were performed during the follicular phase of the menstrual cycle, as determined by progesterone levels (0.8 ± 0.4 g/ml; range, 0.2–1.3 g/ml) and self-reported basal temperature recordings over a 5-day period. None of our subjects reported abnormalities with her menstrual cycle in the 6 mo before testing.

Apparatus. During all tests, subjects breathed through a low-resistance two-way valve (model 2400, Hans Rudolph), and expired gases were sampled at the mouth via a PerkinElmer mass spectrometer (model 1100). Inspiratory and expiratory flow rates were measured separately by pneumotachographs. All signals were displayed on a chart recorder, sent through an analog-to-digital board, and sampled on a computer at 75 Hz. Esophageal temperature was measured from a thermocouple placed intranasally in the lower one-third of the esophagus (Mon-a-Therm 6500).

Arterial blood was obtained from a 20-gauge indwelling plastic catheter inserted in the brachial or radial artery after 1% lidocaine anesthesia was given. Multiple blood samples of 3–4 ml were drawn anaerobically over 20–30 s during a 15-min rest period in the sitting position (on and off the mouthpiece), during the final minute at each grade during a progressive treadmill test to VO₂max, and at regular intervals during a constant-load VO₂max test. A minimum of two blood samples (usually 3–5) was obtained at each workload. Measurements of arterial PO₂, PCO₂, and pH were made with a blood-gas analyzer calibrated with tonometered blood (Radiometer ABL300), and arterial O₂ saturation (SaO₂) and Hb concentration were measured with a CO-oximeter (Radiometer OSM3). Calculated SaO₂ levels (on the basis of the normal average oxyhemoglobin dissociation curve and measured changes in body temperature and pH) were in close agreement with measured SaO₂ levels (r = 0.94). Blood gases were corrected for in vivo esophageal temperature changes during exercise. Esophageal temperature increased 1.7 ± 0.6°C from rest to maximal exercise during the progressive incremental VO₂max test and increased 1.2 ± 0.4°C during the constant-load VO₂max test (P < 0.004).

Protocol. Each subject completed a progressive incremental treadmill exercise test to VO₂max followed by a 20-min rest period, and then a second VO₂max test at a constant workload equivalent to or greater than (10 of the 28 subjects) the maximal workload achieved during the incremental test. For the progressive VO₂max test, a 5–10 min warm-up period at 4–6 miles per hour (mph) with 0% grade was followed by increasing the speed of the treadmill by 2 mph every 2.5 min until a comfortable speed of 6, 8, or 10 mph was reached. At this stage, the slope of the treadmill was increased 2% every 2.5 min until volitional fatigue was reached. All 28 subjects met the criteria for VO₂max (26), showing a plateau in O₂ consumption (VO₂, <150 ml increase) over the last two workloads. For the constant-load VO₂max test, a 3- to 5-min warm-up period was followed by increasing the treadmill, over a 30-s period, to the predetermined speed and grade, on the basis of the maximal workload achieved on the progressive test, and the subjects exercised until volitional fatigue.

Analysis. Comparisons between mean values obtained at the end point of the maximal workload of the progressive VO₂max test and at the endpoint of the constant-load VO₂max test were made by paired t-test. Pairwise comparisons were made for the 12 variables of interest, and the Bonferroni adjustment (α/number of t-tests) was used to modify the level of significance accordingly (P < 0.004). Mean values for each variable were also compared at equivalent time points (isotime) within each of the exercise protocols. Our analysis in this study involved only the data obtained at rest and at maximal exercise. Data obtained during all submaximal workloads during the progressive exercise protocol in these same subjects were reported previously (11).

RESULTS

VO₂ and work rate. The total duration of the progressive protocol was 13.3 ± 1.4 min, with the time spent at the end (maximal) workload averaging 97.3 ± 36.9 s. The duration of the repeat constant-load protocol was significantly longer (P < 0.004) than the final workload of the progressive test at 143.0 ± 31.3 s. The average maximal workload for the progressive test was 8.2 ± 1.7 mph at 6.9 ± 1.9% grade. On the repeat constant-load test, the grade of the treadmill was increased (1.7 ± 0.5%) for 10 of the 28 subjects, so that the average workload for all 28 subjects was higher than the maximal workload for the progressive test at 8.2 ± 1.7 mph and 7.5 ± 1.7% grade (P < 0.004). However, the VO₂ achieved at the end point of the maximal workload of the progressive test (54.7 ± 9.0 ml·kg⁻¹·min⁻¹) was not different (P > 0.004) from the VO₂ achieved at the end of the constant-load test (54.5 ± 8.8 ml·kg⁻¹·min⁻¹). The similarity in VO₂ between tests was consistent with the relative plateau in VO₂ achieved over the final two workloads of the progressive test.

