Increased lung vasoreactivity in children from Leadville, Colorado, after recovery from high-altitude pulmonary edema

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ABSTRACT Cardiac catheterization was performed on seven children after recovery from high-altitude pulmonary edema. All were life-long residents at elevations above 10,000 feet. Three of the seven had developed pulmonary edema without antecedent travel to low altitude but had an upper respiratory infection. Response of pulmonary arterial pressure to 16% inspired oxygen in all seven was compared with that in six well children who resided at a similar altitude and had no history of high-altitude pulmonary edema. With hypoxia the susceptible patients had a greater mean pulmonary arterial pressure (56.3 ± 23.8) than the nonsusceptible children (18.8 ± 3.9, p < .05). Comparison with historical hemodynamic responses in children at high altitudes showed a similar greater mean pulmonary arterial pressure in the susceptible children. Thus, in children from high altitudes, increased pulmonary vasoreactivity to hypoxia may play a role in the pathogenesis of high-altitude pulmonary edema. The development of pulmonary edema in high-altitude residents with upper respiratory infections and no antecedent low-altitude journey is consistent with the presence of other factors such as inflammation, which may play a role in the pathogenesis of the edema. The finding of right ventricular hypertrophy on an electrocardiogram in children from high altitudes may be predictive of their susceptibility to high-altitude pulmonary edema.


HIGH-ALTITUDE PULMONARY EDEMA in Colorado residents of areas of high altitude occurs predominantly in children.1,2 Characteristically the children develop pulmonary edema on return to high altitude after a visit to low altitude. Some children have repeated episodes of high-altitude pulmonary edema, suggesting that they are particularly susceptible. However, the mechanisms of the edema are unknown.

It is known that during the acute episode both children and adults have acutely elevated pulmonary arterial pressure, suggesting that pulmonary hypertension may be a factor in the pathogenesis of the edema.3 Increased pulmonary vasoconstriction to acute hypoxia has been found at low altitude in some adults after recovery from high-altitude pulmonary edema.4 5 Increased pulmonary vasoreactivity could contribute to excessive pulmonary hypertension in susceptible subjects ascending to high altitude. We can find only two reported instances in which hypoxic pulmonary vasoreactivity was measured in children who had recovered from high-altitude pulmonary edema, and both appeared to have large increases in pulmonary arterial pressure during the hypoxic challenge.3 However, at cardiac characterization in one of the two children 1 year later, the hyperresponsiveness was decreased.

We hypothesized that increased vasoconstriction in response to hypoxia plays a role in the pathogenesis of high-altitude pulmonary edema in children who reside at high altitudes. If so, children living at high elevations who have a history of high-altitude pulmonary edema should have larger hypoxic pulmonary pressor responses than do children without such history. To address this question we measured pulmonary vascular responses to acute hypoxia in children from high-altitude areas who were referred to us for heart catheterization between 1978 and 1984. The seven children without other heart and lung disease who had a history of prior high-altitude pulmonary edema and the six normal, or near-normal, children without such history constitute the basis of this report. The measurements of

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pulmonary vascular reactivity in susceptible children could increase our understanding of pathophysiologic mechanisms of high-altitude pulmonary edema.

Methods

Our definition of high-altitude pulmonary edema included (1) respiratory illness, (2) chest roentgenographic infiltrates consistent with pulmonary edema, and (3) response to oxygen therapy with rapid relief of symptoms and clearing of infiltrates. No children with heart disease were included in the study.

Patients. Patient 1 (E. H.) was a 10-year-old boy who developed nausea, cyanosis, pallor, lethargy, tachypnea, and a non-productive cough within 12 hr of return from sea level to his home at 3060 m elevation in Colorado. On admission to the hospital in Salida (2150 m), blood pressure was 100/78 mm Hg and rales were heard over both lung fields. He was treated with furosemide and oxygen with rapid relief of symptoms. A similar episode occurred at age 11 years after his return home from a trip to sea level. He was again treated with oxygen and furosemide with rapid improvement. He continued to reside at 3060 m until cardiac catheterization was performed in Denver (1600 m) 1 year later.

