Pathogenesis of High-Altitude Pulmonary Edema
Inflammation Is Not an Etiologic Factor

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High-altitude pulmonary edema (HAPE) is a life-threatening illness in climbers and tourists ascending to altitudes higher than 2500 m. The pathogenesis of this unique form of pulmonary edema that occurs rapidly in otherwise healthy people has not been entirely illuminated owing to the difficulties of studying the disease early in its evolution and to conflicting data from animal and human investigations. The central issue is whether the alveolar-capillary leak in HAPE is caused by high microvascular pressures or inflammation. Besides revealing a more definitive answer about HAPE itself, resolution of this question may facilitate our understanding, diagnosis, and treatment of other common forms of pulmonary edema, such as congestive heart failure and adult respiratory distress syndrome.

Since the earliest descriptions of HAPE in the 1960s, acute pulmonary artery hypertension has always been associated with it and considered an etiologic factor. Context The pathogenesis of high-altitude pulmonary edema (HAPE) is considered an altered permeability of the alveolar-capillary barrier secondary to intense pulmonary vasoconstriction and high capillary pressure, but previous bronchoalveolar lavage (BAL) findings in well-established HAPE are also consistent with inflammatory etiologic characteristics.

Objectives To determine whether inflammation is a primary event in HAPE and to define the temporal sequence of events in HAPE.

Design, Setting, and Participants Case study from July through August 1999 of 10 subjects with susceptibility to HAPE and 6 subjects resistant to HAPE, all of whom are nonprofessional alpinists with previous mountaineering experience above 3000 m.

Main Outcome Measures Pulmonary artery pressure measurements and BAL findings at low altitude (490 m) and shortly before or at the onset of HAPE at an altitude of 4559 m.

Results Subjects who were HAPE susceptible had higher mean (SD) pulmonary artery systolic blood pressures at 4559 m compared with HAPE-resistant subjects (66 vs 37 mm Hg; \( P = .004 \)). Despite development of HAPE in the majority of HAPE-susceptible subjects, there were no differences in BAL fluid total leukocyte counts between resistant and susceptible subjects or between counts taken at low and high altitudes. Subjects who developed HAPE had BAL fluid with high concentrations of plasma-derived proteins and erythrocytes, but there was no increase in plasma concentrations of surfactant protein A and Clara cell protein. The chest radiograph score was 12.7 for the 3 HAPE-susceptible subjects who developed HAPE before BAL was performed; they were lavaged within 3 to 5 hours. The remainder of the HAPE-susceptible group was lavaged before edema was apparent on radiographs. However, 6 subjects from the HAPE-susceptible group who developed HAPE on the following day had a score on bronchoscopy of 1.5, which increased to 4.6, reflective of mild pulmonary edema. In HAPE cases, there were no elevations in a number of proinflammatory cytokines and eicosanoid and nitric oxide metabolites.

Conclusions Early HAPE is characterized by high pulmonary artery pressures that lead to a protein-rich and mildly hemorrhagic edema, with normal levels of leukocytes, cytokines, and eicosanoids. HAPE is a form of hydrostatic pulmonary edema with altered alveolar-capillary permeability.

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See also p 2275 and Patient Page.
sential pathophysiologic factor.\textsuperscript{1-3} Enhanced hypoxic pulmonary vascular responses in individuals susceptible to HAPE,\textsuperscript{4} abnormally high pulmonary artery (PA) pressures before the onset of HAPE,\textsuperscript{1} and successful prevention and treatment\textsuperscript{1,5-7} with vasodilating drugs further support the primacy of elevated PA pressure. Maggiorini et al\textsuperscript{8} have recently added to this weight of evidence by showing that the high PA pressures extend to the level of the microvasculature. Despite normal left atrial (PA wedge) pressures, patients at the onset of HAPE have elevated pulmonary capillary pressures (>19 mm Hg), which are sufficiently high to cause water accumulation in the lungs.\textsuperscript{9}