Comparison of resting values. Table 1 shows the average resting values measured before the progressive test and the constant-load test. The subjects were still hyperventilating at the end of the 20-min recovery period between the two tests, as resting arterial CO₂ pressure (PaCO₂) was lower (32.1 ± 4.0 vs. 37.5 ± 3.4 Torr, P < 0.004) and resting arterial PO₂ (PaO₂) was higher (102.7 ± 9.7 vs. 100.0 ± 3.7 Torr, P < 0.004) before the constant-load test compared with resting values measured under steady-state control conditions before the progressive test. The pH was more acid (P < 0.004) before the constant-load test, compared with the resting (control) pH measured before the progressive test, due to the lower HCO₃⁻ concentration ([HCO₃⁻]; P < 0.004).

Comparisons at end exercise. The 28 subjects were divided into three groups based on the change (Δ) in PaO₂ and the degree of the resulting EIAH from rest to the end of the progressive exercise test to VO₂max. Six
subjects experienced no EIAH (group 1, ΔPaO2 less than −10 Torr) and had the lowest average Vo2max of all three groups (45.4 ± 7.9 ml · kg⁻¹ · min⁻¹). Group 2 (n = 7) had lowered PaO2 by −10 to −20 Torr (mild EIAH). Group 3 (n = 15) decreased PaO2 by more than −20 Torr (severe EIAH; SaO2 = 90.9 ± 2.4%, range 86.2–92.5%).1 Groups 2 and 3 had similar Vo2max values (56.6 ± 4.5 and 57.5 ± 8.9 ml · kg⁻¹ · min⁻¹, respectively). The greater the EIAH across groups, the wider was the A-aDO2 and the smaller was the hyperventilatory response.

Tables 2 and 3 show the average arterial blood O2 values and ventilatory parameters for the three groups at the end points of progressive and constant-load tests. At the end of the constant-load exercise test at Vo2max, the decrease in PaO2 or SaO2 from rest to end exercise was not as great, and the A-aDO2 was not as wide, as at the end of the progressive test (Table 2). A significant hypocapnia occurred in both tests, with mean PacO2 averaging 0.9 Torr lower (P < 0.004) at the end of the constant-load test. Thus, on average, in all 28 subjects, the 5.9 ± 4.3 Torr higher PaO2 on the constant-load test was due to a 4.8 ± 3.8 Torr narrower A-aDO2 and a 1.0 ± 1.5 Torr lower PaCO2 [i.e., 0.6 ± 1.7 Torr higher alveolar PaO2 (PaAO2)]. All three groups, regardless of their degree of EIAH in the progressive test, showed a nearly identical effect of narrowing their A-aDO2 and increasing their PaO2 and SaO2 between the end of the progressive test and the constant-load Vo2max test. SaO2 was 2.0 ± 0.9% higher in group 3 and 1.5 ± 0.9% higher in the entire group at the end of the repeat constant-load vs. the progressive test. The higher SaO2 was primarily a result of a higher PaO2 (5.9 ± 4.3 Torr, P < 0.004) and lower body temperature (0.5 ± 0.3°C, P < 0.004) at the end of the constant-load vs. the progressive test.

The arterial acid-base status was definable as a metabolic acidosis partially compensated by hyperventilation in all subjects in both tests. The magnitude of the hyperventilatory response was slightly, but significantly, greater in the repeat constant-load test. Comparisons at isotime. Because the constant-load Vo2max test was 46 s or 72% longer (P < 0.004) on average than the end workload of the progressive test, we also compared blood-gas data at equivalent time points in both tests (i.e., progressive test, 82.1 ± 32.4 s; constant-load test, 86.0 ± 29.8 s). Figure 1 shows the individual data for the isotime points of the progressive vs. constant-load tests. Mean data are shown in Tables 2 and 3. The results were similar to the end point comparisons. That is, the A-aDO2 was not as wide and the PaCO2 and SaO2 were higher at the same time point of the constant-load test compared with the progressive test. The magnitude of the increase in PaO2 and decrease in A-aDO2 with the constant-load vs. progressive test, was slightly less for the isotime comparison vs. the

---

1 In group 3, 11 of the 15 subjects also showed EIAH during submaximal exercise. These submaximal data are discussed in detail in a previous paper (11).

