Hypoxia-Induced Pulmonary Blood Redistribution in Subjects With a History of High-Altitude Pulmonary Edema

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Background—Pulmonary hypertension has been suggested to play an important role in development of high-altitude pulmonary edema (HAPE), and individual susceptibility has been suggested to be associated with enhanced pulmonary vascular response to hypoxia. We hypothesized that much greater pulmonary vasoconstriction would be induced by acute alveolar hypoxia in HAPE-susceptible (HAPE-s) subjects and that changes in pulmonary blood flow distribution could be demonstrated by radionuclide study.

Methods and Results—We performed ventilation-perfusion scintigraphy in 8 HAPE-s subjects and 5 control subjects while each was in the supine position and acquired functional images of pulmonary blood flow and ventilation under separate normoxic and hypoxic (arterial oxygen saturation, 70%) conditions. We also measured acceleration time/right ventricular ejection time (AcT/RVET) with Doppler echocardiography under each condition in both groups. Moreover, we assayed human leukocyte antigen (HLA) alleles serologically in the HAPE-s group. Pulmonary blood flow was significantly shifted from the basal lung region to the apical lung region under hypoxia in HAPE-s subjects, although no significant change in regional ventilation was observed. With Doppler echocardiography, HAPE-s subjects showed increased pulmonary arterial pressure during hypoxia compared with control subjects. The magnitude of cephalad redistribution of lung blood flow was significantly higher in the HLA-DR6–positive than in HLA-DR6–negative HAPE-s subjects.

Conclusions—These findings suggest that acute hypoxia induces much greater cephalad redistribution of pulmonary blood flow that results from exaggerated vasoconstriction in the basal lung in HAPE-s subjects. Furthermore, pulmonary vascular hyperreactivity to hypoxia may be associated with HLA-DR6. (Circulation. 2000;101:1418-1422.)

Key Words: echocardiography • genetics • hypoxia • scintigraphy • vasoconstriction

In some mountain climbers who have no cardiopulmonary problems, high-altitude pulmonary edema (HAPE), a severe form of acute mountain sickness, occurs after rapid ascent to altitudes >2500 m above sea level.1–4 HAPE is a rare form of noncardiogenic pulmonary edema. A few cases of HAPE are reported every year in Japan, and some patients have been transported to our institution, Shinshu University Hospital (610 m above sea level), from the “Japan Alps” of the central area of Japan.5 We previously exposed 8 HAPE-susceptible (HAPE-s) and 6 control subjects to 15% and then 10% oxygen and noted a significantly greater increase in both pulmonary arterial pressure and pulmonary vascular resistance in the HAPE-s subjects at both hypoxic levels.6 HAPE-s children also had greater pulmonary arterial pressure than nonsusceptible children, with acute hypoxia of 16% oxygen because of the greater increase in total pulmonary resistance.7 Pulmonary hypertension has been suggested to play an important role in development of HAPE, and individual susceptibility has been suggested to be associated with enhanced pulmonary vascular response to hypoxia.

Lung ventilation-perfusion scintigraphy has been used as a diagnostic method for various pulmonary diseases.8,9 Specifically, it has been part of routine preoperative evaluation for lung cancer resection or bullectomy in patients with chronic obstructive pulmonary disease and for assessment of pulmonary emboli in presence of chronic obstructive disease.10 Mismatch between ventilation and perfusion is often observed in these disorders as a result of uneven pulmonary blood distribution.10,11

We hypothesized that much greater pulmonary vasoconstriction would be induced by acute alveolar hypoxia in HAPE-s subjects compared with controls and that changes in pulmonary blood flow distribution could be demonstrated by ventilation-perfusion scintigraphy. The present study was...
designed to examine ventilatory and pulmonary hemodynamic responses to acute hypoxia in HAPE-s subjects and to identify pathophysiological correlates of HAPE susceptibility. We performed ventilation-perfusion scintigraphy with HAPE-s subjects in the supine position under separate hypoxic and normoxic conditions and compared the results with those from healthy volunteers. We also investigated differences in pulmonary arterial pressure response to acute hypoxia between HAPE-s subjects and control subjects by use of pulsed Doppler echocardiography, which is a useful method for noninvasive evaluation of pulmonary arterial pressure. Moreover, we assayed the human leukocyte antigen (HLA) alleles serologically in HAPE-s subjects to further test the reported association of this antigen with HAPE.