Patient 2 (D. F.) was an 8-year-old girl who developed cough, headache, emesis, and lethargy within 24 hr of return to Leadville (3100 m) from a trip to a lower altitude. She was admitted to the hospital in Leadville where her symptoms improved rapidly with oxygen and furosemide. Two days later the chest roentgenogram was normal. However, within 12 hr of discharge she was readmitted to the hospital because of recurrent symptoms and radiographic infiltrates. She rapidly improved with administration of oxygen. The patient remained in Leadville until cardiac catheterization was performed in Denver 10 days later.

Patient 3 (A. M.), a 4-year-old boy of Leadville, developed coryza, cough, and fever for 3 days and lethargy for 1 day while at home in Leadville. Examination revealed cyanosis, dehydration, lethargy, and fever. The arterial blood oxygen tension was 25 mm Hg. He was treated with oxygen, penicillin, and intravenous fluids and was evacuated to Denver where, on arrival, he was much improved. After remaining in Denver for 10 days he underwent cardiac catheterization there.

Patient 4 (S. S.), a 6-year-old girl of Leadville, had coryza and fever that continued for 2 weeks despite treatment with amoxicillin. Her admission to the hospital in Leadville was preceded by nausea, emesis, cough, dyspnea, and cyanosis over the previous 24 hr. Examination showed a cardiac gallop rhythm and bilateral pulmonary rales. Her arterial oxygen tension was 30 mm Hg. Treatment with oxygen, furosemide, and erythromycin resulted in rapid relief of her dyspnea and, 48 hr later, clearing of the pulmonary infiltrates seen on the chest roentgenogram. She remained in Leadville until cardiac catheterization was performed in Denver 17 days later.

Patient 5 (A. Y.), a 7-year-old boy of Leadville who had coryza, cough, and fever for 1 week and was admitted to the hospital in Leadville where examination showed a temperature of 39.6°C, cyanosis, and a loud systolic murmur and thrill at the lower left sternal border. Arterial blood oxygen tension was 43 mm Hg. Treatment with oxygen and erythromycin resulted in rapid relief of symptoms and lessening of the murmur. The chest roentgenogram was normal 24 hr after admission. When the symptoms and murmur recurred 12 hr after discharge he was treated with oxygen and transferred to Denver for evaluation by catheterization. On arrival, he was free of symptoms and without a murmur. He returned to Leadville where he remained until cardiac catheterization was performed in Denver 3 weeks later.

Patient 6 (M. A.), a 20-month-old female resident at 3060 m in Colorado, had coryza for several days. She awoke with dyspnea, cyanosis, and cough. Examination in Dillon, CO (2750 m) revealed bilateral rales of the lung fields. She was treated with oxygen, with relief of her dyspnea, cyanosis, and cough in 6 hr. The following day she moved with her family to Denver, where she remained until cardiac catheterization was performed 4 months later.

Patient 7 (M. S.), was a 5-year-old boy of Leadville who underwent cardiac catheterization in Denver after having two previous bouts of pulmonary edema at age 3 and 5 years. At age 7 he twice developed cough and cyanosis after returning home from lower altitudes. On both occasions his symptoms rapidly resolved with oxygen and furosemide therapy. Both his brother and sister have also had episodes of pulmonary edema after returning home from lower altitudes.