---

**Table 1.** Resting values measured before progressive maximum exercise test and before repeat constant-load Vo2max test (20 min after progressive exercise) for 28 women subjects

<table>
<thead>
<tr>
<th>Condition</th>
<th>SaO2, %</th>
<th>PaO2, Torr</th>
<th>PacO2, Torr</th>
<th>pH</th>
<th>HCO3, mM</th>
<th>Base Excess, mM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preprogressive</td>
<td>96.5 ± 0.4</td>
<td>100.0 ± 3.7</td>
<td>37.5 ± 3.4</td>
<td>7.44 ± 0.02</td>
<td>25.1 ± 2.2</td>
<td>+1.74 ± 1.82</td>
</tr>
<tr>
<td>Preconstant load</td>
<td>97.3 ± 0.7*</td>
<td>102.7 ± 9.7*</td>
<td>32.1 ± 4.0*</td>
<td>7.37 ± 0.05*</td>
<td>18.4 ± 3.3*</td>
<td>−5.19 ± 3.63</td>
</tr>
</tbody>
</table>

Values are means ± SD. Vo2max, maximal O2 consumption; SaO2, arterial O2 saturation; PaO2, arterial O2 pressure; PacO2, arterial CO2 pressure; HCO3, bicarbonate. *P < 0.004 compared with resting value before progressive exercise test.

**Table 2.** Arterial blood O2 values during peak workload of progressive vs. constant-load exercise at same or increased workload for 28 female subjects divided into 3 groups based on maximum decrease in PaO2 during progressive exercise test to Vo2max

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Progressive End Time</th>
<th>Constant End Time</th>
<th>Progressive Isotime</th>
<th>Constant Isotime</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>95.4 ± 2.1</td>
<td>96.4 ± 1.9</td>
<td>95.5 ± 2.1</td>
<td>97.0 ± 1.4*</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>94.0 ± 1.2</td>
<td>94.8 ± 1.2</td>
<td>94.1 ± 1.3</td>
<td>95.6 ± 1.1</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>90.9 ± 2.4</td>
<td>92.9 ± 2.1*</td>
<td>91.6 ± 2.1</td>
<td>93.6 ± 2.6*</td>
</tr>
<tr>
<td>All 28</td>
<td>6</td>
<td>92.7 ± 2.8</td>
<td>94.3 ± 2.3*</td>
<td>93.0 ± 2.5</td>
<td>94.8 ± 2.5*</td>
</tr>
<tr>
<td>PaO2, Torr</td>
<td></td>
<td></td>
<td>92.8 ± 8.1</td>
<td>98.5 ± 9.3*</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>94.7 ± 6.8</td>
<td>99.8 ± 7.7*</td>
<td>98.2 ± 8.1</td>
<td>98.5 ± 9.3*</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>85.9 ± 3.3</td>
<td>93.8 ± 7.4*</td>
<td>87.1 ± 4.0</td>
<td>89.4 ± 5.0</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>74.4 ± 5.2</td>
<td>79.5 ± 5.8*</td>
<td>74.0 ± 6.2</td>
<td>78.1 ± 8.0</td>
</tr>
<tr>
<td>All 28</td>
<td>6</td>
<td>81.5 ± 9.7</td>
<td>87.4 ± 10.9*</td>
<td>81.3 ± 10.2</td>
<td>85.3 ± 11.2*</td>
</tr>
<tr>
<td>A-aDO2, Torr</td>
<td></td>
<td></td>
<td>98.7 ± 2.8</td>
<td>18.7 ± 3.1</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>23.0 ± 5.9</td>
<td>19.0 ± 7.2*</td>
<td>23.2 ± 7.6</td>
<td>17.8 ± 9.4*</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>32.6 ± 4.0</td>
<td>26.4 ± 7.7*</td>
<td>32.8 ± 4.8</td>
<td>26.9 ± 3.5</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>42.3 ± 6.6</td>
<td>37.9 ± 6.3*</td>
<td>42.1 ± 8.3</td>
<td>36.9 ± 10.1*</td>
</tr>
<tr>
<td>All 28</td>
<td>6</td>
<td>35.7 ± 9.7</td>
<td>31.0 ± 10.4*</td>
<td>35.8 ± 10.5</td>
<td>30.3 ± 11.6*</td>
</tr>
<tr>
<td>PaO2, Torr</td>
<td></td>
<td></td>
<td></td>
<td>35.8 ± 10.5</td>
<td>30.3 ± 11.6*</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>116.9 ± 3.7</td>
<td>118.0 ± 4.2</td>
<td>115.1 ± 5.5</td>
<td>116.3 ± 3.9</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>117.3 ± 4.9</td>
<td>117.7 ± 5.2</td>
<td>119.9 ± 1.9</td>
<td>118.2 ± 4.3</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>115.9 ± 3.0</td>
<td>116.4 ± 3.2</td>
<td>115.9 ± 3.7</td>
<td>113.9 ± 4.7</td>
</tr>
<tr>
<td>All 28</td>
<td>6</td>
<td>116.5 ± 3.6</td>
<td>117.1 ± 3.9</td>
<td>116.7 ± 4.1</td>
<td>115.5 ± 4.7</td>
</tr>
</tbody>
</table>

