Abnormal Circulatory Responses to High Altitude in Subjects with a Previous History of High-Altitude Pulmonary Edema

By Herbert N. Hultgren, M.D., Robert F. Grover, M.D., Ph.D., and L. Howard Hartley, M.D.

SUMMARY
In five men with a history of susceptibility to high-altitude pulmonary edema (HAPE), hemodynamics and pulmonary gas exchange were measured at sea level, and again 24 hours following ascent to an altitude of 3,100 m.

At sea level, all findings were essentially normal including a mean pulmonary arterial pressure (Pra) of 13.8 ± 1.9 mm Hg. None of the subjects developed clinically detectable pulmonary edema at altitude. Wedge pressures and cardiac output remained normal. Pra increased remarkably, being 38.8 ± 10.3 mm Hg at rest and 53.2 ± 11.6 mm Hg during moderate exercise. Acute relief of hypoxia only partially relieved this pulmonary hypertension.

Arterial blood gases were normal at sea level. In spite of hyperventilation at altitude, arterial $O_2$ pressure was only 50.8 ± 6.1 torr at rest and fell to 41.4 ± 3.3 torr during exercise due to a widening of the alveolar-arterial $O_2$ pressure difference to 28.0 ± 6.8 torr.

Hence, these men susceptible to HAPE developed excessive pulmonary hypertension and impaired pulmonary $O_2$ exchange without detectable pulmonary edema following ascent to high altitude. The increase in pulmonary vascular resistance is only partially explained by hypoxic pulmonary vasoconstriction.

Additional Indexing Words:
- Pulmonary hypertension
- Hypoxia
- Pulmonary gas exchange

The pathogenesis of high-altitude pulmonary edema (HAPE) remains an enigma. Once HAPE has developed, four hemodynamic abnormalities have been observed consistently, an elevated pulmonary artery (PA) pressure, normal or decreased PA wedge pressure, an excessive degree of arterial desaturation not corrected by 100% oxygen, and normal or decreased cardiac output.1-4 It is not possible to say whether these abnormalities preceded the development of edema or were a secondary consequence of pulmonary edema. For example, an initial rise in PA pressure could cause the leakage of fluid into the...
perivascular space and thereby contribute to edema formation. On the other hand, the presence of edema fluid in the distal airways could contribute to alveolar hypoxia, and pulmonary vasoconstriction would result. The present study was designed, therefore, to examine the hemodynamic response to high altitude in persons susceptible to HAPE but without clinically evident frank pulmonary edema.

### Methods

Individuals who have experienced an episode of HAPE in the past are likely to develop HAPE upon subsequent exposure to high altitude. On the basis of this observation, each of the five subjects who participated in this study was selected because he had experienced prior episodes of HAPE while climbing or skiing. The diagnosis of HAPE was based on a classical history plus physical signs observed by a physician. The case history of one of these subjects (R.I.) has been published in detail previously. Recovery from each episode of HAPE was complete; at the time of the present study all subjects were in good health and free of cardiovascular or pulmonary disease as judged by spirometry, chest roentgenogram, and electrocardiogram. The subjects were:

- T.W., a student, had one episode of HAPE while climbing in Alaska.
- R.I., a high school teacher and a mountaineer of considerable experience, had HAPE on four occasions while climbing in the Peruvian Andes.
- W.G., an artist, experienced a near-fatal episode of HAPE while climbing in the Peruvian Andes.
- C.H., an executive, had two episodes of HAPE while backpacking in the Sierra Nevada mountains.
- H.R., a biochemist, has had numerous attacks of HAPE over many years while climbing in the mountains of California and Mexico.

### Table 1

**Clinical Data**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (yr)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Vital capacity* (liters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T.W.</td>
<td>22</td>
<td>188</td>
<td>82</td>
<td>5.77</td>
</tr>
<tr>
<td>R.I.</td>
<td>36</td>
<td>173</td>
<td>71</td>
<td>4.65</td>
</tr>
<tr>
<td>W.G.</td>
<td>37</td>
<td>183</td>
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<td>5.26</td>
</tr>
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<td>C.H.</td>
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<td>75</td>
<td>4.72</td>
</tr>
<tr>
<td>K.B.</td>
<td>54</td>
<td>171</td>
<td>82</td>
<td>3.98</td>
</tr>
</tbody>
</table>

*Vital capacity predicted (Pred.) from age, sex, and height, and measured at sea level (S.L.) and high altitude (Alt.).

