Effects of altitude and exercise on pulmonary capillary integrity: evidence for subclinical high-altitude pulmonary edema

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HIGH-ALTITUDE PULMONARY EDEMA (HAPE) is a life-threatening illness that can develop rapidly in otherwise healthy individuals with ascent to altitudes of >2,500 m. This unique form of permeability edema is characterized by high concentrations of large proteins and red blood cells (RBCs) in the alveolar fluid (24, 25). Risk factors for development of HAPE include individual susceptibility, rapid ascent rate, and strenuous exercise. The pathogenesis of HAPE has not been entirely defined. However, high pulmonary vascular pressures, pulmonary venous constriction, and nonuniform hypoxic pulmonary vasoconstriction have been implicated. Estimates of pulmonary capillary pressures (16) and analysis of bronchoalveolar fluid in early HAPE (28) suggest that mechanical stress can induce a permeability edema with high protein and RBC concentrations without evidence of inflammation. Recently, Hopkins and colleagues (13), using quantitative magnetic resonance imaging, found greater hypoxic-induced pulmonary blood flow heterogeneity in HAPE-susceptible (HAPE-S) individuals compared with nonsusceptible controls. Because hypoxic pulmonary vasoconstriction takes place in the precapillary arterioles and if pulmonary vasoconstriction in hypoxia is nonuniform, then HAPE may be the consequence of regional overperfusion. Thus pulmonary capillaries in high-flow regions would be exposed to abnormally elevated transmural pressures and would be vulnerable to mechanical disruption and loss of blood-gas barrier integrity.

Strenuous exercise may be a significant contributing factor for development of HAPE, particularly at low or moderate altitudes. Indeed, some elite athletes develop a permeability pulmonary edema with high protein and RBC concentrations in the absence of inflammation following intense exercise at sea level (14). Like HAPE, the exercise-induced capillary leakage is attributed to regional overperfusion and high capillary pressures with mechanical failure at the blood-gas barrier. Thus we were interested in the effects of heavy exercise in a hypoxic environment in which the combined effects of a marked increase in pulmonary blood flow and nonuniform hypoxic pulmonary vasoconstriction would add significantly to increase the mechanical stress on the pulmonary microcirculation. We postulated that intense exercise at altitude would result in an augmented permeability edema. We recruited eight endurance athletes and examined their bronchoalveolar lavage fluid (BALF) for red blood cells (RBCs), protein, inflammatory cells, and soluble mediators at 2 and 26 h after intense exercise under normoxic and hypoxic conditions. We found that exercise at altitude (3,810 m) caused significantly greater leakage of RBCs [9.2 (SD 3.1) × 106 cells/ml] into the alveolar space than that seen with normoxic exercise [5.4 (SD 1.2) × 106 cells/ml]. At altitude, the 26-h postexercise BALF revealed significantly higher RBC and protein concentrations, suggesting an ongoing capillary leak. Interestingly, the BALF profiles following exercise at altitude are similar to that of early high-altitude pulmonary edema. These findings suggest that pulmonary capillary disruption occurs with intense exercise in healthy humans and that hypoxia augments the mechanical stresses on the pulmonary microcirculation.

bronchoalveolar lavage; pulmonary gas exchange; hypoxia; vascular endothelial growth factor

METHODS

This study received approval from the Human Subjects Institutional Review Board at the University of California, Davis, and each subject gave his or her written, informed consent before participation.

Subjects. Eight healthy, nonsmoking male athletes (aged 24–40 yr), and four healthy control subjects (3 men/1 woman; aged 29–45 yr) were recruited and, after written, informed consent was given, agreed to further study. A screening cardiopulmonary history and physical examination was performed, and all subjects were found to be free of cardiopulmonary disease and had no history of postexercise hemoptysis. The athletes’ characteristics and pulmonary function data are presented in Table 1. All sea-level studies were conducted in the...
Pulmonary Exercise Laboratory and Bronchoscopy Suite at the University of California, Davis Medical Center in Sacramento, CA, and all altitude studies were performed at the University of California, Barcroft Facility (3,810-m altitude) in the White Mountains of California. All subjects had previously been to an altitude of >4,000 m without significant altitude illness. However, no subjects were preacclimatized at enrollment.