Nevertheless, authors of many studies propose that, in addition to the hydrostatic stress, increased alveolar-capillary permeability caused by inflammation may be necessary or causal. A high incidence of preceding upper respiratory tract infection in children developing HAPE,\textsuperscript{10} elevated urinary leukotriene metabolites in patients with HAPE,\textsuperscript{11} and an association of certain major HLA-immunomodulating alleles with HAPE susceptibility\textsuperscript{12} support this notion. More compelling are findings of neutrophils and elevated concentrations of plasma proteins, thromboxane metabolites, and proinflammatory cytokines in bronchoalveolar lavage (BAL) fluid in subjects with well-established HAPE lavaged at high altitude by Schoene and colleagues\textsuperscript{13,14} and Kubo et al several days after the patients were admitted to a lowland hospital.\textsuperscript{15-18} In animals, viral infection\textsuperscript{19} and endotoxin priming\textsuperscript{20} cause more pulmonary edema with hypoxic (10% to 12% oxygen) exposure. Furthermore, extreme hypoxia (0% to 3% oxygen) stimulates vascular endothelial cells, leukocytes, and macrophages in vitro to release proinflammatory cytokines,\textsuperscript{21-23} which can alter capillary permeability in vivo.

Prospective human studies measuring circulating markers of in vivo thrombin and fibrin formation,\textsuperscript{24} cytokines in plasma, systemic transcapillary escape rate of albumin,\textsuperscript{25} and urinary excretion of leukotriene E\textsubscript{2},\textsuperscript{26} found no evidence for inflammation before or with the onset of HAPE, however. The differences in these studies (between those in early HAPE and those cited above in HAPE of longer duration) could be resolved by postulating that inflammation is not a cause or essential cofactor of HAPE but may develop as a consequence. Thus, to investigate the hypothesis that, at HAPE initiation, pulmonary vascular pressures are elevated and inflammation is not present, we performed PA-pressure measurements and BAL in mountaineers at low altitude and shortly before or at the onset of HAPE at 4559 m.

**METHODS**

**Subjects**

Twenty-two nonacclimatized individuals (6 women and 16 men aged 24-52 years) gave informed consent for this study, which was approved by the Ethics Committee of the University Hospital, Zurich, Switzerland, and medical faculty of the University of Heidelberg, Germany. The subjects were all healthy, physically fit, avid, nonprofessional alpinists with mountaineering experience above 3000 m. They were recruited by advertisements in the German and Swiss alpine club journals and by the principal investigators.

Individuals with and without previous episodes of HAPE were sought. They received written information about all the risks involved and were told in particular that the chance of developing HAPE during the study was about 50% for those with a history of HAPE and about 5% to 10% for those without. Nevertheless, it was easier to recruit mountaineers with a history of HAPE than control subjects because the former have a strong interest in determining their susceptibility for its obvious relevance to their mountaineering plans.

All costs of mountain guides, travel, food, and lodging were paid out of the investigators’ research funds. Any medical care and emergency air evacuation was to be borne by the investigators. Owing to the special nature of this study in which it was certain that some subjects would develop HAPE, great care was invested in safety measures for potentially ill subjects, including having the subjects climb a technically easy and heavily traveled route under the direction of experienced local professional guides in radio communication with the investigators at the summit, who could descend if necessary to assist. The summit hut, Capanna Regina Margherita, is a large 3-story structure with heating and electricity and is regularly served by helicopter. The subjects were told that our laboratory contained all equipment necessary for medical triage and support, including oxygen, intravenous fluids, pulmonary arterial vasodilators, corticosteroids, and antibiotics. They were also assured that they could turn back at any time with their guide and that from the summit, air evacuation by helicopter would be provided either on their request or on the advice of the investigators.

Twelve subjects were considered HAPE susceptible because of having had at least 1 episode of HAPE, and 10 subjects with comparable exposures to high altitude without having developed pulmonary edema were considered HAPE resistant. Subjects had baseline low-altitude (490 m) measurements performed in Zurich in the following sequence: medical history and physical examination, transthoracic echocardiography, arterial blood gas measurements, chest radiography, and BAL. Within 3 weeks of their baseline assessment, the subjects climbed to the summit of the Monte Rosa. A climbing ascent was chosen rather than either a helicopter ascent or a simulated ascent in a hypobaric chamber because we wanted to study HAPE under conditions in which it is usually encountered, combining the effects of hypoxia, exertion, cold, and the psychology of climbing. Furthermore, passive ascents would likely have required many more subjects for a sufficient number of early HAPE cases.