Anthropometric and pulmonary function data are presented in table 1.

This investigation involved the collection of hemodynamic data by the technique of right heart catheterization. Control data were obtained at sea level. Several weeks later, each subject traveled to high altitude where the second hemodynamic study was performed. Four of the subjects were residing at sea level and had had no exposure to higher altitudes for at least 6 weeks prior to this second study at altitude. The fifth subject (W.G.) had been living at an altitude of 2,300 m (Estes Park, Colorado) but had spent 2 weeks at sea level immediately prior to the study at high altitude.

All subjects were highly motivated to participate in this investigation by virtue of their personal experiences with HAPE. The nature of the investigation, its objectives, and the possible complications were thoroughly explained to them. All gave their free consent to full participation and signed a standard consent form. To reduce apprehension, each man was familiarized with the catheterization laboratory and the various test maneuvers prior to the first hemodynamic study at sea level. For the second study, rapid ascent to altitude followed by strenuous exercise was employed to simulate the circumstances under which HAPE frequently occurs. Each man traveled from sea level to 3,100-m altitude (Leadville, Colorado) by plane and automobile in 8 hours. Following a night's rest in Leadville, the subject climbed to about 3,900 m and returned to 3,100 m by noon. During the next 2 hours, each subject underwent a careful physical examination, and an electrocardiogram, chest X-ray, and spirometry were obtained. The second hemodynamic study was then performed in the High Altitude Research Laboratory in St. Vincent's Hospital in Leadville.

During each catheterization procedure pulmonary and systemic arterial blood pressures were
measured by using strain-gauge pressure transducers (Statham) referred to midchest level, and recorded with a photographic oscillograph.* Mean pressures were obtained either electrically or by planimetry. Cardiac output (Q̇) was determined by the Fick method for oxygen while the subject inspired ambient air. To determine oxygen uptake (VO₂) the volume of expired air (VE) was measured from the timed collection in a meteorological balloon (sea level) or with a calibrated ventilation meter (Parkinson-Cowan) (high altitude). The expired fraction of oxygen (FEO₂) and carbon dioxide (FECO₂) were

\[
\begin{align*}
(A) \quad P_{A02} &= P_{I02} - P_{ACO2} (FI02) + (1 - FI02)/R \\
(B) \quad P_{A02} &= \frac{R \times P_{I02} + P_{ICO2}}{FI02 (1 - R) + R} - P_{ACO2} \\
&= \frac{1 - (1 - R)FI02}{R + (1 - R)FI02}
\end{align*}
\]

obtained by the micro Scholander method of analysis. Blood samples were drawn simultaneously and anaerobically from the pulmonary and brachial arteries. Oxygen saturation was determined at sea level using a spectrophotometer (Beckman) calibrated by values obtained by Van Slyke analysis. From this and the hemoglobin concentration, the arteriovenous (a-v) difference in O₂ content was calculated. In Leadville, blood O₂ content and capacity were measured by the Van Slyke method. From these the a-v difference in O₂ content was determined directly, and saturations were calculated. At both altitudes, saturations were also calculated from PO₂, pH, and PCO₂ measured with appropriate electrodes (Radiometer). During acute hypoxia, Q̇ was determined only at sea level by means of the indicator-dilution technique using Cardio-Green dye.