**Pulmonary function measurements.** Baseline pulmonary function (SensorMedics 6200 Autobox, SensorMedics, Yorba Linda, CA), including forced vital capacity, forced expiratory volume in 1 s, forced midexpiratory flows, and peak expiratory flow, were determined according to American Thoracic Society criteria (21).

**Maximal exercise testing.** The athletes completed two incremental cycle ergometer exercise tests using a 40-W ramp/min design to determine their maximal O2 uptake for both normoxic (inspired O2 fraction = 0.209) and hypoxic (inspired O2 fraction = 0.129, balance nitrogen) inhaled gases. Expired respiratory gases, ventilation (SensorMedics 2900 Exercise System, SensorMedics), heart rate, and peripheral O2 saturation (finger) were monitored throughout the exercise bouts. The tests were double masked, with the order of the tests (normoxic or hypoxic) randomly assigned and then separated by at least 30 min. These data were used to assign the work rate (90% maximal power output) during the exercise protocols described below.

**Bronchoalveolar lavage.** Bronchoalveolar lavages (BAL) were performed with a 5.0-mm fiberoptic bronchoscopy. Nebulized lidocaine 4% was used for local anesthesia of the nasopharynx. Lavages were performed with five aliquots (20 ml each) of sterile room-temperature normal saline infused and then immediately aspirated through the fiberoptic bronchoscope wedged in a subsegment of the right middle lobe (nonexercise baseline 1 and 2-h postexercise studies) and left lingula (nonexercise baseline 2 and 26-h postexercise studies). The return from the first aliquot collected (bronchial) was discarded. The other four aliquots (alveolar) were pooled. The samples were then transported on ice to the immunology laboratory for immediate processing.

**BAL fluid examination for cell count, protein, and soluble mediators.** Cells counts were determined on the BAL fluid (BALF) with a hemocytometer. Cytospin slides (Shandon, Pittsburg, PA) were stained with Diff-Quik (Scientific Products, McGraw Park, IN), and the differential was determined from a minimum of 300 cells. Absolute differential cell counts were determined from the product of the total white blood cell count and the percent differential for each cell type of interest (alveolar macrophages, lymphocytes, neutrophils, and eosinophils). The cells were separated by centrifugation at 500 g for 10 min at 4°C, and the supernatants were frozen and stored at −80°C for soluble mediator assay.

The supernatant concentrations of the cytokines TNF-α, interleukin (IL)-6, and IL-8, the chemokines regulated on activation, normal T-cell expressed and secreted (RANTES), monocyte chemotactic protein (MCP)-1, and vascular endothelial growth factor (VEGF) were measured by ELISA using commercially available reagents (R & D Systems, Minneapolis MN). The limits of detection for TNF-α, IL-6, and IL-8 were 0.1, 0.08, and 18.1 pg/ml, respectively. The sensitivities of the assays for RANTES and MCP-1 were 2.5 and 5.0 pg/ml, respectively. The lower limit of detection for VEGF was 5.0 pg/ml. This assay measures biologically active VEGF121, and VEGF165. There is no detectable cross-reactivity with other cytokines or adhesion molecules. All samples were assayed in duplicate. To determine activation of the arachidonic acid cascade, the eicosanoids thromboxane B2 and leukotriene B4 were measured by a sandwich ELISA (Cayman Chemical, Ann Arbor, MI). The detection ranges for both assays is 78–1,000 pg/ml. Supernatant protein concentration was determined using a commercially available microassay kit (Bio-Rad, Laboratories, Hercules, CA). The samples were assayed in duplicate and compared with a standard curve prepared with bovine serum albumin (Sigma, St. Louis, MO).

**Study design for the athletes.** The experimental design for the athletes involved four study periods that included 1) baseline nonexercising BALs, 2) normobaric-normoxic exercise and BALs, 3) normobaric-hypoxic exercise and BALs, and 4) hypobaric-hypoxic exercise and BALs (altitude).

Five of the eight athletes completed the baseline, nonexercise BALs. The subjects refrained from exercise for 2 days before the initial baseline BAL, were limited to normal daily activities, and did not exercise between the initial (baseline 1) and subsequent BAL conducted 24 h later (baseline 2). BAL procedures were identical to those described above. These studies were done primarily to determine the baseline nonexercising BAL profiles. In addition, these studies provided further data on the effect of contralateral BALs separated by 24 h.

