High-Altitude Pulmonary Edema Is Initially Caused by an Increase in Capillary Pressure

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Background—High-altitude pulmonary edema (HAPE) is characterized by severe pulmonary hypertension and bronchoalveolar lavage fluid changes indicative of inflammation. It is not known, however, whether the primary event is an increase in pressure or an increase in permeability of the pulmonary capillaries.

Methods and Results—We studied pulmonary hemodynamics, including capillary pressure determined by the occlusion method, and capillary permeability evaluated by the pulmonary transvascular escape of 67Ga-labeled transferrin, in 16 subjects with a previous HAPE and in 14 control subjects, first at low altitude (490 m) and then within the first 48 hours of ascent to a high-altitude laboratory (4559 m). The HAPE-susceptible subjects, compared with the control subjects, had an enhanced pulmonary vasoreactivity to inspiratory hypoxia at low altitude and higher mean pulmonary artery pressures (37±2 versus 26±1 mm Hg, P<0.001) and pulmonary capillary pressures (19±1 versus 13±1 mm Hg, P<0.001) at high altitude. Nine of the susceptible subjects developed HAPE. All of them had a pulmonary capillary pressure >19 mm Hg (range 20 to 26 mm Hg), whereas all 7 susceptible subjects without HAPE had a pulmonary capillary pressure <19 mm Hg (range 14 to 18 mm Hg). The pulmonary transcapillary escape of radiolabeled transferrin increased slightly from low to high altitude in the HAPE-susceptible subjects but remained within the limits of normal and did not differ significantly from the control subjects.

Key Words: edema ■ lung ■ capillaries

High-altitude pulmonary edema (HAPE) is a life-threatening complication of rapid ascents to altitudes higher than 2500 m.1 Exactly what causes HAPE remains unknown. Patients with HAPE have an increase in pulmonary artery pressures and normal left atrial pressure2–7 and enhanced pulmonary vasoreactivity to inspiratory hypoxia8–10 and are improved by pharmacological interventions that decrease pulmonary artery pressures.11–14 These observations are in keeping with the hypothesis that HAPE is caused by a stress failure of the pulmonary capillaries related to inhomogeneous hypoxic vasoconstriction and overperfusion.15 The bronchoalveolar lavage fluid in patients with HAPE, however, has been shown to be rich in high-molecular-weight proteins, cells, and markers of inflammation,16 suggesting increased capillary permeability as a primary event. We therefore designed the present study, which aimed at direct measurements of both pressure and permeability of the pulmonary capillaries in the early stages of HAPE.

Methods

Subjects and Study Design

Thirty nonacclimatized mountaineers, 7 women and 23 men 23 to 60 years old, were included in the study, which was approved by the Ethics Committee of the University Hospital of Zürich. Sixteen had a history of ≥1 episodes of HAPE.

All the subjects underwent a right heart catheterization with pulmonary hemodynamic measurements, including pulmonary capillary pressure, and a measurement of pulmonary capillary permeability as estimated by the transvascular escape of 67Ga-labeled transferrin, at the University Hospital of Zürich (altitude 490 m). The pulmonary hemodynamic measurements were repeated after 10 minutes of breathing an inspired oxygen fraction (FIO2) of 0.12 to produce a decrease in arterial partial pressure of O2 (PaO2) to values normally recorded at an altitude of ~4500 m.

Thereafter, within 2 to 3 weeks, all the subjects ascended in <24 hours from Alagna Valsesia (1130 m) to a research laboratory on Monte Rosa, the Regina Margherita hut (4559 m), with an overnight stay at the Gnifetti hut (3611 m). After a first night at 4559 m, the subjects underwent another measurement of pulmonary capillary permeability and a right heart catheterization with pulmonary hemo-
dynamic measurements. Pulmonary hemodynamic measurements were repeated after 10 minutes by breathing an $FIO_2$ of 0.33 to increase $Pao_2$, to values normally recorded at low altitude. One of the subjects was investigated only at high altitude.

Assessment of HAPE

HAPE was clinically suspected in the presence of dry cough, dyspnea and/or orthopnea, tachypnea (>25 breaths per minute), or central cyanosis and if rales and/or wheezes were present on chest auscultation. Posteroanterior chest radiographs were taken with a mobile unit (TRS, Siemens) with a fixed target-to-film distance of 140 cm at 95 kV and 3 to 6 mAs. At the Capanna Regina Margherita, HAPE was diagnosed if the x-ray film showed clear signs of interstitial and/or alveolar edema compared with the chest radiograph taken at low altitude (Figure 1). Thereafter, chest radiographs were coded and analyzed according to previously described criteria by a radiologist who was unaware of the subjects’ clinical history. Briefly, with the mediastinum used as the vertical axis and the hilum as the horizontal axis, 4 lung areas were assessed separately for the presence of edema. Normal parenchyma was given a score of 0; areas with questionable pathological findings, 1; areas with >50% nonconfluent interstitial infiltration, 2; areas with >50% nonconfluent interstitial infiltration, 3; and areas with alveolar, patchy confluent infiltrates, 4. Any chest radiograph with ≥1 lung quadrant with a score of 2 was considered positive for HAPE.