The hemodynamic studies were conducted with the subjects supine, fasting, and unsedated. A 7 F cardiac catheter was introduced into an antecubital vein under local anesthesia and advanced to the right pulmonary artery under fluoroscopic control. A no. 19 Courmand needle was placed in a brachial artery. During the following maneuvers, blood gases, ventilation, cardiac output, and systemic and pulmonary arterial pressures were obtained; the catheter was also advanced transiently to obtain PA wedge pressure: (1) rest and breathing ambient air; (2) exercise for 6 min with a cycle ergometer (Enco) while breathing ambient air, measurements made during the final 2 min; (3) after 20-min rest, acute hypoxia for 10 min with measurements during the last 2 min (at sea level, ṖI0₂ 70 torr† without CO₂, or ṖD0₂ 54 torr with ṖICO₂ 25 torr; at altitude, ṖI0₂ 46 torr with ṖICO₂ 21 torr); (4) following 20 min on ambient air at altitude, rest while breathing 100% O₂ for 15 min with measurements begun at 13 min; (5) exercise for 6 min without interruption of 100% O₂; (6) also at altitude, rest with ṖO₂ increased to 147 torr to simulate sea level for 15 min with measurements during the final 2 min.

The following formulæ were used to calculate alveolar PO₂ while the subject was breathing ambient air (A), and breathing a gas mixture containing CO₂ (B):

\[
\text{Results}
\]

Rapid ascent to high altitude followed by strenuous exercise had no adverse effect on any of the five subjects. None developed symptoms of “acute mountain sickness” or HAPE. There were no complaints of malaise, weakness, cough, or dyspnea. During the climb, the awareness of hyperventilation was appropriate for any newcomer exercising at altitude. Pulmonary rales and tachypnea were absent. X-ray films of the chest taken soon after the subjects returned to Leadville after the climb were comparable to those at sea level with no change in the size of the cardiac silhouette. The lung fields were clear with the minor exception of a small area of slight infiltration in the right lower lung field of K. B., which had not been present at sea level. Thus, by all the usual clinical criteria, none of these subjects developed pulmonary edema during this experimental exposure to high altitude. Only one subject, K. B., had a significant decrease in vital capacity (table 1).

**Pulmonary Hemodynamics (Table 2)**

At sea level, mean pulmonary arterial pressure (Pra) and wedge pressures were normal during rest and normoxia. With acute

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*Electronics for Medicine, White Plains, New York.

*Circulation, Volume XLIV, November 1971

†Torr is a unit of pressure defined as 1/760 of a standard atmosphere and approximately equal to a millimeter of mercury.8
Pulmonary Vascular Pressure and Resistance

Table 2

<table>
<thead>
<tr>
<th></th>
<th>Pulmonary artery mean and wedge pressures (mm Hg)</th>
<th>Total pulmonary resistance (dyne-sec-cm⁻²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest Air</td>
<td>Hypoxia</td>
</tr>
<tr>
<td></td>
<td>P (_{\text{ra}})</td>
<td>Wedge</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sea level</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T.W.</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>R.I.</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>W.G.</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>C.H.</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>K.B.</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Mean</td>
<td>13.8</td>
<td>7.4</td>
</tr>
<tr>
<td>± sd</td>
<td>1.9</td>
<td>1.1</td>
</tr>
<tr>
<td><strong>High altitude</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperoxia</td>
<td>Hyperoxia</td>
</tr>
<tr>
<td>T.W.</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>R.I.</td>
<td>41</td>
<td>12</td>
</tr>
<tr>
<td>W.G.</td>
<td>47</td>
<td>—</td>
</tr>
<tr>
<td>C.H.</td>
<td>37</td>
<td>11</td>
</tr>
<tr>
<td>K.B.</td>
<td>47</td>
<td>11</td>
</tr>
<tr>
<td>Mean</td>
<td>38.8</td>
<td>10.5</td>
</tr>
<tr>
<td>± sd</td>
<td>10.3</td>
<td>1.7</td>
</tr>
</tbody>
</table>

hypoxia (fig. 1), P\(_{\text{ra}}\) exceeded the upper limit of normal\(^{10, 11}\) in two of the five subjects (R. I. and W. G.), while wedge pressure decreased. When pulmonary blood flow was increased by exercise at sea level (fig. 2), the normal increase in P\(_{\text{ra}}\)\(^{12}\) was exceeded only in subject R. I. (P\(_{\text{ra}}\) 47/18; mean, 33 mm Hg) due to a rise in wedge pressure from 7 to 15 mm Hg combined with an increase in pulmonary vascular resistance (PVR, table 2) instead of the usual decrease.\(^{13}\) Subjects R. I., W. G., and T. W. also exercised at their same respective work loads while breathing a hypoxic gas mixture which lowered arterial O\(_2\) saturation to 60 to 67%. This produced a further rise in P\(_{\text{ra}}\) of only 1 to 3 mm Hg.