Catheterization. Before catheterization all patients underwent standard 12-lead electrocardiographic examinations. Criteria used for diagnosis of right ventricular hypertrophy included a mean QRS axis greater than 100 degrees, an R wave in V1 greater than 1.8 mV, an R/S ratio in V6 greater than 1.5, and an upright T wave in V1. Right and left heart catheterization was performed under meperidine (2 mg/kg im, but no more than 50 mg) and hydroxyzine (1 mg/kg im, but no more than 25 mg) sedation and local anesthesia with 1% lidocaine. Catheter insertion was percutaneous by the modified Seldinger technique via the femoral vessels. Aortic and pulmonary arterial pressures were simultaneously measured through fluid-filled catheters, with the level of the midchest as the zero reference, and recorded on an Electronics for Medicine recorder (White Plains, NY). Blood oxygen saturations were measured on an American Optical (Rochester, NY) oximeter and arterial blood gas tensions were determined on a Corning 165 blood-gas analyzer (Medford, MA). Cardiac output was calculated by the Fick method with the use of hemoglobin and oxygen saturations to calculate arterial and mixed venous contents. We assumed an oxygen consumption of 150 ml/min/m². Measurements were repeated during a 5 to 12 min period while the patients breathed 16% oxygen in nitrogen via a head hood. Then 100% oxygen was administered via the head hood for 5 to 10 min and the measurements were repeated.

Control patients. Three control patients were Leadville residents 8 to 14 months old who underwent catheterization during evaluation for a presumed atrial septal defect or pulmonary hypertension but in whom no abnormalities were found. There were three additional control patients. One was a 3-year-old resident of Leadville in whom cardiac catheterization 6 months after surgical closure of an atrial septal defect showed normal hemodynamics, one was a 4-year-old male resident of Leadville and Vail, CO (2300 m) catheterized for left-transposition of the great arteries and found to have normal hemodynamics, and the third was a 3-year-old female resident of Leadville in whom catheterization at 1½ years after closure of a ventricular septal defect showed normal hemodynamics. None of these control patients had symptoms consistent with high-altitude pulmonary edema.

Results

Clinical findings. The seven patients, four boys and three girls, had nine episodes of high-altitude pulmonary edema, all of which were characterized by cough, radiographic infiltrates (table 1), and response to oxygen therapy. Dyspnea, decreased activity, nausea, emesis, and cyanosis were frequent but not invariable findings (table 1). Five of the nine episodes (two in
E. H., one in D. F., and two in M. S.) occurred upon return to high altitude after a 1 day to several week stay at a lower altitude. Three of the nine episodes (one each in A. M., M. Y., and M. A.) occurred at the resident altitude during a respiratory illness marked by coryza. One patient (S. S.) had coryza during a 1 day visit to a lower altitude before developing high-altitude pulmonary edema.

Chest roentgenograms revealed exclusively upper lobe infiltrates in four of the nine episodes. Diffuse infiltrates were seen on radiographs obtained during the other five episodes. In two of these five, upper lobe infiltrates predominated. In addition, the two siblings of M. S. had a total of three episodes of high-altitude pulmonary edema in which infiltrates were observed exclusively in the upper lobes. None of the chest roentgenograms showed exclusively lower lobe infiltrates.

The four electrocardiograms obtained during acute episodes of high-altitude pulmonary edema demonstrated right ventricular hypertrophy (table 2). Recovery electrocardiograms obtained shortly before catheterization demonstrated persistent right ventricular hypertrophy in all seven patients. When electrocardiograms were obtained both during the acute episode and recovery there tended to be slight improvement demonstrated at recovery, but right ventricular hypertrophy persisted. The electrocardiograms of all patients except M. A., who had a counterclockwise frontal plane vector loop, demonstrated at least two criteria for right ventricular hypertrophy. However, even M. A. had evidence of right ventricular hypertrophy, i.e., an R wave without an S wave in V1 (table 2).

Hemodynamics. At the time of catheterization, the mean hemoglobin concentration in the patients (13.8 ± 0.7 g/100 ml) was not different from that in the control subjects (13.6 ± 0.3 g/100 ml). By analysis of variance mean pulmonary arterial pressure (table 3), mean arterial pressure, cardiac output, and arterial oxygen tension were not different between groups.

