Hypoxic Lung Whiteout: Further Clearing but More Questions from on High

High-altitude pulmonary edema (HAPE) is an uncommon form of life-threatening noncardiogenic pulmonary edema that occurs when a person ascends too high and too fast. It begins within 1 to 2 days of a gain in altitude. It has an incidence of 0.1% to 15%, depending on ascent rate, individual susceptibility (as reflected by previous episodes of HAPE), and likely coexisting cardiopulmonary disease (1). Its pathogenesis, once mysterious, is now understood in some detail.

High-altitude pulmonary edema begins when a critical level of hypoxic pulmonary vasoconstriction (HPV) causes mean pulmonary arterial pressure to exceed 35 to 40 mm Hg (2). This, in association with regional (segmental and subsegmental) differences in the strength of HPV (3) and hypoxic vasoconstriction (2), probably causes capillary pressures to exceed 20 mm Hg in areas of lesser HPV and higher blood flow (2). Pressures of this magnitude in the unconditioned lung microvasculature lead to capillary stress failure (overperfusion edema), in which the alveolar-capillary barrier becomes permeable enough for high-molecular-weight proteins and fluid to leak into the alveolar space. Ultimately, this process disrupts the basement membranes and endothelial and epithelial cell membranes, leading to alveolar hemorrhage (1, 4, 5). The evidence for this chain of events is that high pulmonary arterial pressure precedes HAPE, reduction in pulmonary arterial pressure by any means (descent, oxygen, nitric oxide, portable hyperbaric bags, and pulmonary vasodilators) is effective therapy, and HAPE-susceptible people have very strong pulmonary vascular responses to hypoxia and exercise (1).

Two other theories of pathogenesis may, in association with increased microvascular pressures, lead to or contribute to HAPE. One theory is that HAPE involves a pulmonary inflammatory reaction to hypoxia, leading to increased capillary permeability. According to the other theory, HAPE involves a constitutional or hypoxia-mediated depression of active alveolar sodium and water reabsorption. In this issue, Maggiorini and colleagues (6) explore aspects of all 3 concepts. They studied HAPE-susceptible individuals, who had a 60% to 70% likelihood of developing HAPE under their study conditions (rapid ascent from 1100 m to 4559 m). We owe a debt to these HAPE-susceptible mountaineers who risked an episode of HAPE to undergo research investigations, including, in earlier studies, bronchoscopy (4) and right-heart catheterization (2), at high altitude. Maggiorini and colleagues have performed a well-designed, sophisticated clinical investigation in the mountains, while placing great emphasis on participants’ safety. Their study has yielded important practical answers and has serendipitously generated new intriguing questions about basic lung pathophysiology and pharmacology.

Maggiorini and colleagues tested dexamethasone and tadalafil as new options for HAPE prophylaxis in 29 HAPE-susceptible participants. The participants took dexamethasone (8 mg twice daily), tadalafil (10 mg twice daily), or placebo (twice daily) before and during a 2-day ascent to the Capanna Regina Margherita, a several-story mountain hut on the Monte Rosa straddling the Swiss–Italian border at 4559 m. Incidence of HAPE was 78% in the placebo-treated group but was reduced to 13% and 0% in the tadalafil and dexamethasone groups, respectively. This reduction in risk is equivalent to nifedipine (a 10% incidence) (7) and potentially better than salmeterol (a 33% incidence) (8). 2 established prophylactic drugs tested under the same conditions on the Monte Rosa. Dexamethasone significantly reduced acute mountain sickness (AMS); tadalafil did not. Patients taking dexamethasone had mild but clinically insignificant hyperglycemia.

Why do these drugs prevent HAPE? Tadalafil, a phosphodiesterase-5 inhibitor, reduces HPV and pulmonary hypertension by blocking breakdown of cyclic GMP, the intracellular mediator of the vasodilatory effects of nitric oxide. Although the physiologic rationale for using tadalafil was straightforward, the case for dexamethasone rested on less firm footing. Dexamethasone is superb prophylaxis for AMS and its most extreme expression, high-altitude cerebral edema (9). It also reduces lung water accumulation in acutely hypoxic animals (10), an effect originally attributed to its potent anti-inflammatory effects. Yet patients with nascent HAPE do not have inflammatory cells or pro-inflammatory cytokines in their protein-rich and bloody bronchoalveolar lavage fluid (4). Attention then turned to the possibility that glucocorticoids, like β2-agonists, increase alveolar epithelial sodium (Na+) and water reabsorption by upregulating alveolar epithelial membrane Na+ channels and Na+/K+ -ATPase (1). This observation led to the study that showed that inhaled salmeterol reduced the incidence of HAPE (8). It was unclear whether this result was due to upregulation of sodium transport, because β2-agonists have other potentially protective actions, including HPV inhibition, ventilatory stimulation, and reduction in alveolar capillary permeability (11). Dexamethasone was chosen as possibly a more selective agent to increase alveolar fluid reabsorption because the literature at that time gave little evidence that glucocorticoids stimulate ventilation or blunt HPV (12).