Right Heart Catheterization

Right heart catheterization was performed with a standard thermodilution balloon-tipped pulmonary artery catheter (131H-7F Baxter) inserted via the internal jugular vein. To ensure the safety of the procedure, the internal jugular vein was first located with an ultrasound Doppler device (SonoGuide2, Darbomed AG). Thereafter, the pulmonary artery catheter was floated under constant pressure-wave monitoring into the pulmonary artery for the measurement of mean pulmonary artery pressure ($Ppa$), pulmonary artery occluded pressure (wedge pressure, $Ppao$), pulmonary capillary pressure ($Pc$), and right atrial pressure and for mixed-venous blood sampling. A small polyethylene catheter (Vygon) was inserted into a radial artery or a femoral artery to measure systemic arterial pressure and for arterial blood sampling. Pulmonary and systemic artery pressures were measured with transducers (Homedics AG) connected to a hemodynamic and ECG monitoring system (Sirecust 404, Siemens). The pressure transducers were zero-referenced at midchest, and vascular pressures were measured at end inspiration. Heart rate was determined by a continuously monitored ECG. Cardiac output ($Q$) was measured by thermodilution with 10-mL injections of 5% cold dextrose in water ($8^\circ C$ to $10^\circ C$) and a computer (Vigilance, Baxter), and was calculated as the mean of 3 to 5 determinations.

Determination of the Pulmonary Capillary Pressure

The vascular pressure signals were sampled at 200 Hz with an analog-to-digital converter (RTI 800, Analog Devices) and stored on a personal computer. Pulmonary capillary pressure was computed in triplicate from the pulmonary artery pressure-decay curve obtained after rapid inflation of the balloon of the pulmonary artery catheter and extrapolated back toward time 0 after the occlusion, adjusted to $Ppao$, and extrapolated back toward time 0+150 ms with a purpose-made software.

Assessment of the Pulmonary Capillary Leak

Pulmonary capillary permeability was assessed with a noninvasive measurement of the transvascular protein flux in the lung as initially reported in humans by Gorin et al and adapted by Raijmakers et al. Red blood cells were labeled in vitro with $^{99m}$Tc (300 $\mu$Ci, 11 $\mu$Bq; physical half-life 6 hours) after injection of sodium pyrophosphate (DRN 4342 Technecan PYP, Mallinckrodt). Transferrin was labeled in vivo with intravenous injection of $^{59}$Gallium citrate (100 $\mu$Ci, 4 $\mu$Bq; physical half-life 78 hours) after injection of sodium iodine crystal placed on the midclavicular line over the right (fourth intercostal space) and the left (second intercostal space) lung. Measurements obtained at

![Figure 1. Chest x-ray film at low (A) and high (B) altitude of a representative subject with early HAPE.](image1)

![Figure 2. Pressure-decay curves for determination of $Pc$ in 3 representative subjects at high altitude: a control subject, a HAPE-susceptible subject with no edema (non-HAPE), and a subject with HAPE. Calculated $Pcs$ were 13, 15, and 26 mm Hg, respectively.](image2)
half-life, and spillover of 67 Ga into the 99m Tc window. For each blood sample, a time-matched count rate over the lung was taken and the radioactivity ratio was calculated as the slope of the increase of the radioactivity ratio over time divided by the intercept (Figure 3). The values for both lungs are shown in Figure 2. Altitude-induced increases were most important in the subjects who developed HAPE with a Ppa >22 mm Hg. Ppao was slightly increased in the HAPE-susceptible subjects who did not develop HAPE (Table). The radiographic score was already diagnostic of pulmonary edema (radiographic score 7.0 ± 0.6, range 4 to 10) (Table). The radiographic score became abnormally high in the other 5 subjects during the following nights.

Altitude decreased PaO2 and PaCO2. The altitude-induced decrease in PaO2 was more pronounced in HAPE-susceptible subjects than in control subjects. The HAPE-susceptible subjects with HAPE had a PaO2 of 37 ± 2 mm Hg versus a PaO2 of 43 ± 2 mm Hg in HAPE-susceptible subjects who did not develop HAPE (P = 0.03). PaCO2 was not different in the subgroups.

