Altitude Pulmonary Edema Below 8,000 Feet

What Are We Missing?

Many of the “dogmas of the quiet past” have given way to more well-founded concepts of disease in recent decades, as clinical science developed more precise investigative tools and effective therapies. Some dogmas have remained intact. One of these holds that high-altitude pulmonary edema (HAPE) is unknown or rare below 8,000 to 9,000 feet (2,440 to 2,745 m). Cases of HAPE at lesser altitudes are attributed to preexisting diseases such as skeletal or pulmonary vascular abnormalities. In the current issue of CHEST (see page 49), however, Gabry et al describe 52 lowlanders who acquired HAPE after skiing at 1,400 to 2,400 m between 1992 and 2000. This remarkable account of previously healthy persons is all the more noteworthy because the skiers slept at a mean altitude of 1,300 m. As Hultgren points out, HAPE is usually attributed to altitude of repose, rather than that of daily activity.) Whereas the altitude exposure of these skiers was much more mild than that of previous reports, their illnesses were not. The symptoms, cardiorespiratory signs, and radiographic abnormalities—83% of the patients had bilateral shadows extending over at least half of each lung—were severe. Gas exchange was equally deranged: the mean alveolar-arterial oxygen difference was 45 mm Hg. It is thus no surprise that these persons sought emergency medical care at the nearest hospital in Moutiers. This is a town of approximately 5,000, nestled 500 m (approximately 1,640 feet) above sea level, in the valley where the Isere River wends its alpine way through the Tarentaise region of southeastern France. Some of the tallest peaks in Europe are nearby. For example, Mont Blanc (15,760 feet/4,807 m) is within 45 km (<30 miles). But these lofty heights are not readily accessible from Moutiers since the mountain passes are impassible in winter. Although the patients documented by Gabry et al skied only at lower altitudes, they became very ill nonetheless.

Because their findings are surprising, one wonders if Gabry et al were exhaustive in excluding other conditions that can masquerade as HAPE? Not completely. Infection is the most obvious candidate. Viral pneumonia might mimic HAPE both in its presentation and its rapid resolution in healthy young patients such as Gabry et al describe. For decades preceding the identification of HAPE as a distinct clinical entity, many patients who probably had this condition were thought to have pneumonia. Was it the other way around in the patients of Gabry et al? If so, what type of pneumonia did they have? As the authors point out, influenza pneumonia usually affects the ill, immunosuppressed, or aged, rather than healthy 37-years-olds. This pneumonia has a pro-drome of 1 to 4 days that could be hard to distinguish from acute mountain sickness, but it often lasts 2 to 3 weeks, especially if complicated by secondary bacterial infections. This was clearly not the case in the present patients, all of whom were hospitalized for less than a week. Given the retrospective nature of their analysis, it was beyond the reach of the authors to exclude infection by bacterial cultures or viral isolation from upper or lower airway secretions, or immunofluorescence, polymerase chain reaction, or enzyme-linked immunosorbent assay testing or other means. Future prospective investigations can incorporate such steps, however, thus establishing or excluding infectious etiology from the differential diagnosis in patients who appear to have HAPE at such modest altitudes.

To exclude drug-induced pulmonary edema such as that due to heroin (smoked, snorted, or injected), the authors relied on the history of family and friends, and lack of pinpoint pupils, depressed respirations, and altered consciousness. The latter symptom was present in only 2 of their 52 patients, none of whom were treated with naloxone. Suspicious readers might insist on negative results of specific tests of urine or other body fluids to exclude this and other drugs, including cocaine, as causes of pulmonary edema in altitude visitors. Again, this is beyond the reach of a retrospective study. Assuming accuracy in the diagnosis of HAPE in 52 patients among the 11,420 admitted to the Moutiers emergency department over 9 years, one remains curious as to how many patients had pulmonary edema from other causes over the same time period. For exam-
ple, how many had left ventricular dysfunction found by sonographic or other criteria, thus eliminating the diagnosis of HAPE?

Other aspects of HAPE in these patients merit special notice. While their pulse and oral temperatures were not beyond ranges expected from other studies, the degrees of systemic hypertension and tachypnea were greater. For example, the 336 patients with HAPE in the studies of Hultgren et al., Lobenhoffer et al. and Sophocles had a mean BP of approximately 124/82 mm Hg, much lower than the mean of 170/110 mm Hg observed by Gabry et al. Does this difference reflect a greater degree of sympathoadrenergic stimulation in these patients, which might also have affected their pulmonary circulation? Without additional data, one can only speculate.

Are the patients of Gabry et al. part of the subset of altitude sojourners who are especially vulnerable to HAPE? Such persons when exposed to high altitude have greater pulmonary vascular reactivity and higher plasma levels of endothelin-1, inflammatory cytokines in BAL fluid, or urinary leukotriene E4 when compared to individuals less prone to HAPE. However, the latter finding was not confirmed in a more recent study. Moreover, Swenson et al. recently presented evidence from BAL and echocardiography in both HAPE-susceptible and HAPE-resistant subjects that neither inflammation nor pulmonary capillary fracture are cardinal mechanisms in this condition, although West provided graphic evidence of the latter in an animal model. The response of the patients of Gabry et al. to therapy including nifedipine and oxygen is consistent with the central role of reversible pulmonary hypertension in HAPE. In the present context, it must be recognized that most of the above-mentioned studies of the HAPE-prone subjects were carried out at substantially higher altitudes than that of Gabry et al. Their applicability to lower altitudes is yet to be determined.