Values are means ± SD for endpoints and isotime points for each Vo2max test. SaO2 was calculated using PaO2, pH, and temperature. A-aDO2, alveolar-arterial O2 difference; PaO2, alveolar O2 pressure; Vo2O2, O2 consumption. *P < 0.004 compared with progressive values at end time or isotime period.
We determined the effects of a repeat bout of maximal exercise on EIAH in a group of 28 female subjects who had experienced varying degrees of EIAH during a progressive exercise test. In contradiction to our hypothesis that a second bout of maximal exercise would increase the severity of the EIAH observed during a progressive exercise test to \( V_{O2\text{max}} \), we found that the decrease in \( P_{A\text{O}_2} \) or \( S_{A\text{O}_2} \) was not as great, and the \( A-a\text{DO}_2 \) was not as wide, during a repeat constant-load exercise test at \( V_{O2\text{max}} \) work rate, as at the end workload of the progressive exercise test. This reduced EIAH that was experienced on repeat maximal exercise occurred regardless of the degree of EIAH in the initial progressive test.

Comparison with prior studies. Two previous studies addressed the question of repeat exercise effects in men who were athletes; results were similar (5, 9). However, only a small number of subjects were studied (7–8 subjects), and EIAH was rare or nonexistent.

In agreement with our results, Hanel et al. (9) found no differences in \( P_{A\text{O}_2} \), \( P_{A\text{CO}_2} \), \( S_{A\text{O}_2} \), or \( pH \) during two 6-min “all-out” bouts of ergometer rowing, separated by a 2-h recovery period. In the seven subjects who completed the two exercise bouts, the \( S_{A\text{O}_2} \) averaged 95% (range, 86–96%) during the first rowing period (\( P_{A\text{O}_2} \), 77–102 Torr) and 94% (range, 90–96%) during the second rowing period (\( P_{A\text{O}_2} \), 77–99 Torr). Although it is evident that at least one subject experienced EIAH, data were reported for individual subjects so as to determine whether the response was different in those subjects who showed impaired gas exchange during the first exercise bout.

Caillaud et al. (5) reported that the drop in \( P_{A\text{O}_2} \) and the increase in \( A-a\text{DO}_2 \) observed during an incremental exercise test to \( V_{O2\text{max}} \) were accentuated during submaximal exercise in a second incremental test. However, they found no difference between the two tests in pulmonary gas exchange (\( P_{A\text{O}_2} \), \( A-a\text{DO}_2 \), and \( P_{A\text{CO}_2} \)) at maximal exercise. Exercise was performed on a cycle ergometer, using a 30-W/min ramp increase in work rate (mean duration, 13 min), with a 30-min recovery period separating the two tests. Among the eight subjects, the average \( P_{A\text{O}_2} \) at maximal exercise was 86 Torr, with a mean \( A-a\text{DO}_2 < 32 \) Torr. Because blood-gas changes in PaCO2 and arterial pH for the maximal exercise test at \( V_{O2\text{max}} \) show the time course for the change in PaO2 during exercise.
measurements were not corrected for changes in body temperature during the exercise. \( P_aO_2 \) was actually higher and A-a\( D_O_2 \) was significantly narrower than data reported in the study. Therefore, these subjects appeared to experience only marginal or no EIAH.