The true surprise of Maggiorini and colleagues’ study is that dexamethasone was 100% effective and that it reduced pulmonary arterial pressure, which is the likely explanation for its effectiveness. The authors could not rule
out their hypothesized mechanism—dexamethasone-stimulated alveolar fluid reabsorption—because they did not test for this effect directly. However, dexamethasone did not affect 2 indirect measures of increased transmembrane sodium transport (nasal mucosal potential difference and circulating leukocyte messenger RNA for epithelial membrane Na\(^+\) channels and Na\(^+\)/K\(^+\)-ATPase). Thus, we have the novel finding that dexamethasone inhibits HPV in the mountains. Although previous work gave no inkling, very recent animal and in vitro studies find that glucocorticoids increase pulmonary vascular endothelial nitric oxide production by upregulating endothelial nitric oxide synthase (13). This mechanism fits nicely with data in HAPE-susceptible persons, in whom hypoxia-driven pulmonary and vascular endothelial nitric oxide generation is lower than in HAPE-resistant people (14, 15).

Although stimulation of nitric oxide generation remains the most compelling explanation for dexamethasone’s efficacy, other glucocorticoid effects, both genomic (requiring hours to days for gene transcription) or rapid nongenomic (within minutes), could be at play. During hypoxia, HAPE-susceptible individuals experience greater sympathetic activation of α-adrenergic effenter pathways (16), which may contribute to greater hypoxic pulmonary vasoconstriction (17). Glucocorticoids could mediate a reduction in sympathetic tone, as evidenced by the remarkably lower heart rates and systemic blood pressure in the dexamethasone-treated group in Maggiorini and colleagues’ study. Dexamethasone, even in the adult lung, stimulates surfactant production (18). Surfactant lowers alveolar surface tension, which reduces the transmural gradient driving fluid into the alveolar space (19). Last, dexamethasone may limit fluid leak across the alveolar capillary barrier by strengthening cell-to-cell tight junctions (20).

How should this investigation influence the management of HAPE? Tadalafil and dexamethasone offer 2 new, effective options for preventing HAPE. According to their likely mechanism of action, both should be effective in treating established HAPE. This point, nevertheless, needs to be tested, especially in the case of dexamethasone; if its protection depends on genomic changes, its onset of action may be too slow for emergent therapy. Although the reflex is often to reach for a prescription pad, physicians should counsel people traveling to high altitude, particularly those with a history of altitude intolerance, about safe ascent rates. As a useful rule, once above 3000 m, any further gain in altitude should be limited to no more than 300 to 350 m/d. If signs or symptoms suggestive of HAPE develop, the mountaineer should stop or descend. Prudent ascent rates are effective because they allow time for multiple mechanisms of adaptation at the organ and cellular level to maintain adequate tissue oxygen delivery and strengthen the pulmonary microvasculature (5). However, HAPE-susceptible individuals or rescue team members who must ascend at unsafe rates should consider prophylaxis with nifedipine, tadalafil, or dexamethasone. Taking dexamethasone for a long time while on an extended trek could lead to hyperglycemia, hypercalciuria, protein catabolism, and immune suppression. It will be interesting to see whether inhaled corticosteroids can substitute for oral dosing, which would avoid these adverse effects.

High-altitude pulmonary edema is an uncommon affliction. Why is elucidating its pathogenesis important? Research on HAPE may help us to understand and better treat some common lowland pulmonary edemas. The fluid leak in pulmonary embolism, reperfusion injury in a newly transplanted lung or after pulmonary arterial thromboembolectomy, congestive heart failure, severe mitral stenosis, and neurogenic pulmonary edema may share with HAPE a pathogenesis of capillary stress failure and overperfusion edema. It is intriguing to speculate that the pulmonary vascular hyperreactivity of HAPE-susceptible persons (many, perhaps most, of whom never get to high altitude and experience HAPE) accounts for the severe secondary pulmonary hypertension sometimes seen with sleep apnea, heart failure, or lung disease. To paraphrase the poet William Blake, “Great questions are posed when men and mountains meet. This is not done by musing in the street.”

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References