High-Altitude Pulmonary Edema: Diagnosis, Prevention, and Treatment

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Abstract

High-altitude pulmonary edema (HAPE) is a lethal, noncardiogenic form of pulmonary edema that afflicts susceptible individuals after rapid ascent to high altitude above 2,500 m. Prevention of HAPE is achieved most effectively by gradual ascent allowing time for proper acclimatization. Certain prophylactic medications may further reduce the risk of ascending to high altitude in individuals with a prior history of HAPE. The most effective and reliable treatment of HAPE is immediate descent and administration of supplemental oxygen.

Introduction

High-altitude pulmonary edema (HAPE) is a life-threatening, noncardiogenic form of pulmonary edema afflicting certain individuals after rapid ascent to high altitude above 2,500 m (approximately 8,200 ft). HAPE is the most common cause of death related to high altitude. The reported incidence of HAPE ranges from an estimated 0.01% of skiers traveling from low altitude to Vail, CO (2,500 m), to 15.5% of Indian soldiers rapidly transported to altitudes of 3,355 and 5,940 m (approximately 11,000 to 18,000 ft) (11).

Primary risk factors that increase the incidence of HAPE include a prior history of the condition, rapid ascent rates, higher altitudes achieved, heavy exertion, cold ambient temperatures, and preexisting respiratory infection. The presence of conditions or anatomic abnormalities that increase pulmonary blood flow or pressure, including primary pulmonary hypertension, intracardiac shunts such as an atrial septal defect or patent foramen ovale, and congenital absence of a pulmonary artery, also increases the risk of HAPE.

Pathophysiology

Exaggerated hypoxic pulmonary vasoconstriction, elevated pulmonary artery pressures, and high-permeability noncardiogenic edema resulting from stress failure of pulmonary capillaries in focal areas of the lung characterize HAPE. The abnormally high pulmonary artery pressures associated with HAPE most likely are due to multiple factors, including increased sympathetic activity, decreased nitric oxide, and elevated endothelin-1 levels (24).

Travel to high altitude is associated often with strenuous exertion and cold exposure, both of which result in an exaggerated increase in sympathetic activity in HAPE-susceptible persons that directly correlates with rises in pulmonary artery pressures. Nitric oxide is a mediator of exaggerated hypoxic pulmonary vasoconstriction, and its decreased availability may play a major role in the susceptibility to and development of HAPE. HAPE-susceptible individuals demonstrate significantly reduced levels of exhaled nitric oxide with a resultant elevation in pulmonary artery pressure at high altitude (4,7). Phosphodiesterase-5 inhibitors, such as tadalafil and sildenafil, increase cyclic guanosine monophosphate-mediated pulmonary vasodilation, reducing altitude-related pulmonary hypertension, improving exercise tolerance, and providing further evidence of the role of nitric oxide in HAPE pathogenesis (21). HAPE-susceptible individuals also exhibit higher levels of endothelin-1, which is a potent endothelium-derived pulmonary vasoconstrictor. Endothelin-1 antagonism decreases pulmonary artery pressures in healthy volunteers at high altitude (16) and HAPE-sensitive individuals exposed to hypoxia (19).

A small prospective study of physiologic lung function in mountaineers with radiographically confirmed HAPE demonstrated reduced compliance and impaired gas exchange, as well as pronounced nocturnal hypoxemia, ventilatory control instability (increased number of periodic breathing cycles), and sympathetic stimulation (elevated nocturnal heart rates), when compared with healthy controls (5). A recent small study comparing HAPE-sensitive and resistant mountaineers demonstrated an exaggerated rise in systolic pulmonary artery pressure by Doppler echocardiography in response to hypoxic exercise in the susceptible group (17). This suggests that significant increases in systolic pulmonary artery pressure during hypoxic exercise from basal resting normoxic levels may allow a clinician to predict HAPE susceptibility in an individual.