The profile of the ascent and the timing of investigations were as follows.

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The subjects ascended by cable car to 3200 m and then climbed to 3611 m (day 1), where they spent the night in a mountain hut. In the morning (day 2), they climbed in 4 to 6 hours to the research laboratory of the Capanna Regina Margherita, Italy, at 4559 m (barometric pressure, 440 mm Hg), where they stayed for the next 2 days. Subjects were examined on arrival (day 2) and on the mornings of days 3 and 4 and whenever signs or symptoms of HAPE developed. On day 3, a medical history, physical examination, transthoracic echocardiograph, arterial blood gas measurement, and chest radiograph were repeated, after which BAL was performed.

**Assessment of HAPE**

High-altitude pulmonary edema was suspected clinically and confirmed if the radiograph showed patchy opacities compatible with interstitial or alveolar edema in at least 1 quadrant and on the right side of the chest radiography showed arterial saturation below 70%. Posteroanterior and lateral chest radiographs were taken by using a mobile unit (TRS, Siemens, Stockholm, Sweden) with a fixed distance of 140 cm at 95 kV and 3 to 6 mA/s. The chest radiographs were scored retrospectively by a radiologist unaware of the clinical history of the subjects. Arterial blood samples were analyzed with a Model 278 Ciba-Corning Diagnostics Analyzer (Ciba-Corning, Dietikon, Switzerland) calibrated at 37°C.

**Echocardiography**

By using an echocardiography machine with simultaneous electrocardiogram (Hewlett Packard 1500, Boston, Mass), cross-sectional echocardiograms were obtained with subjects lying semiprone in the left lateral position. Doppler signals were recorded with a 3.5-MHz transducer. Tricuspid regurgitant flow was identified and recorded in continuous mode. Color flow imaging was used to guide alignment of the Doppler cursor with the regurgitant jet to identify its maximum velocity. Doppler measurements were made from the parasternal, right ven-

tricular inflow, and 4-chamber views. The peak instantaneous systolic pressure drop from right ventricle to right atrium (ΔP) was calculated from the peak velocity (V) of the tricuspid regurgitant signal by using the modified Bernoulli equation (ΔP = 4V²). Measurements were made on 3 cardiac cycles, and a mean value was taken. The jugular venous pressure was measured by inspection and added to diastolic pressure to calculate the systolic PA pressure.

**Bronchoscopy and Bronchoalveolar Lavage**

All subjects were monitored by electrocardiography and pulse oximetry and provided with oxygen by nasal cannula at 2 to 3 L/min. Atropine sulfate (0.4 mg) was given intravenously. In some subjects, light sedation with midazolam (1-2 mg) was also given intravenously. Upper airway anesthesia was accomplished by gargling and spraying the posterior pharynx with 2% lidocaine. A flexible fiberoptic bronchoscope (Pentax model FB-15BS; Pentax, Tokyo, Japan) was then passed through the mouth and advanced to a wedged position in a subsegment of the right middle lobe, after which 5 aliquots of 30-mL sterile pyrogen-free normal saline were instilled and removed by gentle suction. A mean (SD) of 55% (7%) of the instilled fluid was recovered.

**Serum and Lavage Assays**

The combined BAL aliquots were filtered through 10 × 10-cm gauze pads to remove mucus. Total cell counts were performed immediately on unspun samples in a hemocytometer, and the remaining fluid was centrifuged for 10 minutes at 3000g. The supernatant was withdrawn and stored in liquid nitrogen for later biochemical and mediator analysis. A sample of the cell concentrate was resuspended in a balanced salt solution for determination of viability (Trypan blue exclusion). Another sample was air-dried on a glass slide and stained with Diff-Quik (Scientific Products, McGraw Park, Ill) for differential cell count on 200 cells.

Total protein was measured by the bicinchoninic acid method (Pierce Chemical Co, Rockford, Ill); albumin and IgG, by radioimmunoassay (Calbiochem, La Jolla, Calif). The contribution of bleeding to the total protein concentration in BAL fluid was calculated by multiplying the plasma total protein concentration by the ratio of BAL hematocrit to blood hematocrit. This calculated bleeding-derived protein concentration was then divided by the BAL total protein concentration to yield the percentage of BAL protein caused by bleeding.