Exposure to high altitude provoked a remarkable degree of pulmonary hypertension in these subjects. At rest at high altitude while breathing ambient air with an average P\(_{\text{a}O_2}\) of 64 torr, the mean P\(_{\text{ra}}\) was 39 mm Hg (range, 22-47 mm Hg). In every individual, P\(_{\text{ra}}\) was higher at altitude than during more severe acute hypoxia at sea level (P\(_{\text{a}O_2}\) < 48 torr; fig. 3). Wedge pressures were normal (range, 8-12 mm Hg) in the four subjects in whom it could be obtained. Therefore, at high altitude PA diastolic pressure was significantly higher than wedge pressure, whereas at sea level these two pressures had been equal.\(^{16}\) Hence, the pulmonary hypertension at high altitude was the result of a three- to fivefold increase in pulmonary vascular resistance.

At altitude, acute hypoxia achieved by breathing 30% or 100% O\(_2\) failed to relieve the pulmonary hypertension completely, although some lowering of P\(_{\text{ra}}\) did occur (fig. 3). Conversely, acute hypoxia intensified the pulmonary hypertension by elevating P\(_{\text{ra}}\) to 54 mm Hg (range, 43-61 mm Hg).

Exercise at high altitude also accentuated pulmonary hypertension (fig. 2). When pulmonary blood flow was approximately doubled, P\(_{\text{ra}}\) increased from 39 mm Hg to 53 mm Hg while total pulmonary resistance decreased in all subjects except one (K. B.). Four of the subjects repeated the same exercise work load while breathing either 30% O\(_2\) or 100% O\(_2\). With this acute relief of hypoxia P\(_{\text{ra}}\) was significantly less in all four subjects by 10 mm Hg. However, in only one subject (T. W.) was P\(_{\text{ra}}\) reduced to his sea level value.

Circulation, Volume XLIV, November 1971
Ascent to an altitude of 3,100 m exposed these subjects to a reduced atmospheric pressure of 535 torr and a lowering of \( P_{O_2} \) from 149 torr to 102 torr. Hyperventilation was clearly present with \( P_{ACO_2} \) reduced to 30.4 ± 3.2 torr and an associated alkaline pH of 7.493 ± 0.034. The resulting \( P_{A0_2} \) was 64.4 ± 3.6 torr. If \( P_{AO_2} \) were reduced acutely from 100 torr to 64 torr at sea level, the expected effect would be a narrowing of the \( P(\text{A-a})_0_2 \). However, our subjects had no change in \( P(\text{A-a})_0_2 \) and as a result \( P_{A0_2} \) was 50.8 ± 6.1 torr. In three subjects, the resting value of \( P_{AO_2} \) was within the range observed in normal men adapted to an altitude of 3,100 m for 10 days, i.e., 56.1 ± 3.0 torr (fig. 4), but in subjects R. I. and K. B., \( P_{AO_2} \) was 45 and 44 torr, respectively.

During exercise at altitude, \( P_{AO_2} \) decreased in every subject (fig. 4). The values of \( P_{AO_2} \) of 41.4 ± 3.3 are significantly lower than the \( P_{AO_2} \).
Sea level (SL) data from figure 1 are expressed as mean ± standard deviation for PRA at both normal and low PAO2. The five subjects susceptible to HAPE, after being at high altitude for 24 hours, had mean resting pulmonary arterial pressures (PRA) while breathing ambient air (PAO2 60–70 torr), which was markedly elevated (open circles) and higher than resting PRA during acute hypoxia at sea level (SL). Acute hyperoxia in four of these subjects lowered PRA (closed circles) but not to sea level (SL) values. The shaded rectangle indicates the more modest levels of PRA reported in normal subjects exposed to a PAO2 of 50–60 torr for 24 hours.19,20

of 51.6 ± 3.1 torr observed during comparable exercise in men adapted to this same altitude for 10 days.19 This fall in PAO2 occurred largely as a result of a widening of the P(A-a)O2 difference from 13.8 ± 4.6 torr at rest to 28.0 ± 6.8 torr during exercise even though PAO2 increased to 69.8 ± 6.5 torr. Again, as at sea level, subject RI had the lowest PAO2 (36 torr) during exercise.