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Clinical Diagnosis

Early manifestations of HAPE include decreased exercise tolerance and a prolonged recovery period after exertion at altitude. Dyspnea on exertion, chest discomfort, and dry cough develop, followed by dyspnea at rest as the disease progresses. In severe cases, the cough becomes productive of blood-tinged, frothy sputum. Physical examination typically reveals tachycardia and tachypnea. Auscultation reveals rales, often asymmetrical in distribution, and usually found in the right mid-lung initially. A low-grade fever is common. Cyanosis and orthopnea may become prominent in severe cases.

The electrocardiogram in HAPE patients invariably demonstrates sinus tachycardia and may have changes suggestive of acute pulmonary hypertension, including right axis deviation, right bundle branch block, right ventricular hypertrophy by voltage (tall R wave over the right precordial leads), and right atrial enlargement (peaked P waves in leads II, V1, and V2). Hemodynamic measurements reveal high pulmonary artery pressure and pulmonary vascular resistance, as well as low to normal pulmonary wedge pressures, cardiac output, and systemic arterial blood pressure (11).

Radiographic findings in HAPE are consistent with noncardiogenic edema, including a generally normal heart and left atrial size and no evidence of pulmonary venous prominence such as Kerley lines. Typically, there is pulmonary artery prominence along with patchy, peripheral infiltrates, which may be unilateral or bilateral and show a predilection for the right middle lung. Ultrasound scoring of "comet tail" artifacts, which are produced by microreflections from interstitial or alveolar edema, in one study demonstrated much higher scores and lower oxygen saturation in HAPE patients compared with controls (10). Comet tail scores decreased as HAPE cleared in these patients. Another sonography study of comet tails demonstrated a high prevalence of clinically silent interstitial edema mirrored by decreased oxygen saturation in climbers (20). Although the mere presence of comet tails does not appear to be unequivocal evidence of clinically relevant HAPE, ultrasound does appear to be a potentially valuable tool for monitoring patient progression through serial comet tail scoring.

Prevention

A clear relationship exists between rate of ascent and HAPE. Gradual ascent is therefore the primary recommended method for preventing HAPE. At elevations above 2,500 m (approximately 8,200 ft), sleeping altitudes should be limited to an ascent rate of 300 to 350 m (approximately 1,000 to 1,200 ft) per day. An extra acclimatization day with rest should be added for every 600 to 1,200 m (approximately 2,000 to 4,000 ft) above 2,500 m (approximately 8,200 ft). Pharmacologic prophylaxis is recommended as adjunctive therapy for individuals with a prior history of HAPE and those who must ascend more than 3,000 m (approximately 10,000 ft) in a 24-h period, as may be required in some rescue or military operational scenarios (11,24).

A single randomized, placebo-controlled study, as well as extensive clinical experience, has demonstrated the benefit of nifedipine (60 mg of sustained release preparation daily in divided doses) in the prevention of HAPE in susceptible persons (2). Salmeterol, a long-acting, inhaled beta-agonist, demonstrated a 50% reduction in the incidence of HAPE in susceptible individuals when used at very high doses (125 μg twice daily) (22). However, since clinical experience with salmeterol at high altitude is limited, this medication is not recommended as a single agent prophylactic measure but may be considered as a supplement to nifedipine in patients with a clear history of recurrent HAPE (13).

A randomized, placebo-controlled trial demonstrated that both tadalafil (10 mg twice daily) and dexamethasone (16 mg twice daily in divided doses) are effective in preventing HAPE in susceptible individuals (15). Although the use of dexamethasone is well documented as a prophylactic measure to prevent acute mountain sickness, larger studies are required to confirm the role of this drug in the prevention of HAPE. If confirmed, dexamethasone may make an excellent choice to prevent multiple forms of high-altitude illness when rapid ascents are required for rescue or similar scenarios. An open-label study of the effects of adding tadalafil to acetazolamide prophylaxis in climbers on Mount Kilimanjaro demonstrated a statistically significant reduction in high-altitude illness, primarily due to a decrease in the incidence of HAPE in the group receiving the phosphodiesterase inhibitor (12). These most recent data seem to further support a potential role for tadalafil and other drugs in this class in the prevention of HAPE. A double-blind, randomized, placebo-controlled trial evaluated the effects of sildenafil on pulmonary artery pressures at altitude in healthy volunteers at high altitude (3). There was no significant difference in systolic pulmonary artery pressures between the sildenafil and placebo groups, but symptoms of acute mountain sickness were greater in the former, suggesting that sildenafil should not be used as routine prophylaxis in the absence of a history of HAPE susceptibility or other HAPE risk factors.