**Results**

**Ventilation-Perfusion Scintigraphy**

In the perfusion lung images, pulmonary blood flow was dominant in middle region under room air in both groups. Under hypoxic conditions, apparent redistribution occurred away from base and toward apex in 7 of 8 HAPE-s subjects. HAPE-s subject 6 showed no redistribution of pulmonary blood flow with hypoxia. However, flow distribution was unchanged in all control subjects during hypoxia. On the other hand, in the ventilation lung images, ventilation was not changed under either condition in both groups. A representative perfusion scintigraphic study of a HAPE-s subject is shown in the Figure. Red areas represent increased radioactivity.

**Comparison Between Conditions in Each Group**

Table 1 shows percentages of regional distribution counts to whole right lung on functional image of pulmonary blood flow ($Q$) under each condition (normoxia and hypoxia) in each group. Percentage of radioactivity counts of $Q$ to whole right lung in the apex was significantly increased (from 26.1% to 34.8%; $P<0.05$), and that in the base was significantly decreased (from 36.4% to 29.1%; $P<0.05$) by hypoxia compared with normoxia in HAPE-s subjects. However, no significant changes existed in control subjects under hypoxic conditions. Comparison of HAPE-s subjects with control subjects showed significance for redistribution toward apex (34.8% versus 25.2%; $P<0.01$).

Table 2 shows percentages of regional distribution counts to whole right lung on functional image of ventilation ($V$)
under each condition (normoxia and hypoxia) in each group. No significant differences were noted between normoxia and hypoxia in HAPE group or in the comparison between groups. In control subjects, percentage of radioactivity counts of $V$ to whole right lung in the apex was significantly decreased by hypoxia compared with normoxia (from 25.4% to 22.3%; $P_{<0.05}$).

Doppler Echocardiography

Doppler echocardiographic data are shown in Table 3. All subjects had good-quality pulsed-wave Doppler tracings from the right ventricular outflow tract. No significant difference existed in ratio of acceleration time to right ventricular ejection time (AcT/RVET) between groups before hypoxia, but AcT/RVET during hypoxia in HAPE-s subjects was significantly lower than in the control group (0.31±0.01 versus 0.38±0.02; $P<0.05$).

We used AcT/RVET as an index of pulmonary hypertension because a good relationship existed between AcT/RVET and pulmonary arterial pressure or pulmonary vascular resistance measured by cardiac catheterizations in HAPE-s and normal subjects.$^6$ AcT/RVET was decreased under hypoxic condition concomitant with increased pulmonary arterial pressure.

HLA-DR6 and Ventilation-Perfusion Scintigraphy

HLA-DR6 was positive in 5 of 8 HAPE-s subjects (subjects 2, 4, 5, 7, and 8). In both HLA-DR6–positive and HLA-DR6–negative subgroups, percentages of regional distribution counts to whole right lung on functional image of $Q$ and $V$ under each condition (normoxia and hypoxia) are shown in Table 4. Percentage of radioactivity counts of $Q$ to whole right lung in the apex was significantly increased (from 26.3% to 37.5%; $P<0.05$) and in the base was significantly decreased (from 36.5% to 27.0%; $P<0.05$) by hypoxia compared with normoxia in HLA-DR6–positive subjects. However, no significant changes were seen in $Q$ in HLA-DR6–negative subjects under hypoxic conditions. Comparison of $Q$ between subgroups showed significance for redis-