To simulate sea level O2 pressure acutely, P102, was increased from 102 torr to 147 torr in subjects R. I. and W. G. (table 4). This widened the P(A-a)O2 to values in excess of those measured at sea level, and failed to elevate PAO2 to sea level values, particularly during exercise. Thus, the P(A-a)O2 was wider in these five subjects who had been at altitude of 3,100 m for 24 hours, at rest and during exercise with or without acute normoxia, than in normal subjects adapted to this same altitude for 10 days.19

**Cardiac Output (Table 5)**

At rest, the cardiac output (Q) was normal levels19 in two subjects (T. W. and W. difference in O2 content which was 4.30 ± 0.78 (sd) vol% at sea level and 4.49 ± 0.61 vol% after 24 hours at altitude. Values for Q were the same at low and high altitude, being 6.66 ± 1.80 and 6.61 ± 0.86 liters/min, respectively. However, the mean resting heart rate

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**Figure 3**

**Figure 4**

Partial pressure of oxygen in arterial blood (PAO2) at values of O2 uptake from rest to exercise. Shaded areas indicate the normal range (±1 sd) for sea level residents (upper) and for men adapted to altitude of 3,100 m for 10 days (lower).19 The five subjects susceptible to HAPE (closed circles) have values at sea level which are normal at rest, but in subject RI, PAO2 is low during exercise. After these five subjects had been at 3,100-m altitude for 24 hours, two had low values of PAO2 at rest, and all values were low during exercise.
HIGH-ALTITUDE PULMONARY EDEMA

Table 3

Pulmonary Gas Exchange

<table>
<thead>
<tr>
<th>Subject</th>
<th>SaO₂ (%)</th>
<th>pH</th>
<th>Paco₂ (torr)</th>
<th>PaO₂ (torr)</th>
<th>P (A-a)O₂ (torr)</th>
<th>SaO₂ (%)</th>
<th>pH</th>
<th>Paco₂ (torr)</th>
<th>PaO₂ (torr)</th>
<th>P (A-a)O₂ (torr)</th>
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<tbody>
<tr>
<td>T.W.</td>
<td>98.4</td>
<td>7.425</td>
<td>40</td>
<td>99</td>
<td>7</td>
<td>97.4</td>
<td>7.380</td>
<td>40</td>
<td>94</td>
<td>9</td>
</tr>
<tr>
<td>R.I.</td>
<td>96.6</td>
<td>7.364</td>
<td>39</td>
<td>85</td>
<td>22</td>
<td>94.5</td>
<td>7.309</td>
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<td>29</td>
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<tr>
<td>W.G.</td>
<td>97.4</td>
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<td>41</td>
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<td>15</td>
<td>97.4</td>
<td>7.325</td>
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<td>15</td>
</tr>
<tr>
<td>C.H.</td>
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<td>46</td>
<td>82</td>
<td>8</td>
<td>96.8</td>
<td>7.325</td>
<td>43</td>
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<td>25</td>
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<tr>
<td>K.B.</td>
<td>96.5</td>
<td>7.440</td>
<td>36</td>
<td>80</td>
<td>21</td>
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<tr>
<td>Mean</td>
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<td>40.4</td>
<td>85.6</td>
<td>14.6</td>
<td>96.5</td>
<td>7.350</td>
<td>41.0</td>
<td>87.0</td>
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<td>3.6</td>
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<td>1.4</td>
<td>0.029</td>
<td>2.4</td>
<td>6.6</td>
<td>9.1</td>
</tr>
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</table>

Sea level (P₁O₂ = 149 torr)