What are some of the clinical issues raised by this report? Three come immediately to mind. One is the possibility that patients who present with HAPE could be just the tip of the clinical iceberg. This is suggested by recent observations of Cremona et al. and also from higher altitudes (Monte Rosa, 4,559 m). As they discovered, three fourths of 262 climbers with no evidence of HAPE had an increase in closing volume suggestive of subclinical pulmonary edema. No similar studies have as yet been done at lower altitudes. Secondly, those responsible for military operations at altitude might also take notice, for such scenarios can resemble that of the present report: unacclimatized young men arrive at 6,000 to 8,000 feet of altitude (1,830 to 2,440 m) and immediately engage in vigorous physical activity in the cold, and later bivouac at that altitude. The work of Gabry et al. supports the use of prophylactic acetazolamide for mountain sickness or salmeterol or nifedipine for HAPE in this setting, pending more confirmatory studies in the present context. Thirdly, the mean sleeping altitude of the present patients (1,300 m/4,262 feet) is lower than the equivalent cabin pressures of commercial aircraft. While cold and exertion are not part of lengthy air travel and HAPE has not been reported in this setting, the report of Gabry et al. may lower the threshold of clinicians to consider supplemental oxygen for their pulmonary patients who plan such travel.

Has this report of HAPE at an altitude under 2,400 m overturned another quiet dogma? Not yet. More compelling evidence is needed to make the case. Moutiers seems a logical place to collect further evidence, and perhaps delve deeper into the mechanisms contributing to HAPE, if its occurrence at this lower altitude is confirmed. But the needs of “the stormy present” may force us to “think anew and act new” about where else HAPE may be encountered—for example, in the conditions mentioned above. Such considerations add impetus to the need for a closer look at lung fluid balance at these modest altitudes. One hopes that efforts aimed at earlier identification of those on the verge of HAPE will soon bear positive fruit.

Lawrence W. Raymond, MD, ScM, FCCP
Charlotte, NC

Dr. Raymond is Director of Occupational and Environmental Medicine at Carolinas HealthCare System in Charlotte, NC, and Professor of Family Medicine at the University of North Carolina at Chapel Hill.

Correspondence to: Lawrence W. Raymond, MD, ScM, FCCP, Director of Occupational and Environmental Medicine, Carolinas HealthCare System, PO Box 32861, Charlotte, NC 28232; e-mail: lwr@med.unc.edu

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Cheyne-Stokes Respiration and Congestive Heart Failure

Are Oxygen Stores the Critical Factor?

Cheyne-Stokes respiration (CSR) is a pattern of increasing, followed by decreasing, ventilation leading to a period of apnea. CSR is associated with several conditions, including CNS dysfunction, ascent to high-altitude and, as investigated in this issue of CHEST (see page 59) congestive heart failure. Typically, CSR is most obvious during non-rapid eye movement sleep when metabolic control of breathing predominates. The initiation of CSR may depend on a narrow difference between the resting end-tidal CO2 (PetCO2) and the apneic threshold for CO2. This enhances the likelihood that apnea will occur under conditions that favor a decrease in CO2 and an increase in the apneic threshold such as a transient arousal followed by the onset of sleep. As reviewed, once initiated, CSR is maintained, in part, by the interactive effect of fluctuations in CO2 and O2 on central and peripheral chemoreceptors. The increasing ventilation results from progressive elevation of CO2 levels above the apneic threshold plus a progressive decrease in O2. The decreasing ventilation results from a progressive decline of CO2 and increase in O2 due to hyperpnea from chemoreceptor stimulation. As discussed, apnea is then the result of a CO2 level below the apneic threshold possibly combined with little or no hypoxic stimulation. Several factors may make CSR more likely to be present. These include a delayed circulation time from the heart to the respiratory chemoreceptors (eg, from congestive heart failure), chemoreceptors that are overly sensitive to CO2, frequent arousals, various reflexes, upper airway instability, and the interactive effect of an increase in CO2 with a decrease in O2 that is known to produce greater than additive respiratory chemostimulation.

CSR is common in patients with heart failure and appears to occur in approximately 40% of patients with an ejection fraction < 45%. For reasons that are not fully defined, patients with CSR associated with congestive heart failure appear to have a higher mortality than those without CSR. In addition, CSR disrupts sleep and can lead to symptoms such as insomnia and daytime sleepiness. Although the pattern of CSR is well established, it is unclear if there are at least two subsets of CSR, one which involves the CNS without any upper airway instability (ie, without potential partial or complete obstruction) and one which is combined with at least the potential for partial or complete upper airway obstruction. This confusion stems, in