Using a crossover double-masked design, the athletes were randomly assigned to either the normoxic or hypoxic exercise protocol initially, and then they returned −2 wk later to complete the second exercise bout. With each visit, the subjects were instrumented with a radial artery catheter, EKG, and pulse oximeter. The exercise bout consisted of a warm-up followed by three high-intensity rides of 5-min duration at 90% maximal power output for the given inspired O2 tension, with a 5-min low-intensity (30% maximal) ride between each high-intensity bout. Arterial blood gases and blood samples were collected during the last minute of each high-intensity ride. Expired respiratory gases, ventilation, heart rate, and peripheral O2 saturation (finger probe) were monitored throughout the exercise periods. After the exercise, subjects rested quietly while breathing ambient air with arterial blood collected at 15 and 30 min and at 1, 2, and 26 h after the exercise bouts. Arterial blood was analyzed in duplicate (ABL 520, Radiometer, Copenhagen, Denmark) immediately after collection for pH, arterial Po2, arterial PaO2, arterial hemoglobin O2 saturation, and hemoglobin concentration. Blood-gas values were measured at 37°C and corrected for blood temperature determined at the time of collection with a rapid-response thermistor (Physitemp Instruments, Clifton, NJ). At 2 and 26 h after the exercise bouts, BALs were performed as described above. Subjects refrained from exercise for 2 days before each of the studies, were limited to normal daily activities, and did not exercise between the 2- and 26-h BALs.

**Table 1. Anthropometric and pulmonary function data for athletes**

| Age, yr | 30.5 (SD 5.5) |
| Height, cm | 175.6 (SD 5.5) |
| Weight, kg | 70.4 (SD 7.8) |
| FVC, % predicted | 111.7 (SD 8.6) |
| FEV1, % predicted | 110.8 (SD 7.8) |
| FEV1/FVC | 0.80 (SD 0.04) |
| FEF25–75%, l/s | 4.9 (SD 1.0) |

Values are means (SD). FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; FEF25–75%, mean forced expiratory flow during the middle 50% of the forced vital capacity.

**Table 2. Maximal exercise data for athletes**

| VO2max, ml·kg⁻¹·min⁻¹ | 63.1 (SD 5.1) |
| HRmax, beats/min | 186.0 (SD 14.0) |
| WRmax, W | 355.5 (SD 26.8) |
| WR50%max, W | 319 (SD 24.1) |

| P | 0.004 | <0.001 | <0.001 | <0.001 |

| P(O2) (148 Torr) | P(O2) (87 Torr) |

Values are means (SD). NA, not applicable; VO2max, maximal oxygen consumption; Po2, inspired oxygen tension; HRmax, heart rate at maximal exercise; WRmax, work rate at maximal exercise; WR50%max, work rate at 90% maximal exercise for Po2.
The altitude studies were conducted at the University of California, Barcroft Research Facility (3,810 m) following a 24-h acclimatization period. Subjects were transported from sea level to altitude by car, with a travel time of ~8 h. The athletes completed an identical exercise protocol and BAL procedure as described for the sea-level studies. The arterial blood gas, blood sample, and BALF collections were identical to those described for the sea-level studies.

Study design for the control subjects. The four control subjects underwent four resting baseline bronchoscopies, two BALs at sea level separated by 24 h, and two BALs at altitude separated by 24 h. Subjects refrained from exercise for 2 days before the studies, were limited to normal daily activities, and did not exercise between bronchoscopies. BAL procedures were identical to those described for the athletes. These studies were done to determine the effect of acute altitude exposure on resting BAL profiles. In addition, these studies provided further data on the effect of contralateral BALs separated by 24 h and established resting baseline BAL profiles for nonathlete controls.

Statistical analysis. Total cell counts and absolute differential cell counts were normalized by logarithmic transformation. The differences in the cell counts, protein concentrations, and soluble mediator concentrations, among the four exposure conditions and three time points, were compared with repeated-measures ANOVA. Multiple comparisons were made with the Tukey-Kramer honestly significant difference test. Blood-gas data were analyzed using repeated-measures ANOVA, with multiple pairwise comparisons made with the Tukey-Kramer honestly significant difference test. The overall alpha level was set at 0.05. Data are presented as means (SD) unless otherwise indicated.