Cytokine concentrations were measured in duplicate by enzyme-linked immunosorbent assays (ELISAs) by using commercially available kits in dilutions that allowed interpolation from simultaneously run standard curves: interleukin 1β, interleukin 6, and interleukin 8 (R & D Systems Inc, Minneapolis, Minn) and tumor necrosis factor-α (NBS Biologicals Ltd, Huntingdon Kembs, England). Leukotriene B4 was measured by reverse phase high-pressure liquid chromatography. Prostaglandin E2 and thromboxane B2 were measured by immunoassay with commercial kits (Cayman Chemicals, Ann Arbor, Mich). Clara cell protein in BAL fluid and plasma was measured by a latex immunoassay. Surfactant protein A in BAL fluid and plasma was measured by a sandwich ELISA technique.

Lavage concentrations of nitrate and nitrite were measured by reducing both species to nitric oxide with vanadium chloride and hydrochloric acid and measuring nitric oxide by a chemiluminescence detector (Sievers Instruments Inc, Boulder, Colo).

**Statistical Analysis**

The statistical analysis was performed with StatView (Abacus Concepts, Berkeley, Calif). Data are presented as mean (SD). Group comparisons were performed with a 2-way repeated-measures analysis of variance to compare differences between low and high altitude and subject groups. Bonferroni-Dunn corrections for multiple comparisons were performed when appro-
RESULTS

One subject in Zurich and 5 at high altitude were unable to undergo bronchoscopy because of unsuccessful upper airway anesthesia or severe headache with acute mountain sickness as assessed by the Lake Louise Consensus questionnaire. Thus, BAL data at both altitudes were obtained in 10 HAPE-susceptible and 6 HAPE-resistant subjects. All HAPE-resistant subjects remained well at high altitude, except for symptoms of mild acute mountain sickness. In the HAPE-susceptible group, 3 developed HAPE on day 2 before bronchoscopy, 6 developed HAPE on day 3, and 1 remained well throughout. The chest radiograph and slightly hemorrhagic BAL fluid obtained from a representative subject with HAPE diagnosed before bronchoscopy are shown in Figure 1. For purposes of data presentation at high altitude, the HAPE-susceptible subjects are divided into those who had HAPE on bronchoscopy (HAPE-susceptible ill; n = 3) and those who did not have HAPE by clinical examination and chest radiography on bronchoscopy (HAPE-susceptible well; n = 7) but of whom 6 met criteria for HAPE the following day.

PA Pressure, Arterial Blood Gas Analysis, and Chest Radiography

Systolic PA pressures are shown in Figure 2. They were not significantly different between the HAPE-resistant and HAPE-susceptible groups at low altitude. At high altitude, mean systolic PA pressures were higher in both groups. The HAPE-susceptible subjects, however, had significantly higher pressures. The mean systolic PA pressure in the HAPE-susceptible subjects was 66 mm Hg vs 37 mm Hg in the HAPE-resistant group at 4559 m.

Arterial blood gas data and chest radiograph scores on bronchoscopy are presented in Table 1. Arterial saturation and PaO2 in all subjects at low altitude were normal. At high altitude immediately before BAL, there were statistically significant differences in arterial saturation and PaO2 among the 3 groups, demonstrating a continuum of declining arterial saturation and PaO2 from those well at high altitude to those with the earliest onset of HAPE. In HAPE-resistant subjects, the chest radiograph scores remained 0 at high altitude, indicating no evidence of interstitial or alveolar edema. In the 3 HAPE-susceptible subjects who developed HAPE before BAL was performed, the mean chest radiograph score was 12.7. The 6 HAPE-susceptible subjects who developed HAPE on the day following BAL had a mean score on bronchoscopy of 1.5, which rose the next day to 4.6, reflective of mild pulmonary edema.