In agreement with our results, these previous studies (5, 9) show that simply repeating maximal exercise will not cause EIAH. However, the development of EIAH during the first exercise period is crucial to testing our hypothesis. If the subjects are not hypoxemic after the first period of maximal exercise, there would be no reason to suspect that the high capillary pressures experienced during the exercise induced any ultrastructural changes to the blood-gas barrier which would impair gas exchange during the second period of heavy exercise.

Implications for mechanisms causing EIAH. Our results demonstrate that the EIAH experienced during the initial progressive exercise test cannot be attributed to a mechanism(s) that persists long after the exercise and/or one which is aggravated by subsequent exercise bouts. These data thus appear to speak against our basic premise that the high vascular pressures experienced during heavy exercise, which cause structural

Fig. 1. Identity plots showing individual subject data for isotime points during peak workload at termination of progressive exercise test to maximal \( O_2 \) consumption (\( V_{O2max} \)) vs. constant-load test at maximal workload. A: arterial \( O_2 \) pressure (\( P_aO_2 \)). B: alveolar-arterial \( O_2 \) difference (A-a\( D_O_2 \)). C: arterial \( O_2 \) saturation (\( S_aO_2 \)). D: arterial \( CO_2 \) pressure (\( P_aCO_2 \)). Group 1, \( \Delta \); group 2, \( \circ \); group 3, \( \bullet \). These data were obtained after 82 ± 32 s of progressive test and 86 ± 30 s of constant-load test. See mean values in Table 2.

Fig. 2. Individual time course data for \( P_aO_2 \) during maximal workload of progressive exercise test to \( V_{O2max} \) (A) and for constant-load \( V_{O2max} \) test at maximal workload (B).
stress failure of the capillary endothelium, are responsible for the EIAH. The evidence for parenchymal damage is based on direct histological findings obtained postexercise in the Thoroughbred horse (31), in situ findings in the isolated perfused lung (3, 29, 32, 34), and indirectly in the human (1, 4, 14). Certainly the evidence for damage in the human athlete seems clear and it appears to be long-lasting after maximal exercise (14); however, this does not mean that the structural changes were sufficiently widespread or that they caused a diffuse interstitial edema of a magnitude which would interfere with pulmonary gas exchange.

Evidence for accumulation of extravascular lung water as a result of severe exercise has been controversial (4, 8). Our concern in the present study was not whether significant edema actually occurred during severe exercise but whether it caused the EIAH. If heavy progressive exercise had produced widespread permeability changes in the capillary endothelium sufficient to cause the EIAH, we would expect to see a further progressive widening of the A-aDO2 and a fall in PaO2 with continued exposure to high vascular pressures with repeated maximal exercise. We did not.

Our findings are most consistent with a functionally based mechanism for EIAH that is present only during the exercise period or shortly thereafter. These mechanisms include nonuniformities in the distribution of V˙A/Q˙c and/or failure of alveolar to end pulmonary capillary equilibrium for O2 (7, 30), the development of mild interstitial pulmonary edema (26), and/or mechanical time-constant inequalities in the airways (30). In the highly trained subjects, it is also possible that short red blood cell transit times, in at least a portion of the pulmonary circulation, might occur secondary to the maximal expansion of the pulmonary capillary blood volume at a time when pulmonary blood flow continues to increase (7, 15). Our present findings cannot distinguish between these factors.

Two sets of our own findings concerning the nature of EIAH do support our suggestion of a functional basis for EIAH. First, hypoxemia was observed to develop in the first minute or so during both the maximal workload of the progressive test and the constant-load test at maximal workload, and hypoxemia did not worsen thereafter (Fig. 2). Second, and more importantly, a previous report of exercise responses in these women subjects showed that, of the 22 subjects with EIAH at maximal exercise, the majority showed excessive A-aDO2 and significant EIAH beginning to develop during submaximal exercise (at 50–75% of V˙O2max) (11). In earlier studies (7), EIAH was also detected at submaximal exercise intensities in many highly trained young men who were athletes. Given the greater likelihood of increasing pulmonary capillary transmural pressures as maximal exercise is prolonged, at least over a few minutes, and the unlikelihood of moderate exercise intensity causing excessive pulmonary vascular pressures sufficient to cause injury to the vascular
endothelium, these findings also support our proposal for a functional transient cause of EIAH. Effects of experimental protocol on EIAH. We used a nonrandomized application of two quite different exercise tests, with the longer progressive maximal test always preceding the shorter (repeat) constant-load VO2max test. Thus we were unable to specifically dissect out the effects of progressive vs. constant-load test protocols on EIAH or the effect of test duration per se on EIAH. We think it unlikely that these differences in the progressive vs. constant-load type of maximal exercise test would explain our negative findings with repeat maximal exercise. First, we note that the repeat constant-load test was longer and usually at a slightly higher work load than the peak work load of the progressive test. Second, although the occurrence of EIAH during incremental exercise to VO2max has been well documented (7, 12, 15, 22), EIAH has also been observed during intense exercise at a constant work load (7, 9, 13). In the present study, although the hypoxemia was not as severe or prevalent in the repeat constant-load test, it was still present in the majority of subjects who experienced EIAH in the progressive test.