Altitude increased Q, Ppa, Pc, and Ppao. The latter change was slight and significant in the HAPE-susceptible subjects only. Altitude-induced increases in Ppa and Pc were more pronounced in the HAPE-susceptible subjects than in the control subjects. Representative pressure-decay curves (Ppa–Ppao) obtained in a control subject, a HAPE-susceptible subject without HAPE, and a subject with HAPE are shown in Figure 2. Altitude-induced increases were more important in the subjects who developed HAPE with a Ppa >35 mm Hg and a Pc >19 mm Hg (Figure 5). Pc was correlated to Ppa (r2 = 0.76, P < 0.001) and, as shown in Figure 6, to Ppao and to the radiographic score.

The PLI remained within normal limits in all subjects. There was no difference between the PLIs of the HAPE-susceptible subjects who developed edema, those who did not, and the control subjects (F of the ANOVA = 1.95, P = 0.16) (Figure 7). The PLI increased slightly in both HAPE-susceptible subjects who did not develop HAPE (8.5 ± 0.5 to 11.9 ± 0.9 × 10−3/mm/min, P = 0.02) and in those who developed HAPE (8.2 ± 0.6 to 11.7 ± 1.4 × 10−3/mm/min, P = 0.04), but not in control subjects (10.0 ± 0.5 to 9.3 ± 0.8 × 10−3/mm/min, P = 0.32) (F of the ANOVA = 5.34, P = 0.03). In patients with ARDS, the PLI was definitely higher (Figure 7).
With supplemental O\textsubscript{2}, Pa\textsubscript{O\textsubscript{2}} and Pa\textsubscript{CO\textsubscript{2}} increased and Ppa and Q\textsubscript{˙} decreased, but there was a decrease in Pc in the HAPE-susceptible subjects only.

**Discussion**

The main finding of the present study is that early HAPE is characterized by an increase in pulmonary capillary pressure, whereas capillary permeability as assessed by the transvascular escape of radiolabeled transferrin remains within the limits of normal.

HAPE generally occurs in circumstances not easily compatible with invasive studies. Direct measurements of pulmonary vascular pressures by right heart catheterization, however, have been reported previously in a total of 20 patients with HAPE.2–7 In these patients, Ppa was on average 42 mm Hg.

**Table 1.**

<table>
<thead>
<tr>
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<th>Low Altitude (490 m)</th>
<th>High Altitude (4559 m)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>Control</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>HAPE-susceptible</td>
<td>15</td>
</tr>
<tr>
<td>Pa\textsubscript{O\textsubscript{2}}, mm Hg</td>
<td>Control</td>
<td>92 ± 2</td>
</tr>
<tr>
<td></td>
<td>HAPE-susceptible</td>
<td>92 ± 4</td>
</tr>
<tr>
<td>Pa\textsubscript{CO\textsubscript{2}}, mm Hg</td>
<td>Control</td>
<td>34 ± 1</td>
</tr>
<tr>
<td></td>
<td>HAPE-susceptible</td>
<td>37 ± 1</td>
</tr>
<tr>
<td>Q\textsubscript{˙}, L · min\textsuperscript{−1} · m\textsuperscript{−2}</td>
<td>Control</td>
<td>3.3 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>HAPE-susceptible</td>
<td>3.1 ± 0.2</td>
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<tr>
<td>Ppa, mm Hg</td>
<td>Control</td>
<td>14 ± 1</td>
</tr>
<tr>
<td></td>
<td>HAPE-susceptible</td>
<td>16 ± 1</td>
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<tr>
<td>Pc, mm Hg</td>
<td>Control</td>
<td>10 ± 1</td>
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<tr>
<td></td>
<td>HAPE-susceptible</td>
<td>9 ± 1</td>
</tr>
<tr>
<td>Ppao, mm Hg</td>
<td>Control</td>
<td>8 ± 1</td>
</tr>
<tr>
<td></td>
<td>HAPE-susceptible</td>
<td>7 ± 1</td>
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<tr>
<td>Pulmonary leak index, 10\textsuperscript{−3}/min</td>
<td>Control</td>
<td>10.0 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>HAPE-susceptible</td>
<td>8.4 ± 0.5</td>
</tr>
</tbody>
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Mean values are given as mean ± SEM. P<0.05 *vs control, †vs low-altitude baseline, ‡vs low-altitude hypoxia, §vs high-altitude baseline.

**Figure 4.** Individual Ppa and Pc in 14 control subjects and 15 HAPE-susceptible subjects while breathing 12% oxygen for 10 minutes at low altitude. Non-HAPE indicates HAPE-susceptible subjects without HAPE. Horizontal bars show means. **P<0.01 vs control subjects.