BAL Analysis

Figure 2 also shows the BAL red blood cell and albumin concentrations. There were statistically significant differences between the HAPE-resistant and HAPE-susceptible groups at high altitude in the number of red blood cells in BAL fluid and the concentration of albumin, a serum-derived protein. Figure 3 plots individual BAL red blood cell count and albumin concentration against PA systolic pressures at high altitude and shows that red blood cells may appear in the alveolar space in some individuals at systolic PA pressures higher than 60 mm Hg, in contrast to albumin that rises from normal concentrations with pressures as low as 35 mm Hg.

The IgG results and the remainder of the BAL fluid cell counts, leukocyte differential percentages, and total protein levels are shown in Table 2 with the lavage and plasma concentrations of surfactant protein A and Clara cell protein levels, 2 naturally occurring airspace proteins. There were no differences in total BAL leukocyte counts or leukocyte differential between low and high altitude and HAPE-resistant and HAPE-susceptible subjects, despite the development of HAPE in the majority of the HAPE-susceptible subjects. At high altitude, the HAPE-resistant subjects had a slight but statistically significant increase in total protein, albumin, and IgG concentrations but not in red blood cells. In the HAPE-susceptible subjects without radiographic evidence of edema (HAPE-susceptible well) on bronchoscopy, plasma-derived protein and red blood cell levels were statistically increased by a factor of roughly 10- to 20-fold. In the 3...
were no significant differences for thromboxane, prostaglandin E₂, and leukotriene B₄ concentrations. At high altitude, lavage nitrate-nitrite concentrations rose significantly in the HAPE-resistant subjects but fell significantly in both HAPE-susceptible groups.

**COMMENT**

The main study finding is that early HAPE is characterized by high PA pressures that lead to a protein-rich and mildly hemorrhagic edema, with normal levels of leukocytes, cytokines, and eicosanoids. These data demonstrate that the leak in early HAPE is a noninflammatory unidirectional breach of the alveolar-capillary barrier. Given that abnormally high PA pressures in HAPE are associated with increased capillary pressure but not elevated left atrial pressure,³ we conclude that HAPE is a form of hydrostatic pulmonary edema with altered alveolar-capillary permeability.

How increased hypoxic pulmonary vasoconstriction leads to increased microvascular pressure is unresolved. Hultgren et al⁴ proposed that hypoxic pulmonary vasoconstriction may be regionally heterogeneous, leading to areas of underperfusion and overperfusion. The combination of higher flow in areas of weaker vasoconstriction with extremely high PA pressure could explain edema formation in the capillaries downstream of these arterial resistance vessels if the longitudinal pressure drop across these vessels is insufficient to lower the pressure below a threshold of 19 mm Hg at the point of entry into the alveolar microvasculature. Unevenness of regional hypoxic pulmonary vasoconstriction has been detected with nuclear blood flow imaging in humans with HAPE susceptibility⁵,⁶ and by high-resolution microsphere techniques in animals.⁷,⁸ In addition, pulmonary venoconstriction, which accounts for 20% of total hypoxic pulmonary vasoconstriction,⁹ may be a critical factor because it causes pressure elevation upstream in the alveolar microvasculature consistent with measurements reported by Maggiorini et al.⁸ Both of these mechanisms can account for high microvascular pressures without the need to invoke occult left ventricular dysfunction, which has never been demonstrated in any catheterization studies.¹ ³,⁴,⁸

The mechanisms underlying individual differences in hypoxic pulmonary vasoconstriction and propensity to develop HAPE may involve nitric oxide, since HAPE-susceptible individuals have lower exhaled nitric oxide levels than HAPE-resistant individuals with acute normobaric hypoxia (fraction of inspired oxygen = 0.12) and at 4559 m.⁴⁰,⁴¹ We now show that susceptible subjects have decreased nitrate-nitrite concentrations in BAL fluid at high altitude, while resistant subjects have increased concentrations, fur-
High-altitude pulmonary edema (HAPE) is a form of acute pulmonary edema that occurs at high altitudes. It is characterized by high-pressure hydrostatic leak with features of altered alveolar-capillary membrane permeability. Although HAPE is an uncommon form of edema, investigations such as ours can shed light on our understanding of other types of pulmonary edema. For instance, our findings may have direct relevance to neurogenic pulmonary edema, a not uncommon consequence of elevated intracranial pressure in which pulmonary artery pressures can be suddenly elevated as high as those in HAPE and in which alveolar fluid may have high protein concentrations.