The administration of 16% O₂ decreased arterial oxygen tension to comparable levels in the two groups (table 3). The mean pulmonary arterial pressure during hypoxia in the susceptible patients was greater than in room air and greater than that in the control subjects during hypoxia (figure 1). Also, patients S. S. and A. M., who developed the most severe pulmonary hypertension during hypoxia, showed the most rapid

**TABLE 1**
Clinical characteristics of patients during episodes of high-altitude pulmonary edema

<table>
<thead>
<tr>
<th>Patient</th>
<th>E. H.</th>
<th>M. S.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episode</td>
<td>Episode</td>
<td>D. F.</td>
</tr>
<tr>
<td>Cough</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Radiographic infiltrate</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Decreased activity</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nausea/emesis</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Fever</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rales</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Low-altitude trip</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Coryza</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>O₂ therapy</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Diuretic therapy</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*Defined as lethargy, or exercise intolerance by history from parent.
*Temperature >38.5° C.

**TABLE 2**
Electrocardiographic data in seven patients during acute high-altitude pulmonary edema and after recovery

<table>
<thead>
<tr>
<th>Patient</th>
<th>Acute</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. H.</td>
<td>110°</td>
<td>9.5</td>
</tr>
<tr>
<td>D. F.</td>
<td>150°</td>
<td>13.5</td>
</tr>
<tr>
<td>A. M.</td>
<td>165°</td>
<td>20.0</td>
</tr>
<tr>
<td>S. S.</td>
<td>120°</td>
<td>7.0</td>
</tr>
<tr>
<td>A. Y.</td>
<td>115°</td>
<td>9.0</td>
</tr>
<tr>
<td>M. A.</td>
<td>-15°</td>
<td>3.0</td>
</tr>
<tr>
<td>M. S.</td>
<td>235°</td>
<td>20.0</td>
</tr>
</tbody>
</table>

*Abnormal T wave in V1.
### TABLE 3

Hemodynamics in patients who recovered from high-altitude pulmonary edema and in control subjects also residing at high altitudes (>10,000 feet)

<table>
<thead>
<tr>
<th>Patient or subject</th>
<th>Age</th>
<th>PPA (mm Hg)</th>
<th>PAo (mm Hg)</th>
<th>CI [l/(min m²)]</th>
<th>Pao₂ (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RA 16% O₂</td>
<td>100% O₂</td>
<td>RA 16% O₂</td>
<td>100% O₂</td>
</tr>
<tr>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. H. 10 yr</td>
<td>22</td>
<td>51</td>
<td>15</td>
<td>82</td>
<td>87</td>
</tr>
<tr>
<td>D. F. 8 yr</td>
<td>22</td>
<td>35</td>
<td>18</td>
<td>82</td>
<td>85</td>
</tr>
<tr>
<td>A. M. 4 yr</td>
<td>25</td>
<td>63</td>
<td>23</td>
<td>70</td>
<td>73</td>
</tr>
<tr>
<td>S. S. 6 yr</td>
<td>20</td>
<td>100</td>
<td>23</td>
<td>88</td>
<td>100</td>
</tr>
<tr>
<td>A. Y. 7 yr</td>
<td>16</td>
<td>52</td>
<td>12</td>
<td>77</td>
<td>77</td>
</tr>
<tr>
<td>M. A. 20 mo</td>
<td>25</td>
<td>37</td>
<td>20</td>
<td>67</td>
<td>65</td>
</tr>
<tr>
<td>M. S. 5 yr</td>
<td>25</td>
<td>—</td>
<td>—</td>
<td>83</td>
<td>—</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>21.7</td>
<td>56.3&lt;sup&gt;a&lt;/sup&gt;&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8.5</td>
<td>77.7</td>
</tr>
<tr>
<td>±SD</td>
<td></td>
<td>3.4</td>
<td>23.8</td>
<td>4.4</td>
<td>8.0</td>
</tr>
<tr>
<td>Control subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 8 mo</td>
<td>18</td>
<td>18</td>
<td>—</td>
<td>63</td>
<td>60</td>
</tr>
<tr>
<td>2 11 mo</td>
<td>14</td>
<td>15</td>
<td>—</td>
<td>70</td>
<td>66</td>
</tr>
<tr>
<td>3 14 mo</td>
<td>18</td>
<td>20</td>
<td>—</td>
<td>68</td>
<td>65</td>
</tr>
<tr>
<td>4 3 yr</td>
<td>16</td>
<td>18</td>
<td>11</td>
<td>77</td>
<td>72</td>
</tr>
<tr>
<td>5 4 yr</td>
<td>13</td>
<td>16</td>
<td>14</td>
<td>82</td>
<td>70</td>
</tr>
<tr>
<td>6 3 yr</td>
<td>21</td>
<td>26</td>
<td>21</td>
<td>72</td>
<td>62</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>16.7</td>
<td>18.8</td>
<td>15.3</td>
<td>72.0</td>
</tr>
<tr>
<td>±SD</td>
<td></td>
<td>2.9</td>
<td>3.9</td>
<td>5.1</td>
<td>6.7</td>
</tr>
</tbody>
</table>