### Table 2. Percentage of Radioactivity Counts to Whole Right Lung in 3 Regions of Interest on Ventilation During Normoxia and Hypoxia in HAPE-s and Control Subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Normoxia, %</th>
<th>Hypoxia, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Apex</td>
<td>Middle</td>
</tr>
<tr>
<td>HAPE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>24.6</td>
<td>38.0</td>
</tr>
<tr>
<td>2</td>
<td>28.7</td>
<td>35.4</td>
</tr>
<tr>
<td>3</td>
<td>25.7</td>
<td>36.6</td>
</tr>
<tr>
<td>4</td>
<td>27.5</td>
<td>34.3</td>
</tr>
<tr>
<td>5</td>
<td>30.1</td>
<td>40.1</td>
</tr>
<tr>
<td>6</td>
<td>31.0</td>
<td>38.0</td>
</tr>
<tr>
<td>7</td>
<td>23.5</td>
<td>35.7</td>
</tr>
<tr>
<td>8</td>
<td>24.3</td>
<td>43.7</td>
</tr>
<tr>
<td>All</td>
<td>26.8</td>
<td>37.7</td>
</tr>
</tbody>
</table>

* $P_{<0.05}$ vs normoxia.

### Table 3. Doppler Echocardiographic Data in HAPE-s and Control Subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>AcT/RVET</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normoxia</td>
</tr>
<tr>
<td>HAPE</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.33</td>
</tr>
<tr>
<td>4</td>
<td>0.40</td>
</tr>
<tr>
<td>5</td>
<td>0.34</td>
</tr>
<tr>
<td>6</td>
<td>0.47</td>
</tr>
<tr>
<td>8</td>
<td>0.49</td>
</tr>
<tr>
<td>Mean±SEM</td>
<td>0.41±0.03</td>
</tr>
</tbody>
</table>

* $P_{<0.05}$ vs normoxia.

**Control**

|         |          |         |
|---------|----------|         |
| 1       | 0.47     | 0.42    |
| 2       | 0.48     | 0.43    |
| 3       | 0.41     | 0.38    |
| 4       | 0.41     | 0.34    |
| 5       | 0.44     | 0.32    |
| Mean±SEM | 0.44±0.01 | 0.38±0.02* |

* $P_{<0.05}$ vs normoxia; † $P_{<0.05}$ between groups.
 distribution toward apex (37.5% versus 28.7%; P<0.05). On the other hand, no significant differences existed in V between normoxia and hypoxia in either subgroup or in the comparison between subgroups.

Discussion

Hypoxic pulmonary vasoconstriction has been suggested to play a crucial role in the mechanisms that contribute to HAPE. However, how such a condition leads to edema formation is unclear, although an abnormal increase in pulmonary arterial pressure is a hallmark of HAPE. Because from a radiologic standpoint HAPE is often perihilar (patchy but not basal as in cardiac edema) and first seen around the large vessels, transarterial leakage proximal to resistance vessels has been proposed to explain how arterial but not capillary hypertension might cause pulmonary edema with homogeneous vasoconstriction. The patchiness led Hultgren earlier to propose that vasoconstriction might be inhomogeneous, which would lead to overperfusion of unconstricted regions of lung and cause local capillary leakage. To clarify whether vasoconstriction is homogeneous or inhomogeneous in response to hypoxia in HAPE-s subjects, we investigated regional ventilation and perfusion shifts and pulmonary hemodynamic responses to acute alveolar hypoxia by use of ventilation-perfusion scanning and Doppler echocardiography.