How increased microvascular pressures in HAPE cause high-permeability edema is not readily explained by classical hydrostatic (Starling) forces, which should generate a protein-poor alveolar edema. Thus, to explain a hydrostatic high-permeability leak, West and colleagues proposed the concept of alveolar capillary stress failure. This lesion is characterized by high-pressure-induced traumatic breaks in the basement membranes of the alveolar capillary barrier that permit the passage of plasma and blood cells. Similar structural alterations in the alveolar-capillary barrier have also been described in a perfused rabbit lung when pulmonary venous pressure was elevated and may explain the occasional patient presenting with blood-tinged sputum in acute congestive heart failure. In this model of hydrostatic edema, some regions of alveolar flooding had high protein contents, an observation that challenges the dogma that hydrostatic pulmonary edema is entirely described by passive and selective filtration of plasma dictated by simple osmotic and pressure gradients. Recent BAL findings of increased total protein and C-reactive protein concentrations in human cardiogenic pulmonary edema give further credence to the concept that sufficiently high microvascular pressures in the lung can lead to changes in vascular permeability to molecules of large molecular weight. Our lavage data in HAPE, therefore, fit this newer paradigm of hydrostatic pulmonary edema, which resolves the conundrum of a hydrostatic leak with features of altered alveolar-capillary membrane permeability. Although HAPE is an uncommon

**Table 2. Bronchoalveolar Lavage Cell Counts, Leukocyte Differential, and Proteins at Low and High Altitude**

<table>
<thead>
<tr>
<th></th>
<th>Low Altitude (490 m)</th>
<th>High Altitude (4559 m)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Resistant 490 m</td>
<td>Susceptible 490 m</td>
</tr>
<tr>
<td></td>
<td>8100 (4200)</td>
<td>6300 (3500)</td>
</tr>
<tr>
<td>Total leukocytes, cells/µL</td>
<td>3 (1)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Macrophages</td>
<td>94</td>
<td>95</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Albumin, mg/dL</td>
<td>0.4 (0.2)</td>
<td>0.6 (0.2)</td>
</tr>
<tr>
<td>IgG, mg/dL</td>
<td>0.2 (0.2)</td>
<td>0.3 (0.2)</td>
</tr>
<tr>
<td>Surfactant protein A, mg/dL</td>
<td>0.7 (0.3)</td>
<td>0.9 (0.3)</td>
</tr>
<tr>
<td>Surfactant protein B, mg/dL</td>
<td>0.7 (0.3)</td>
<td>0.9 (0.3)</td>
</tr>
<tr>
<td>Surfactant protein C, mg/dL</td>
<td>0.7 (0.3)</td>
<td>0.9 (0.3)</td>
</tr>
<tr>
<td>Plasma surfactant protein A, ng/mL</td>
<td>40 (12)</td>
<td>37 (14)</td>
</tr>
<tr>
<td>Plasma surfactant protein B, ng/mL</td>
<td>40 (12)</td>
<td>37 (14)</td>
</tr>
<tr>
<td>Plasma surfactant protein C, ng/mL</td>
<td>40 (12)</td>
<td>37 (14)</td>
</tr>
</tbody>
</table>

*P<0.05 vs 490 m at baseline and P<0.05 vs HAPE-resistant at 4550 m.
1P<0.05 vs 490 m at baseline, P<0.05 vs HAPE-resistant at 4550 m, and P<0.05 vs HAPE-susceptible well at 4559 m.
1P<0.05 vs baseline.
Leukotriene B4, pg/mL 547 (45) 521 (67) 499 (53) 537 (49) 512 (66)
Interleukin 8, pg/mL 107 (24) 129 (21) 181 (34) 165 (33) 190 (45)

Table 3. Bronchoalveolar Lavage Cytokine, Eicosanoid, and Nitrate-Nitrite Concentrations at Low and High Altitude