<table>
<thead>
<tr>
<th>Subject</th>
<th>SaO₂ (%)</th>
<th>pH</th>
<th>Paco₂ (torr)</th>
<th>PaO₂ (torr)</th>
<th>P (A-a)O₂ (torr)</th>
<th>SaO₂ (%)</th>
<th>pH</th>
<th>Paco₂ (torr)</th>
<th>PaO₂ (torr)</th>
<th>P (A-a)O₂ (torr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T.W.</td>
<td>87.8</td>
<td>7.450</td>
<td>32</td>
<td>52</td>
<td>11</td>
<td>83.2</td>
<td>7.475</td>
<td>33</td>
<td>44</td>
<td>21</td>
</tr>
<tr>
<td>R.I.</td>
<td>84.8</td>
<td>7.470</td>
<td>33</td>
<td>45</td>
<td>15</td>
<td>74.5</td>
<td>7.444</td>
<td>31</td>
<td>36</td>
<td>29</td>
</tr>
<tr>
<td>W.G.</td>
<td>91.3</td>
<td>7.503</td>
<td>33</td>
<td>55</td>
<td>9</td>
<td>81.6</td>
<td>7.461</td>
<td>31</td>
<td>44</td>
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</tr>
<tr>
<td>C.H.</td>
<td>91.0</td>
<td>7.540</td>
<td>26</td>
<td>58</td>
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<td>72.5</td>
<td>7.488</td>
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<td>42</td>
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</tr>
<tr>
<td>K.B.</td>
<td>83.1</td>
<td>7.500</td>
<td>28</td>
<td>44</td>
<td>21</td>
<td>79.1</td>
<td>7.470</td>
<td>22</td>
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<td>87.6</td>
<td>7.493</td>
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<td>50.8</td>
<td>13.8</td>
<td>78.2</td>
<td>7.468</td>
<td>29.6</td>
<td>41.4</td>
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<tr>
<td>± sd</td>
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<td>0.034</td>
<td>3.2</td>
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<td>4.6</td>
<td>0.016</td>
<td>4.3</td>
<td>3.3</td>
<td>6.8</td>
</tr>
</tbody>
</table>

High altitude (P₁O₂ = 102 torr)

Abbreviations: SaO₂ = oxygen saturation of arterial blood; Paco₂ and PaO₂ = pressure of CO₂ and O₂ respectively in arterial blood; P(A-a)O₂ = difference between alveolar and arterial O₂ pressures; P₁O₂ = O₂ pressure in inspired air.

Discussion

This investigation was designed to study the circulatory responses to high altitude in a group of men known to be susceptible to...
HAPE. Hemodynamic observations were made within 24 hours after arrival at an altitude of 3,100 m, and following several hours of mountain climbing to higher altitudes. This special protocol has not been employed in previous investigations. Therefore, a strictly comparable normal frame of reference is not available. We recognize the importance of examining circulatory adjustments during the first day or two at high altitude, since these initial responses are known to differ from those following more prolonged adaptation.15

Pulmonary Hemodynamics

Direct measurements of PPa during the first few days at high altitude have been reported in only two previous investigations. Kronenberg and associates21 observed that when four normal men were taken from sea level to 3,800 m (Pb, 475 torr), PAO2 decreased to about 57 torr, and resting PPa rose from 10 ± 1 to 21 ± 4 mm Hg (fig. 3) and plateaued at that level after 24 hours. Similar results were reported by Vogel and associates22 who studied four normal men residing at 1,600-m altitude. Within 24 to 48 hours following ascent to 4,300 m (Pb, 455 torr) where PAO2 was decreased to about 53 torr, resting PPa increased from 12 ± 1 to 21 ± 3 mm Hg (fig. 3). Our subjects at 3,100 m had less airway hypoxia (PAO2, 64 torr) and yet had a much greater degree of pulmonary hypertension (39 ± 10 mm Hg).

Exercise at high altitude which increased pulmonary blood flow to about 15 liters/min increased PPa to 29 ± 5 mm Hg in the report of Kronenberg and associates,21 and to 26 ± 3 mm Hg in the study of Vogel's group.22 In our subjects with a comparable Q, PPa was twice as high, 53 ± 12 mm Hg (fig. 2). With longer periods of adaptation, the PPa observed in eight normal men at 3,100 m for 10 days19 was 15 ± 3 mm Hg at rest and increased to only 26 ± 5 mm Hg during exercise. We may conclude, therefore, that in our five subjects prone to develop HAPE, the pulmonary hypertension which they developed in the present investigation was grossly abnormal.