In the present study, we showed that acute hypoxia caused a significant cephalad redistribution of lung blood flow in HAPE-s subjects. Conversely, ventilation did not redistribute with hypoxia. Moreover, pulsed Doppler echocardiography confirmed the larger increase in pulmonary arterial pressure with hypoxia in HAPE-s versus control subjects. One interpretation of these findings is that hypoxic pulmonary vasoconstriction occurs to a greater extent in basal than in apical lung in HAPE-s subjects. An increased pulmonary blood flow in the apex, because of relative enhancement of basal hypoxic vasoconstriction, would represent a more-uniform perfusion during hypoxia. Hypoxic ventilation/perfusion ratios are likely to be more uniform in HAPE-s subjects. Another interpretation based on the perfusion studies is that more intense vasoconstriction in the bases may lead to higher precapillary intravascular pressures, although more of the pulmonary blood flow may go to the apices during hypoxia. Endothelium proximal to resistance vessels might be stretched, which leads to transarteriolar leakage. Thus, exaggerated vasoconstriction in basal lung would result in increased precapillary filtration pressure and edema formation. These possibilities appear consistent with radiographic evidence that pulmonary edema is first detected in the perihilar tissues that surround large vessels rather than in lung bases and periphery.

An alternative interpretation to these data is to postulate that an increase in pulmonary arterial pressure leads to recruitment of reserve vessels and to a more-even distribution over the whole lung. These reserve vessels are predominantly located in the apex of the lung in upright individuals. Some of this reserve is probably still available when these persons change to a horizontal position. Because pulmonary capillary recruitment was remarkably increased during hypoxia, the perfusion shift from the basal to the apical lung regions is likely to be caused by recruitment of pulmonary reserve vessels because of increased pulmonary arterial pressure.

HLA-DR6-positive HAPE-s subjects showed a significant cephalad redistribution in pulmonary blood flow compared with HLA-DR6-negative HAPE-s subjects. Moreover, HAPE-s subject 6, in whom HLA-DR6 was negative, did not exhibit redistribution of pulmonary blood flow with hypoxia. We recently reported significant associations of HAPE and pulmonary hypertension with HLA-DR6. These findings indicate that HLA-DR6 may relate not only to pulmonary hypertension, but also to enhanced pulmonary vascular response to hypoxia. HLA-DR6 is suspected to be a possible contributor to individual susceptibility in development of some types of HAPE.

Pulmonary ventilation-perfusion scintigraphy with radioactive agents has been widely used as a simple and noninvasive technique to assess pulmonary ventilation and perfusion in various heart and pulmonary diseases. This method has especially high diagnostic specificity in pulmonary thromboembolism and chronic obstructive pulmonary disease. The inequality on ventilation-perfusion image, which is caused by impaired pulmonary blood flow and normal ventilation, is an important feature to the understanding of the pathogenesis of such disorders. Similar to our data, a significant increase was seen in relative perfusion of upper portions of the lungs in supine subjects during hypoxia measured by a $^{133}$Xe tech-
nique,\textsuperscript{10} which suggests that vasoconstriction was greatest in lower lung zones because the vessels there are more responsive to hypoxia. Radionuclide studies have proved useful for assessment of ventilatory and pulmonary hemodynamic responses to hypoxia and helpful for distinguishing HAPE-s subjects. However, further studies that apply methods with higher spatial resolution are necessary to clarify a crucial assumption of hypoxic pulmonary vasoconstriction to examine the pathogenesis of HAPE.\textsuperscript{16}

In summary, perfusion scintigraphy demonstrated that acute hypoxia caused a greater-than-normal shift in pulmonary blood flow from basal to apical lung in HAPE-s subjects, which suggests that basal pulmonary arterioles react more strongly to hypoxia. In contrast, ventilation did not shift with hypoxia in ventilation scintigraphy. Moreover, the HAPE-s subjects with HLA-DR6 exhibited a significantly greater cephalad redistribution of pulmonary blood flow compared with HAPE-s subjects without HLA-DR6. We conclude that relative enhancement of hypoxic pulmonary vasoconstriction in the base may be a constitutional abnormality in HAPE-s subjects and that pulmonary vascular hyperreactivity to hypoxia may be associated with HLA-DR6.

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References
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