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>490 m</th>
<th>4559 m</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Resistant</td>
<td>Susceptible</td>
<td>Resistant</td>
</tr>
<tr>
<td>Interleukin 1k, pg/mL</td>
<td>0.4 (0.1)</td>
<td>0.4 (0.1)</td>
<td>1.8 (0.4)</td>
</tr>
<tr>
<td>Interleukin 8, pg/mL</td>
<td>107 (24)</td>
<td>129 (21)</td>
<td>181 (34)</td>
</tr>
<tr>
<td>Tumor necrosis factor α, pg/mL</td>
<td>9.5 (2.7)</td>
<td>9.9 (2.4)</td>
<td>8.1 (2.3)</td>
</tr>
<tr>
<td>Leukotriene B4, pg/mL</td>
<td>547 (45)</td>
<td>521 (67)</td>
<td>499 (53)</td>
</tr>
<tr>
<td>Prostaglandin E2, pg/mL</td>
<td>13 (3)</td>
<td>14 (4)</td>
<td>13 (4)</td>
</tr>
<tr>
<td>Thromboxane, pg/mL</td>
<td>24 (3)</td>
<td>14 (3)</td>
<td>43 (6)</td>
</tr>
</tbody>
</table>
| Nitrate-nitrite, µM | 2.4 (0.4) | 2.9 (0.3) | 3.4 (0.3)* | 1.2 (0.4)+ | 1.3 (0.5)+

*P<.05 vs 490 m at baseline.
†P<.05 vs HAPE-resistant at 4559 m.

veolar hemorrhage as a marker of capillary stress failure, only 0.2% and 1.1% of total protein can be attributed to alveolar bleeding in the HAPE-susceptible well and HAPE-susceptible ill subjects, respectively. Furthermore, Figure 3 reveals that albumin flux into the lung occurs at lower PA pressures, with an approximate systolic PA pressure threshold of less than 40 mm Hg compared with more than 60 mm Hg for red blood cells. Although it is possible that milder capillary stress failure permits plasma but not red blood cell movement into the alveoli, several findings militate against early capillary stress failure in human HAPE. First is the lack of change in BAL fluid leukotriene B4, which is markedly increased in BAL fluid of rabbit lungs subjected for several minutes to high capillary pressures that generate histologically identifiable capillary stress failure.52 Second, stress failure theoretically leads to a bidirectional protein leak. However, we show that 2 endogenous air-space proteins, surfactant protein A and Clara cell protein, do not appear in the bloodstream, in contrast to the injury and leak in adult respiratory distress syndrome,31,32 a high-permeability but nonhydrostatic lung injury. Last, Bartsch et al33 found no evidence of activated intravascular coagulation in HAPE, except in the most advanced cases. If stress failure occurs early, one would expect that exposure of alveolar basement membranes, as shown in animal models,43,44 would initiate activation of platelets and the extrinsic pathway of coagulation.25

Our findings suggest a component of high-pressure–mediated alteration in the normal selectivity of the alveolar-capillary barrier to molecules with large molecular weight. Such noninjurious hemodynamically induced effects on a structurally intact barrier include relaxation of the tight junctions between cells of the capillary endothelium and alveolar epithelium that permit greater unidirectional intercellular passage of macromolecules.51 Another route may be that of transcellular passage through vesicular channels that form with high intracapillary pressure.52 Both mechanisms are compatible with the nontraumatic, noninflammatory, unidirectional leak characteristics found in early HAPE and may explain why recovery from HAPE can in many cases be so rapid with any means of PA pressure reduction: descent, oxygen, or vasodilators.53,54

Although HAPE develops in the absence of any local or systemic inflammation, inflammatory activation occurs in later stages.13–18 A secondary inflammatory reaction may occur in response to the injury of capillary stress failure if HAPE remains untreated for several days. Furthermore, if the local tissue PO2 falls into a range of less than 15 to 20 mm Hg, which is likely to occur in advanced HAPE in severely edematous lung regions and systemic postcapillary venules, there may be spontaneous cytokine release by vascular endothelial cells and leukocytes,51–24 leading to increased capillary permeability and neutrophil recruitment to the lung. Last, edematous lungs from any cause are more prone to bacterial infection, which in some cases might explain intense inflammation. Nevertheless, these explanations of secondary inflammation in HAPE do not exclude the possibility that pulmonary edema will occur at modest altitudes in some individuals by a preceding or concurrent infectious or inflammatory state, as demonstrated in animals19,20 and suggested by epidemiologic data in children with HAPE.21 In fact, Irwin and colleagues55 have shown that this HAPE-like condition develops in hypoxic rats primed with endotoxin and that it can occur without elevated PA pressures.