This pulmonary hypertension is the result of an increase in pulmonary vascular resistance, since pulmonary blood flow and pulmonary...
capillary wedge pressure were normal. However, the nature of the increased resistance is not known. Hypoxic pulmonary vasoconstriction apparently accounts for a portion of the increased vascular resistance, since acute relief of hypoxia reduced the pulmonary hypertension but did not eliminate it completely (fig. 3). It is noteworthy that this marked pulmonary hypertension was observed in the presence of respiratory alkalosis (pH, 7.493 at rest), in view of the reports that alkalosis tends to minimize hypoxic pulmonary hypertension. An increase in blood flow during exercise was accommodated by a decrease in pulmonary vascular resistance (except in K.B.) indicating that the elevated resistance was partially labile. Kronenberg and associates observed that after their subjects had been at high altitude for 24 hours acute relief of hypoxia reduced Prea considerably, but not completely to normal.

**Pulmonary Gas Exchange**

Lowering PO2 for brief periods of time narrows P(A-a)O2. For example, when Kreuzer and associates exposed eight supine young men to a reduction in PO2 from 150 to 75 torr for 10 min, P(A-a)O2 decreased from 12 ± 5 to 6 ± 3 torr. When hypoxia is prolonged for hours, however, the response is somewhat different. Reeves and associates studied seven subjects in whom PO2 was lowered from 145 to 80 torr for 3 hours in a decompression chamber (PaO2, 427 torr). The P(A-a)O2 widened from 6 ± 2 to 12 ± 1 torr and increased further during sleep. Kronenberg’s group reported that when PO2 was reduced from 150 to 90 torr (PaO2, 475 torr), P(A-a)O2 widened from 3 ± 2 to 8 ± 3 torr after 24 hours, with a further widening to 11 ± 3 torr after 72 hours. Other investigators have not observed a widening of P(A-a)O2 but rather an absence of any significant narrowing of P(A-a)O2 during the initial days at altitude. Hansen and co-workers reported that in 16 young men taken from sea level to 4,300 m (Po2, 86 torr) for 1 to 4 days, P(A-a)O2 was 8 torr at both altitudes. Similarly, Vogel and associates studying four men residing at 1,600 m found P(A-a)O2 to be 8 ± 2 torr when Po2 was 122 torr, and 6 ± 4 torr after 24 to 48 hours at 4,300 m. Our observation on the five subjects of the present investigation are compatible with the above, i.e. P(A-a)O2 of 15 ± 7 torr at sea level and 14 ± 5 torr after 24 hours at 3,100 m (Po2 102 torr).

Kronenberg and associates observed that in four men with 4 to 5 days of adaptation to 3,800-m altitude, strenuous exertion for several hours widened P(A-a)O2 to 9 ± 2 torr from a preexercise value of 2 ± 2 torr. Since our five subjects were also studied following a number of hours of strenuous exercise, it is perhaps surprising that wider values of P(A-a)O2 were not observed.

Arterial blood gases were obtained from two of our subjects breathing 100% O2 at altitude. P(A-a)O2 was wider than in normal subjects at sea level: T. W., 68 torr (normal, 13 ± 6 torr), and K. B., 146 torr (normal, 32 ± 18 torr). Kronenberg and associates also found that breathing 100% O2 after 24 hours at 3,800 m produced an abnormally wide P(A-a)O2 of 117 ± 10 torr. Such findings are usually interpreted as indicating an abnormally large intrapulmonary veno-arterial shunt.

Thus, the results of many investigations indicate that during the first hours and days at high altitude PaO2 is lower than after a more prolonged period of adaptation. Our subjects do not appear to be exceptional in this respect. Hypoventilation is not the cause. Rather, P(A-a)O2 is widened probably as a result in part of increased intrapulmonary vascular shunting. This may be an indication of subclinical pulmonary edema. In addition, the grossly increased pulmonary vascular resistance could well disrupt the distribution of pulmonary blood flow relative to the distribution of ventilation (and diffusion).