RESULTS

All subjects tolerated the bronchoscopies well. Five athletes completed all aspects of the study design, which included eight BALs and six exercise bouts. The remaining three athletes completed all the sea-level exercise studies and postexercise BALs. There were no other complications associated with the exercise bouts or arterial catheterization. At altitude, most of the subjects had complaints of mild sleep disturbances. One athlete complained of headache and nausea ~6 h after arrival at altitude. These symptoms spontaneously resolved with rest, and the athlete completed the exercise protocol and BALs without difficulty.

Anthropometric, pulmonary function, and maximal exercise data. The athletes’ physical and resting pulmonary function data are shown in Table 1. All of the athletes had normal resting pulmonary function values. Table 2 shows the results of the maximal exercise studies and the work rates used for the normoxic and hypoxic exercise protocols at sea level and altitude. The maximal O₂ uptake values and maximal power outputs during hypoxic exercise were significantly lower (P < 0.001) than for normoxic exercise [16.9 (SD 4.6) and 15.9 (SD 3.8), respectively].

Baseline nonexercising BALF profiles. BALF profiles for the athletes and control subjects for all conditions and all time points are shown in Tables 3 and 4, respectively. The baseline, nonexercising BALF profiles for both subject groups were within normal values and not different from each other (2, 14, 15). Twenty-four hours later, the BALF profiles for both groups were similar. However, the 24-h BALF was obtained from the left lingula where the percent fluid recovery was ~20% lower in both subject groups (P < 0.05). Interestingly, in both subject groups, IL-8 (a neutrophil chemotactic agent) was significantly elevated in the 24-h BALF (P < 0.05). Otherwise, the nonexercising 24-h BALF cell count and protein and mediator concentrations were similar to that reported previously (2, 14, 15).

Control subjects also endured two nonexercising BALs at altitude (Table 4). These studies were conducted to determine the effect of altitude exposure alone on the BALF profiles. The control subjects followed an identical routine as the athletes, except they did not exercise. After a 24-h acclimatization period, the initial BALF RBC counts were similar to that seen previously.
at sea level for both the controls and athletes. Twenty-four hours later, the BALF RBC counts trended higher but were not statistically different from the initial altitude values or sea-level values.

Exercise, inspired O₂ tension, and BALF RBC concentration. Significantly, elevated RBC counts were found in the BALF of all athletes 2 h after all of the exercise bouts (Table 3, Fig. 1). After sea-level normoxic exercise, RBC concentrations were increased more than fivefold greater than nonexercising baseline values \( (P < 0.001) \). Following 24 h of recovery, RBC counts were still elevated above baseline values \( (P < 0.001) \) but were significantly lower than 2 h postexercise \( (P < 0.001) \). Intense exercise while breathing 12.9% \( \text{O}_2 \) (inspired \( \text{PO}_2 = 89 \text{ Torr} \)) further augmented the BALF RBC concentrations in the BALF. At 2 h after hypoxic exercise, the mean RBC concentrations were over 10-fold greater than baseline values and 2-fold greater than that seen 2 h after normoxic exercise. After 24 h of recovery at sea level, the BALF RBC concentrations remained elevated compared with baseline values \( (P < 0.001) \) but were lower than 2 h postexercise \( (P < 0.001) \). Intense exercise at altitude (inspired \( \text{PO}_2 = 89 \text{ Torr} \)) resulted in a similar increase in the BALF RBC concentrations compared with hypoxic exercise (inspired \( \text{PO}_2 = 87 \text{ Torr} \)) at sea level. At altitude, the 2-h postexercise BALF RBC concentration was 9-fold greater than the baseline nonexercising value and 1.7-fold greater than 2 h after sea-level normoxic exercise. However, after 26 h of recovery at altitude, RBC concentrations in the BALF were –2-fold greater than 2 h postexercise \( (P < 0.001) \), 7.5-fold greater than 26 h after both sea-level normoxic and hypoxic exercise \( (P < 0.001) \), and over 35-fold greater \( (P < 0.001) \) than baseline nonexercising sea-level values.