**Figure 5.** Individual Ppa and Pc in 14 control subjects and in 16 HAPE-susceptible subjects at high altitude. Horizontal bars show means. *P<0.05, **P<0.01 vs control; †P<0.01 vs non-HAPE.
mm Hg but ranged from 13 to 113 mm Hg. This variability may be explained by variable altitude of occurrence, frequent evacuation to lower altitude at time of diagnosis, and treatments with diuretics and/or oxygen. Conversely, left atrial pressure as assessed by occluded (or wedge) Ppa was consistently low or normal.2–7 The present results show that severe pulmonary hypertension with a normal left atrial pressure is a constant finding in untreated HAPE. They also confirm that pulmonary hypertension tends to be severe, with mean pulmonary artery pressure often 30 to 40 mm Hg in asymptomatic HAPE-susceptible subjects,8 and mild, with mean pulmonary artery pressure most often between 20 and 30 mm Hg, in normal subjects with good tolerance to high altitude.22,23 In addition, our results are in keeping with previous reports of variably enhanced pulmonary vasoreactivity to hypobaric hypoxia in HAPE-susceptible subjects8 –10 and with studies showing an only partial reversibility of Ppa with supplemental oxygen breathing after a few hours of hypoxia.22,23

The present study is the first to report Pc determinations in normal volunteers. At low altitude, the values were compatible with a normal longitudinal distribution of pulmonary vascular resistance in all the subjects.18 Pulmonary capillary pressures increased at altitude but were on average 6 mm Hg higher in the HAPE-susceptible subjects than in the control subjects. In addition, there was a threshold of 19 mm Hg for Pc, above which pulmonary edema developed. This threshold value for edema formation is in keeping with previous experimental observations in dogs of a Ppa-independent critical capillary pressure of 17 to 24 mm Hg, above which lungs continuously gain weight.24 Why oxygen breathing only partially reversed altitude-induced increase in Pc is not clear but could be explained by early remodeling of small pulmonary venules.

There are 2 different explanations for increased Pc in HAPE-susceptible subjects. The first relies on inhomogeneous hypoxic vasconstriction causing regional overperfusion of capillaries,1 leading to stress failure.15 It is difficult, however, to conceive that the tip of the pulmonary catheter always went to pulmonary arteries perfusing edematous lung regions. The second relies on hypoxic constriction occurring either at the smallest arterioles or at the venules, or both. Occlusion studies on isolated dog lungs have shown that the venous component of hypoxic pulmonary vasconstriction may amount to 20% of the total increase in pulmonary vascular resistance.25 The capillary-venous segment, as determined by arterial occlusion, has been estimated, on the basis of comparisons with direct micropuncture pressure measurements, to include not only the capillaries but also small arterioles, up to 100 to 150 μm in diameter.26 One study suggested that these smallest arterioles leak in the presence of markedly increased Ppa.27 As previously suggested,13 a hypoxic pulmonary venous constriction might offer a more satisfactory explanation for increased Pc in HAPE.

The 67Ga-labeled transferrin protein transport ratio has been reported to be a sensitive and specific marker of acute lung injury that discriminates between cardiogenic pulmonary edema and ARDS.20 In the present study, 67Ga PLIs were within the normal range at low and high altitude and were not

Figure 6. Correlations between pulmonary capillary pressure and Paco2 and radiographic score at high altitude.

Figure 7. PLI in 14 control subjects and 16 HAPE-susceptible (HAPE-s) subjects at high altitude and in 8 patients with ARDS. Non-HAPE indicates HAPE-susceptible subjects who did not develop HAPE. **P<0.01 vs control, †P<0.01 vs non-HAPE, ‡P<0.01 vs HAPE. Horizontal bars show means.
different between those subjects who developed HAPE and those who did not. There was, however, a slight but significant tendency of the capillary leak index to increase from low to high altitude in the HAPE-susceptible subjects. This may be explained by an early transcapillary leak of protein due to very high capillary pressures. Early inflammatory changes cannot be excluded either. In addition, because hemoptysis occurs in HAPE, it is also possible that the pulmonary capillary leak index in our subjects with HAPE would have underestimated capillary permeability changes because of passage of tagged red blood cells into the alveolar space.

The absence of a major increase in pulmonary capillary leak index in HAPE seems to contrast with reported increases in protein and inflammatory mediators in bronchoalveolar lavage fluid in subjects with HAPE. These measurements, however, were obtained in subjects at a later stage of HAPE than in the present study. Conversely, elevated concentrations of markers of inflammation have also been reported in bronchoalveolar lavage fluid of patients with pulmonary edema secondary to left heart failure. A likely scenario therefore may be that markedly increased capillary pressures (possibly with focal areas of stress failure) lead to secondary inflammatory changes.

In summary, we found that subjects with early HAPE have pulmonary capillary pressures >19 mm Hg and a 67Ga PLI within the normal range, suggesting that HAPE is initially a hydrostatic-type pulmonary edema.

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References

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