All patients underwent catheterization in Denver. A. M., M. A., and control subject 5 were catheterized 10 days, 5 months, and 4 months, respectively, after their arrival in Denver; the remaining patients and subjects were catheterized within 3 days. Paco₂ values in room air and during hypoxia, respectively, in the patients in whom it was measured were as follows: 37 and 32 mm Hg for E. H., 33 and 33 mm Hg for D. F., and 38 mm Hg (during hypoxia only) for A. M., and 44 and 44 mm Hg for A. Y. The values for the control subjects in whom it was measured were: 37 and 34 mm Hg for subject 4, 41 and 43 mm Hg for subject 5, and 38 and 38 mm Hg for subject 6.

RA = room air.

<sup>a</sup> Calculated from arterial oxygen saturation, assuming pH of 7.4.

<sup>b</sup> Significant at p < .05 by analysis of variance when compared with control subjects at similar inspired oxygen levels.

<sup>c</sup> Significant at p < .05 by analysis of variance when compared with same group at room air.

rate of pressure increase (figure 2). There was no change in aortic pressure in the susceptible patients, whereas in the controls there was a significant decline (table 3). The cardiac output values in the susceptible patients were not different from the values in the control patients. In the two patients in whom wedge pressure was determined, no change was noted with hypoxia (E. H. 4 and 4 mm Hg; A. Y. 3 and 3 mm Hg). While the percent change in total pulmonary resistance in room air to that during hypoxia for the three susceptible patients in whom it could be calculated (138 ± 58%) was greater than that for control patients (29 ± 5%), insufficient data was available to accurately analyze changes in pulmonary arteriolar resistance. Instead, the ratio of the pulmonary-to-aortic pressure was calculated. The ratio for the susceptible patients (0.28 ± 0.07) was not different from that for control subjects (0.23 ± 0.05) while breathing room air. With hypoxia the ratio in the susceptible patients (0.68 ± 0.21) was greater than during normoxia and was greater than the ratio in the control subjects during hypoxia (0.29 ± 0.02), despite a lower mean aortic pressure in the latter.

**Discussion**

The results of this study show that children living at high altitude who have experienced at least one episode of high-altitude pulmonary edema have increased pulmonary arterial vasoreactivity to hypoxia when compared with children who reside at a similar altitude but who have not developed high-altitude pulmonary edema. Thus, hypoxia caused a large but variable increase in pulmonary arterial pressure in the susceptible patients, but only a small change in the control subjects, although the two groups had comparable arterial oxygen tensions. One major drawback of our study was that the control subjects tended to be younger than those with a history of pulmonary edema. This difficulty arises because catheterization and hypoxic challenge of normal children is not a routine or ethical practice. However, previously published data<sup>4</sup> indicate that infants are more reactive to hypoxia than...
adolescents in whom pulmonary arterial pressure and hemoglobin saturation data were recorded in room air and during hypoxia. A comparison of the data of Vogel et al. with that from our susceptible children was made with the arterial oxygen tension as a measure of stimulus and the pulmonary arterial pressure as a measure of response (figure 3). Even though our susceptible patients underwent cardiac catheterization in Denver, they showed a larger increase in pulmonary arterial pressure, beginning at higher oxygen tensions, suggesting an increased pulmonary vasoreactivity to hypoxia. We conclude that an increased vasoreactivity to hypoxia is present after recovery in children who have had high-altitude pulmonary edema. Whether or not increased vasoreactivity has a role in the adult who develops high-altitude pulmonary edema when journeying from low to high altitude cannot be concluded from this investigation.