Exercise, inspired O₂ tension, and BALF protein concentration. Significantly, elevated total protein concentrations were found in the BALF of all athletes 2 h after each of the exercise bouts (Table 3, and Fig. 1). After 26 h of recovery at sea level, BALF protein concentrations returned toward baseline nonexercising values. At 26 h postexercise, BALF protein concentrations at altitude were significantly greater than 2 h postexercise and all respective sea-level values. In the control subjects, neither a prior BAL nor altitude exposure significantly altered BALF protein concentration.

Exercise, inspired O₂ tension, and BALF inflammatory cell counts. Total and absolute differential white blood cell counts in BALF were not affected by exercise or inspired O₂ tension (Tables 3 and 4). In all cases at 2 h postexercise, the percentage of macrophages harvested from the BALF were significantly greater \( (P < 0.05) \) than nonexercising values. However, this most likely reflects a demargination of activated macrophages from the alveolar epithelium, making them easier to harvest in the BALF. Macrophage engulfment is the primary mechanism for air space clearance of excessive protein and RBCs. Figure 2 shows an activated alveolar macrophage phagocytizing RBCs. This sample was harvested from an athlete 2 h after exercise at altitude. At 26 h postexercise, the percentage of macrophages in the BALF had returned to baseline values. At altitude, the BALF inflammatory cell profiles (initial and 24 h) for the control subjects were not different from each other, from baseline, or from the athletes.

Exercise and inspired O₂ tension on soluble mediators in the BALF. All inflammatory mediator values for both the athletes and control subjects are presented in Tables 3 and 4, respectively. TNF-α was not detected in any of the BALF of either the athletes or control subjects. Both leukotriene B₄ and thromboxane B₂ were not detected in the BALF of either the athletes or control subjects under sea-level resting conditions. In the athletes, both mediators were detectable at 2 and 26 h after each exercise bout; however, there was no clear effect of inspired O₂ tension. Interestingly, after a day at altitude, control subjects had detectable levels of both leukotriene B₃ and thromboxane B₂ in the BALF at each time point. These are very modest changes in both mediators and are within the normal ranges.

IL-8, MCP-1, and RANTES are all inflammatory cell chemoattractant mediators. There was no effect of exercise, inspired O₂ tension, or altitude exposure on BALF levels of the chemoattractant mediators (MCP-1, RANTES). However, BALF IL-8 levels were significantly elevated at the nonexercising baseline 24-h time point at sea level. This finding suggests that there is an inflammatory response (albeit modest) in the contralateral lung (left lingula) following a previous BAL (right middle lobe). Interestingly, this did not result in an inflammatory cell response with recruitment of neutrophils.
The baseline, nonexercising BALF VEGF concentrations for both subject groups were within normal values and not different from each other. Bronchoalveolar fluid VEGF concentrations following normoxic exercise were not different from nonexercising values. Exercise under hypoxic conditions (12.9% O₂ at sea level or 3,810-m altitude) resulted in an increase in the BALF VEGF concentrations at 2 h postexercise compared with nonexercising values. However, the post-hypoxic exercise values were different than post-normoxic exercise. In all cases, at 26 h postexercise, the BALF VEGF concentrations had returned toward nonexercising baseline levels.

Cardiopulmonary and gas-exchange values during exercise and recovery. Figure 3 shows the cardiopulmonary data (means ± SE) for each inspired O₂ tension at rest, during the last minute of each exercise bout, and during recovery. Ventilation, O₂ uptake, and heart rate were all significantly elevated during each exercise bout and returned to baseline values by 2 h postexercise. At altitude, the measured O₂ uptake values were 30% lower than sea-level normoxic exercise and 20% lower than sea-level hypoxic exercise.

Blood-gas and gas-exchange data (means ± SE) are shown in Fig. 4. A significantly widened alveolar-arterial O₂ difference (A-aΔO₂) was seen with each exercise bout (Fig. 4C). The exercise-induced gas-exchange abnormality was significantly worse at altitude compared with acute normobaric hypoxia. In each condition, the gas-exchange dysfunction resolved within 30 min after termination of exercise. Interestingly, at 2 h postexercise, the A-aΔO₂ again widened (P < 0.001). At sea level, the 26-h postexercise A-aΔO₂ had returned to baseline values. However, at altitude, the 26 h postexercise A-aΔO₂ remained widened (P < 0.001).

