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REVIEW ARTICLE

Update on High-Altitude Pulmonary Edema: Pathogenesis, Prevention, and Treatment

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High-altitude pulmonary edema (HAPE) is a life-threatening noncardiogenic form of pulmonary edema (PE) that afflicts susceptible persons after rapid ascent to high altitude above 2500 m. Its pathogenesis is related to increased sympathetic tone, exaggerated hypoxic pulmonary vasoconstriction, uneven hypoxic pulmonary vasoconstriction with overperfusion of some regions of the pulmonary vascular bed, increased pulmonary capillary pressure, stress failure of pulmonary capillaries, and alveolar fluid leak across capillary endothelium resulting in interstitial and alveolar edema. Prevention of HAPE is most effectively achieved by gradual ascent with time for acclimatization, although recent small studies have highlighted a number of pharmacologic options. Inhaled salmeterol prevents HAPE presumably by increasing alveolar fluid clearance, the phosphodiesterase-5 inhibitor tadalafil works by acting as a pulmonary vasodilator, and dexamethasone seems to prevent HAPE by stabilizing the capillary endothelium, along with other potential effects. These investigations have yet to be validated in widespread clinical practice. Nifedipine, which prevents HAPE via its effects as a pulmonary vasodilator, has a longer history of clinical use. The most effective and reliable treatment of established HAPE is immediate descent and/or adequate flow supplemental oxygen to maintain arterial saturation above 90%, accompanied by rest from strenuous physical activity. Use of a portable hyperbaric chamber is an effective temporizing measure, and nifedipine may be used for treatment of HAPE, although only as an adjunct to descent and/or supplemental oxygen if these methods of treatment are not immediately available to a person with HAPE.

Key words: altitude illness, pulmonary edema, high altitude, mountaineering, HAPE

Introduction and clinical description

High-altitude pulmonary edema (HAPE) is a life-threatening noncardiogenic form of pulmonary edema (PE) that develops in nonacclimatized persons after rapid ascent to altitudes above 2000 to 3000 m. HAPE is primarily a pulmonary disorder, whereas acute mountain sickness (AMS) and the much less frequent high-altitude cerebral edema, are neurologic disorders. First described in the English language medical literature in 1960 by Houston[1] and Hultgren,[2] HAPE is characterized by cough, progressive dyspnea with exertion, and decreased exercise tolerance, generally developing within 2 to 4 days after arrival at high altitude. The cough typically begins as a dry cough that progresses to a cough productive of pink, frothy sputum, rarely producing frank blood.[3] Symptoms of AMS, including headache and nausea, may accompany HAPE, but 50% of persons with HAPE experience no AMS symptoms.[4] On physical examination, persons with HAPE have tachycardia, tachypnea, low-grade fever, and inspiratory crackles on lung auscultation, which are typically bilateral but may be unilateral in early HAPE, often heard in the right middle lobe.[4] The latter diagnostic finding is not particularly specific for early HAPE, because focal crackles may be heard in the absence of any high-altitude illness after ascent to high altitude.[5,6] As HAPE progresses, crackles may become diffuse. On chest radiography, HAPE is characterized by patchy bilateral alveolar infiltrates that may be unilateral in the right hemithorax in early HAPE.[6] A retrospective review of 60 cases of severe HAPE (requiring hospitalization) found more homogeneous, confluent infiltrates in the late stage of the disease, suggesting progression from its initial patchy distribution with increasing severity (Figure 1).[7] HAPE