In conclusion, our lavage and PA pressure data on early HAPE combined with the catheterization data of Maggiorini et al8 demonstrate that HAPE is a unique noninflammatory unidirectional breach of the alveolar-capillary barrier. The edema is a protein-rich mildly hemorrhagic fluid arising from elevated PA and capillary pressures but normal low atrial pressures. Our study should put to rest the idea that inflammation in HAPE is pathogenic and thus prevent needless further investigation in this direction with potentially potent immune-modulating drugs. Increased protein concentrations in alveolar lavage fluid should not be taken necessarily as evidence for an inflammatory process, because it is now clearly established that high PA and microvascular pressures may lead to inflammatory-like permeability changes in the lung microvasculature.

Author Contributions: Study concept and design: Swenson, Maggiorini, Gibbs, Mairbäurl, Bärtsch. Acquisition of data: Swenson, Maggiorini, Mongovin, Gibbs, Greve, Mairbäurl, Bärtsch. Analysis and interpretation of data: Swenson, Maggiorini, Gibbs, Mairbäurl, Bärtsch. Drafting of the manuscript: Swenson, Bärtsch. Critical revision of the manuscript for important intellectual content: Swenson, Maggiorini, Mongovin, Gibbs, Mairbäurl, Bärtsch. Statistical expertise: Swenson, Bärtsch. Obtained funding: Swenson, Maggiorini, Bärtsch. Administrative, technical, or material support: Maggiorini, Mongovin, Gibbs, Mairbäurl, Bärtsch. Study supervision: Maggiorini, Gibbs, Bärtsch. Funding/Support: Pentax Inc provided the fiberop-
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REFERENCES
LETTERS

Comment. Very little US family medicine training occurs in rural areas. In the aggregate, 7.5% of family medicine training in the United States occurs in rural areas, although 22.3% of Americans live in rural places. Establishing rural family medicine training programs in rural areas is one strategy that contributes to the production of rural physicians, but it has not been widely adopted in the United States.

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5. Rabinoivitz HK, Diamond JJ, Markham FW, Payntr NP. Critical factors for designing programs to increase the supply and retention of rural primary care physicians. JAMA. 2001;286:1041-1048.

CORRECTIONS

Incorrect Units and Wording: In the Original Contribution entitled “Pathogenesis of High-Altitude Pulmonary Edema: Inflammation Is Not an Etiologic Factor” published in the May 1, 2002, issue of THE JOURNAL (2002;287:2228-2235), there were incorrect units in Figures 2 and 3 and Table 2. The units of bronchoalveolar lavage red blood cells should have been 10^7/mL (Figures and Table), and those of total protein should have been mg/dL (Table). The last sentence under “Echocardiography” should have read “The jugular venous pressure was measured by inspection and added to ΔP to calculate the systolic PA pressure.”

Numbers Reversed: In the Original Contribution entitled “Cardiovascular Disease Outcomes During 6.8 Years of Hormone Therapy: Heart and Estrogen/Progestin Replacement Study Follow-up (HERS II)” published in the July 3, 2002, issue of THE JOURNAL (2002;288:49-57), 2 numbers were reversed. On page 53, the fourth sentence in the “Adjusted and per Protocol Analyses” section should read “By the end of follow-up in HERS II, the proportion of statin use was 63% for the hormone group and 67% for the placebo group (P = .01).”

Incorrect Year and Wording: In the Medical News & Perspectives article entitled “Walking in Beauty at Sage Memorial Hospital” published in the July 3, 2002, issue of THE JOURNAL (2002;288:29-34), an incorrect year appeared on page 29 in the second sentence in the photo caption. It should read “Right, Louis A. Kazal, Jr, the hospital’s medical director from 1996 to 1999, in front of a mural outside the old gymnasium, now the Wellness Center.” On page 34, the second sentence in the “Volunteers Are Welcome” section should read “For example, Preston Manning, MD, a now retired Mayo Clinic-trained surgeon, ‘helped out’ for 2 years.”

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