DISCUSSION

We hypothesized that intense exercise during hypoxic stress would cause a more pronounced disruption of pulmonary capillary integrity than exercise under normoxic conditions. Thus the primary goal of this investigation was to determine the effects of high-intensity exercise at moderate altitude on lung blood-gas barrier integrity in healthy humans without a history of postexercise hemoptysis. We found that heavy exercise during both normobaric and hypobaric hypoxia resulted in significantly greater leakage of RBCs and protein into the alveolar space than that seen with normoxic exercise. We found that at sea level, following 24 h of recovery under normoxic conditions, the BALF protein concentrations were
similar to baseline nonexercising values. However, RBC counts in the BALF remained elevated above baseline nonexercising values but were significantly lower than that found at 2 h postexercise. This most likely reflects a slower alveolar clearance of RBCs via phagocytosis rather than ongoing capillary leak. Interestingly, with recovery at 3,810-m altitude, both alveolar RBC and protein concentrations were significantly higher than the 2-h postexercise and non-baseline exercising values. These findings provide support for the hypothesis that loss of pulmonary capillary integrity occurs with intense exercise in healthy humans (11, 14, 32–34). Furthermore, in combination, hypoxia and severe exercise appear to augment the mechanical stresses on the pulmonary capillaries, leading to greater disruption of pulmonary blood-gas barrier integrity. In addition, these data suggest that the persistent hypoxic stress following exercise at altitude may promote ongoing capillary leak.

**Intense exercise, blood-gas barrier integrity, and gas exchange.** Exercise-induced disruption of pulmonary blood-gas barrier integrity occurred in all of our athletes, with BALF RBC and protein concentrations similar to that reported previously (14). Hopkins et al. (14) specifically recruited athletes with a history suggestive of exercise-related lung bleeding, and thus these athletes may be susceptible to exercise-induced pulmonary capillary injury. Our athletes had no history of postexercise hemoptysis, and yet we found five- and twofold increases in BALF concentrations of RBCs and total protein, respectively, following intense normoxic exercise compared with nonexercising baseline values. In a subsequent study, Hopkins et al. (15) found no evidence of increased capillary permeability following prolonged (1 h) submaximal (75–80% maximal O₂ uptake) exercise in a similar group of elite cyclists. Our results in combination with previous studies (11, 14, 15) suggest that the mechanism for the capillary leak may be related to the relatively high pulmonary vascular pressures (7, 20, 31) and regional overperfusion that occur during short-duration high-intensity exercise.

We found that the A-aDO₂ widened significantly during intense exercise (1, 5, 10, 36). The mechanisms responsible for the gas-exchange inefficiency during exercise likely includes ventilation-perfusion inequality (9, 10), diffusion limitation, arteriovenous intrapulmonary right-to-left shunting (6, 27), and post-pulmonary shunting. Similar to that reported previously (22), our subjects recovered rapidly from the exercise, and by 30 min postexercise, pulmonary gas exchange had returned to resting preexercise values. However, at 2 h postexercise, we found that the arterial PO₂ falls and the A-aDO₂ again widens significantly. Other investigators have observed a small reduction in lung diffusion capacity after exercise and have suggested that this reflects a persistent alteration in the structure of the blood-gas barrier (17, 18). Our finding of a widened A-aDO₂ that is temporally associated with BALF evidence of capillary leak pulmonary edema is compatible with this hypothesis. In summary, our findings confirm and expand those of Hopkins et al. (14) and others (11) and provide further evidence for exercise-induced mechanical disruption of the pulmonary blood-gas barrier in healthy humans.

**Intense exercise, hypoxia, and HAPE.** The most compelling finding of our study is that alveolar hypoxia in combination with heavy exercise further augmented the capillary leak, resulting in significantly higher BALF RBC and protein concentrations than found with normoxic exercise or altitude exposure alone. Furthermore, with persistent exposure to hypoxic stress, the BALF RBC concentrations increased 40-fold.
over nonexercising levels at both sea level and altitude. Swenson and colleagues (28) exposed a group of HAPE-prone and HAPE-resistant subjects to moderate altitude (4,559 m). Bronchial lavages performed within 1 day of ascent to altitude revealed elevated RBC counts and protein concentrations in HAPE-prone subjects with clinically evident HAPE and those who developed HAPE within the next 24 h (early HAPE). Interestingly, the BALF profiles found in early HAPE are similar to those found in our athletes following intense exercise and recovery at altitude. We did not obtain chest radiographs, nor were our subjects outwardly ill. However, all our subjects demonstrated a gas-exchange disturbance with a fall in arterial PO₂ and widened A-aDO₂ at both 2 and 26 h after exercise at altitude. Our subjects descended following the 26-h BAL; thus it is unclear whether they would have developed HAPE the next day like the HAPE-prone subjects. Indeed, the altitude BALF profiles for the HAPE-resistant subjects are similar to our 2-h posthypoxic exercise values. Swenson et al. (28) did not do serial BALs, and thus the progression of the capillary leak in the HAPE-resistant subjects is unclear. Whether the postexercise BALF profiles observed at altitude represent subclinical HAPE (4) or early HAPE (28) with the potential for progression to full-blown HAPE is uncertain.