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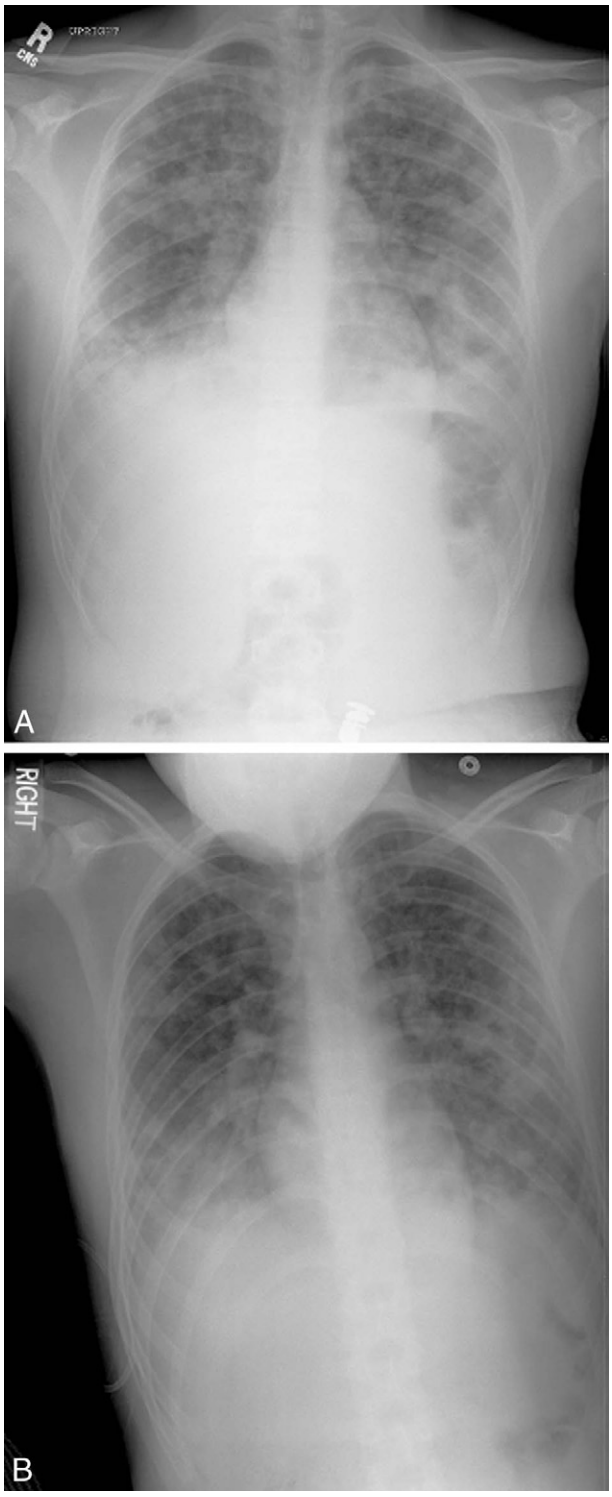

Figure 1. Panel A, Chest radiograph of a 15-year-old male with high-altitude pulmonary edema after helicopter evacuation from an altitude of 11 000 feet (3353 m) to 4500 feet (1372 m). The chest radiograph shows dense bilateral patchy alveolar infiltrative change and normal cardiac and mediastinal width. **Panel B,** Chest radiograph from the same patient after 1 day of treatment with supplemental oxygen delivered by nasal cannula at a flow rate of 4 L/min. The chest radiograph shows improvement in bilateral infiltrates.

is characterized by increased pulmonary artery (PA) pressure with a normal cardiac output and pulmonary capillary wedge pressure. HAPE-related hypoxemia is variable, with a mean arterial oxygen saturation of 74% observed in one study at a ski resort at 2928 m (normal average saturation at that altitude is approximately 92%) (Table 1).[3,4]

Risk factors and susceptibility

Factors that increase the incidence of HAPE include a prior history of HAPE,[8] faster rates of ascent, higher altitudes, male sex,[4,9] cold ambient temperatures,[9,10] preexisting respiratory infection,[11] and intense exercise.[12] Most HAPE-susceptible persons (at least 1 prior episode of HAPE) can travel to high altitude on subsequent trips without developing HAPE if they ascend at a gradual rate to allow time for acclimatization once above 2000 m.[13] As demonstrated in children by Durmowicz and colleagues[11] and anecdotally observed in adults, preexisting respiratory tract infection is a risk factor for the development of HAPE, presumably due to the alteration of vascular permeability by inflammatory mediators. Priming with endotoxin and preexisting viral respiratory infection has been found to increase pulmonary vascular permeability and protein content in edema fluid of rats exposed to high altitude, further supporting this theory.[14,15]

Evidence also exists for an association between a predisposition to HAPE and the HLA-DR6 and HLA-DQ4 alleles, suggesting an immunogenetic susceptibility to HAPE.[16] Because these studies were conducted in the somewhat restricted gene pool of entirely Japanese individuals, more comprehensive investigation of this intriguing possibility is warranted.[17]

Preexisting conditions or anatomic abnormalities that lead to increased pulmonary blood flow or intravascular pressure may predispose to HAPE, even at altitudes less than 2500 m. These include primary pulmonary hypertension,[18] congenital absence of one pulmonary artery (PA),[19] or intracardiac shunt. The latter includes left-to-right shunts, such as atrial septal defect,[20] ventricular septal defect,[21] and the more well-studied patent foramen ovale (PFO).[22] It has been theorized that, as a result of rising pulmonary vascular resistance (PVR) during hypoxic pulmonary vasoconstriction (HPV), a PFO may reverse direction and begin shunting blood from the right