Although as a group susceptible patients showed an excessive rise in pulmonary arterial pressure during acute hypoxia, one patient in this group did not show such a response when compared with the data of Vogel et al. Indeed, a large range of pressure increases were seen in the susceptible group. This finding is reminiscent of that by Hultgren and Grover, who also showed that some adults with a history of high-altitude pulmonary edema did not show an increased pulmonarypressor response to hypoxia when tested at low altitude,
indicating that pulmonary vascular reactivity may not
in itself cause high-altitude pulmonary edema. Fur-
thermore, a report from this institution has previously
described infants from areas of high altitude with
symptomatic high-altitude pulmonary hypertension. 11
These infants present with failure to thrive and cor
pulmonale and have a high mortality rate if not moved
to lower elevations. On evaluation they show an exag-
gerated and rapid pulmonary arterial vasoconstrictive
response to hypoxia. Yet, none has been known to
have had an episode or illness resembling high-altitude
pulmonary edema. Thus, vasoreactivity by itself may
not be sufficient to cause pulmonary edema. Although
our findings indicate a relationship between suscepti-
Bility to high-altitude pulmonary edema and increased
pulmonary vasoreactivity to hypoxia, some other fac-
tor or factors must be involved.

Clues to other factors may have been that several of
the children in the present study developed pulmonary
edema during an upper respiratory illness while resid-
ing at high altitude, i.e., without a prior trip to lower
altitude. We suspect that a propensity of some Lead-
ville children to develop pulmonary edema during a
coryza-like illness indicates a susceptibility to high-
altitude pulmonary edema. If so, the finding is unique
to our study, although others have indicated the pres-
ence of upper respiratory illness in their case re-
ports. 3, 12 A possible explanation for the association of
upper respiratory illness and pulmonary edema at high
altitudes is that nasal obstruction further intensifies
the hypoxia of altitude. In particular, nasal obstruction
increases the frequency and duration of apneic spells
during sleep. 13 Another possibility is that viral respira-
tory infections could increase permeability in the pul-
monary vascular bed or alter the alveolar epithelial
barrier. 14 The recent finding of high protein in the fluid
from lung lavage of patients with high-altitude pulmo-
nary edema indicates the presence of increased vascul-
ar permeability. 15 The combination of increased vas-
cular pressure plus an increase in endothelial or
epithelial permeability may result in a much higher
extravascular lung water content than would increased
pressure or permeability alone. 16

One would anticipate that the pulmonary arterial
pressure during the acute high-altitude pulmonary ede-
ma in our patients would be higher than that observed
after recovery. 3, 17 Clinical evidence of acute elevation
of pressure was observed on the electrocardiograms
available for study. That pressures were higher during
the acute episode than after recovery was suggested by
more rightward QRS vectors and higher right-sided
voltages during edema. However, even after recovery,
the seven susceptible patients continued to show in-
creased right ventricular forces, suggesting persistent
pulmonary hypertension during continued high-alti-
tude residence. If this is the case, the clinical data are
consistent with increased pulmonary pressures in the
susceptible children during continued residence at high
altitude. Perhaps electrocardiographic manifestations
of augmented pulmonary hypertension may prove to
be a screening technique to uncover those children
susceptible to high-altitude pulmonary edema.

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