HAPE-prone individuals tend to have higher pulmonary arterial pressures (8, 23, 30), smaller lung volumes (7, 19, 26, 29), a steeper pulmonary pressure-flow relationship even during normoxic exercise at sea level (7), and an altered epithelial sodium and water transport mechanism (23) than HAPE-resistant people. Our subjects were trained athletes who had been to altitudes greater than 4,000 m multiple times without developing HAPE. Furthermore, our athletes had large lungs with both forced vital capacity and forced expiratory volume in 1 s of >110% predicted; thus our subjects could be considered HAPE-resistant. Indeed, large lungs may be protective against HAPE because they possess a greater vascular cross-sectional area, which could limit mechanical stresses, such as capillary distending pressures and volumes and wall shear stress, during exercise at altitude. However, despite the potential protective factor of large lungs, we found that strenuous exercise at altitude results in a significant disruption of pulmonary capillary integrity and thus may be an important contributing factor for development of HAPE, particularly at low or moderate altitudes.

Like HAPE, the exercise-induced capillary permeability is likely attributed to regional overperfusion, with high capillary pressures resulting in mechanical failure at the blood-gas barrier. West et al. (35) introduced the concept of pulmonary capillary stress failure after demonstrating disruptions to the capillary endothelium, alveolar epithelium, and their respective basement membranes in a rabbit lung model when pulmonary arterial pressures exceeded 40 Torr. Assuming pulmonary capillary pressure is approximately halfway between arterial and venous pressure and that most of the pressure loss is in the capillaries (3), West (34) has estimated capillary transmural pressures to exceed 40 Torr in dependent regions of the human lung at maximal exercise. We did not measure pulmonary vascular pressures, and this may be a limitation of the present study. However, previous studies using similar subjects and exercise conditions have shown that pulmonary arterial and occlusion pressure rise progressively with increasing exercise intensity (7, 21, 31). Moreover, pulmonary blood flow distri-
bution may be quite heterogeneous, even within isogravitational planes (12, 13), resulting in regional overperfusion during maximal exercise. Indeed, as regional blood flow increases, the capacity for the capillary to distend may be exceeded, thus further increasing capillary pressure (37). Furthermore, during exercise, pulmonary vascular input impedance increases as the arterial compliance falls. As a result, pulsatile blood is forced through less distensible vessels with transmission of high-pressure pulses to the pulmonary capillaries. Thus, during maximal exercise, capillary distending pressures, due primarily to regional overperfusion, may be markedly higher in some lung regions than estimates derived from pulmonary arterial and wedge pressures (7, 20, 31). Furthermore, heavy exercise under hypoxic conditions may be synergistic, in which the combined effects of marked increases in pulmonary blood flow and nonuniform hypoxic pulmonary vasoconstriction would add significantly to regional overperfusion and augment the mechanical stress on the pulmonary microcirculation.

In conclusion, we found that intense exercise during both normobaric and hypobaric hypoxia resulted in significantly greater leakage of RBCs and protein into the alveolar space than that seen with normoxic exercise. The magnitudes of the BALF protein and RBC concentrations following exercise at altitude are very similar to those seen in early HAPE. These findings provide further support for the hypothesis that pulmonary capillary stress failure develops with intense exercise in healthy humans and that alveolar hypoxia further augments the mechanical stresses, leading to greater disruption of pulmonary blood-gas barrier integrity. Furthermore, persistent hypoxic stress following exercise at altitude may promote ongoing capillary leak.

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