We were surprised that our heavy exercise protocol actually appeared to improve gas exchange during the subsequent period of maximal exercise. Todaro et al. (28) reported similar findings which were attributed to the hyperventilatory effects of intermittent exercise. These authors noted a relatively small exercise-induced decrease in PaO2 (6.8 to −9.8 Torr) which was less during intermittent vs. progressive exercise (the intermittent exercise consisted of 1-min supreme maximal exercise and 3-min rest periods). They argued that the postexercise hyperventilation, which increased PaO2, improved gas exchange during the subsequent exercise bout. Similarly, our subjects also were hyperventilating while at rest after the termination of the 20-min recovery period and before the repeat exercise bout. However, during the repeat maximal exercise, the ventilatory response was almost identical to that at the maximal workload of the progressive exercise and therefore was not a factor in explaining the improved PaO2 on this repeat maximal exercise bout. It is not entirely clear why the developing acidosis during maximal exercise was not associated with a hyperventilatory response either at end exercise or over the time course of the exercise (see Fig. 3). In many, but not all, of our women subjects, expiratory flow limitation was significant at maximal exercise and was shown to constrain the ventilatory response (19).

An alternative explanation for the moderate but significant improvement in gas exchange during repeat maximal exercise might be provided by Widimsky et al. (33), who showed that pulmonary vascular resistance was lower during repeat exercise of moderate intensity, compared with the initial period of exercise, also of moderate intensity. If this effect could also be documented at maximal exercise, then perhaps this reduced vascular resistance might lead to a more uniform perfusion distribution and a narrower A-aD02 with repeat exercise. However, these proposed mechanisms for the higher PaO2 and narrowed A-aD02 during the repeat test are purely speculative. Given the differences between the two exercise protocols, we caution against overinterpretation of the small (but quite consistent) improvement in gas exchange.

Implications for postexercise reductions in DLCO. Our results question the relevance of the postexercise reduction in DLCO to the pulmonary O2 exchange during exercise. It has been argued that the persistent decrease in DLCO for many hours after maximal exercise indicates a structural alteration to the alveolar capillary membrane (18, 20, 24). However, it has also been reported that a second bout of maximal ergometer rowing did not worsen the decrease in postexercise DLCO, nor was the reduction in DLCO related to the decrease in PaO2 or SaO2 during the exercise (9). These findings also argue against significant injury to the blood-gas barrier, thus affecting pulmonary gas exchange during heavy exercise, and question the physiological importance of the postexercise decrease in resting DLCO. Later studies that measured regional electrical impedance and atrial natriuretic peptide concentration indicated that about one-half of the postexercise reduction in resting DLCO was explained by a redistribution of pulmonary blood volume to more distal regions (10). Any reduction in central blood volume would be restored during subsequent exercise.

In summary, we demonstrated that previous maximal exercise does not precipitate widening of the A-aD02 or worsening of EIAH during maximal exercise. These results suggest that EIAH is not caused by a mechanism which persists after the initial exercise period and is aggravated by subsequent exercise, as might be expected of exercise-induced structural alterations at the alveolar-capillary interface. Rather, our present findings, along with evidence of EIAH onset at submaximal exercise (11), are more consistent with a functionally based mechanism—likely Va/Qmaldistribution—which is present only during the exercise period or shortly thereafter.

This work was supported by the National Heart, Lung, and Blood Institute and (in part) by Research Fellowships from the American Heart Association of Wisconsin (to C. M. St. Croix) and from the Parker B. Francis Foundation (to C. A. Harms).

Address for reprint requests: C. M. St. Croix, John Rankin Laboratory of Pulmonary Medicine, Dept. of Preventive Medicine, 504 N. Walnut St., Univ. of Wisconsin-Madison, Madison, WI 53705.

Received 1 December 1997; accepted in final form 18 May 1998.

REFERENCES