**Cardiac Output**

Previous investigations have shown that the initial phase of circulatory adaptation to high altitude is characterized by tachycardia and a cardiac output that is greater than at sea level. The response of our subjects, therefore, was somewhat atypical, in that cardiac output was not increased. While heart rate was clearly greater than in men adapted to
3,100 m for 10 days, it was comparable to the tachycardia observed by Kronenberg's group, after 24 hours at 3,800 m. The reduction in stroke volume, therefore, remains unexplained. Studies of prolonged exercise indicate a progressive increase in heart rate which offsets a gradual decrease in stroke volume, the net effect being a maintenance of cardiac output. This is not a consequence of a reduced blood volume, for example, dehydration, and in fact plasma volume has been found to increase following prolonged exercise. Perhaps this is the explanation for the slight decrease in hematocrit observed in our subjects at altitude. Such a decrease in hematocrit following prolonged exercise has also been observed by Pugh at sea level as well as by Hultgren and co-workers at altitude.

Pathogenesis of HAPE

The salient observation in this investigation is the remarkable degree of pulmonary hypertension which developed in our five subjects when rapid ascent to altitude was combined with prolonged exercise. These subjects were selected for their known susceptibility to HAPE, although none of them developed clinically detectable pulmonary edema during the course of this investigation. Therefore, since marked pulmonary hypertension developed in the absence of frank pulmonary edema, it is reasonable to postulate that a rapid rise in pulmonary arterial pressure may contribute to edema formation. This sequence of events would be in agreement with the observations of Whayne and Severinghaus who showed that, in rats exposed to hypoxia plus exercise, the pulmonary arteries developed a perivascular cuff of edema fluid.

At altitude, the increase in pulmonary vascular resistance in our subjects was much greater than during acute hypoxia at sea level (fig. 3). Furthermore, acute relief of hypoxia at altitude did not restore the pulmonary vascular resistance to normal. These observations imply that hypoxic pulmonary vasoconstriction accounts for only a portion of the increased vascular resistance; the other contributing factor has not been identified. Autopsy findings in men dying of HAPE reveal widespread fibrin deposits in the pulmonary capillaries and in other organs throughout the body. This raises the possibility that HAPE may be the pulmonary manifestation of a form of transient disseminated intravascular coagulation. Occlusion of scattered portions of the pulmonary vascular bed by hypoxic vasoconstriction or fibrin deposition may result in the transmission of the high pulmonary artery pressure to the unobstructed or "unprotected" portions of the pulmonary capillary bed with resulting patchy edema. Pulmonary edema observed in clinical and experimental pulmonary embolism may have a similar mechanism. This concept has been proposed by Hultgren and Grover and experimental studies have supported this view.

Our subjects at altitude had hypoxemia, hypocapnia, and alkalosis, a combination of stimuli known to provoke constriction of systemic veins. This peripheral vasoconstriction has been shown to be exaggerated in persons susceptible to HAPE. A reduction in the capacity of peripheral systemic veins would tend to redistribute the blood volume and could account for the increase in the volume of blood within the lungs observed during the first 2 to 3 days at high altitude. Such an increase in pulmonary blood volume may well have occurred in the subjects of the present investigation and could explain the decrease in vital capacity observed in K. B. at altitude (table 1). Unfortunately, the techniques we employed did not permit the calculation of central blood volume, but if this did increase it could be an additional factor in the pathogenesis of HAPE.

Acknowledgments

The authors express their thanks to Dr. M. D. Flamm for his assistance with the cardiac catheterization procedures at sea level. The excellent technical assistance of Gail Jamieson, Harry Miller, Sharon Snider, Virginia Smith, R.N., M. E. Stone, and A. L. van Kessel is greatly appreciated. We remain grateful to the Sisters of Charity at St. Vincent's Hospital in Leadville for providing facilities for the High Altitude

*Circulation, Volume XLIV, November 1971
HIGH-ALTITUDE PULMONARY EDEMA

Research Laboratory. The manuscript was skillfully prepared by Mrs. Jane Martinez.

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Circulation. 1971;44:759-770
doi: 10.1161/01.CIR.44.5.759
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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