Regardless of which drug is utilized to reduce the risk of HAPE, ideally, any chemoprophylaxis should be initiated on the day prior to ascent and continued until either descent is initiated or the individual has spent 5 d at the target maximum elevation (13).

Table 1 outlines the classification scheme for grading the strength of recommendations, and quality of evidence, as developed by the American College of Chest Physicians (ACCP). Recommendations for strategies to prevent HAPE are summarized and graded in Table 2.

Treatment

The most reliable and effective treatment for HAPE is immediate descent of at least 1,000 m (approximately 3,280 ft), supplemental oxygen to achieve an arterial saturation greater than 90%, or both (13). Descent should be passive since physical exertion will exacerbate likely the patient's condition. Keeping the patient warm will minimize cold-induced sympathetic contribution to HAPE. If evacuation to a lower altitude is unsafe or impossible (*e.g.,* severe weather) and supplemental oxygen is unavailable, a portable hyperbaric chamber (*e.g.,* Gamow® bag, Certec® bag, and PAC®) can be used at 2 to 4 $lb \cdot inch^{-2}$ for several hours to simulate a descent of 1,500 m or more (approximately 5,000 ft) as a temporizing measure until actual descent can

Table 1.
ACCP classification for grading evidence and recommendations in clinical guidelines.

Grade	Description	Benefits versus Risk and Burdens	Methodological Quality of Supporting Evidence
1A	Strong recommendation, high-quality evidence	Benefits clearly outweigh risks and burdens or vice versa	RCTs without important limitations or overwhelming evidence from observational studies
1B	Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risks and burdens or vice versa	RCTs with important limitations or exceptionally strong evidence from observational studies
1C	Strong recommendation, low-quality or very low-quality evidence	Benefits clearly outweigh risk and burdens or vice versa	Observational studies or case series
2A	Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burdens	RCTs without important limitations or overwhelming evidence from observational studies
2B	Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burdens	RCTs with important limitations or exceptionally strong evidence from observational studies
2C	Weak recommendation, low-quality or very low-quality evidence	Uncertainty in the estimates of benefits, risks, and burdens; benefits, risks, and burdens may be closely balanced	Observational studies or case series

Adapted from Guyatt G, Guttermnan D, Baumann MH, *et al*. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an ACCP task force. *Chest*. 2006;129:74–81.

RCT, randomized controlled trial.

be effected (11,13,24). It is important to remember that patient access is limited severely while inside a portable hyperbaric chamber. Close monitoring through transparent chamber sections is mandatory in order to quickly detect patient deterioration.

If none of the given methods are feasible or available for treating a HAPE patient, adjunctive pharmacologic therapy may be considered but should not be regarded as a substitute for descent or supplemental oxygen. Pharmacotherapy primarily focuses on reduction of pulmonary artery pressure through the use of vasodilators. A single, nonrandomized, unblinded study in individuals with mild HAPE demonstrated that nifedipine therapy resulted in a 50% reduction in systolic pulmonary artery pressure, narrowing of the alveolar-arterial oxygen gradient, and improvement in radiographic scores as pulmonary edema cleared (18). However, a recent prospective, cross-sectional study demonstrated no additional benefit of nifedipine compared with placebo when used in combination with descent and supplemental oxygen (6). This further supports the fundamental principle that HAPE treatment must focus on descent and supplemental oxygen, and that nifedipine should not be considered as monotherapy, unless descent is impossible and oxygen or hyperbaric chamber is unavailable.

Phosphodiesterase inhibitors, such as tadalafil or sildenafil, cause pulmonary vasodilation and decrease pulmonary artery pressure, providing a strong physiologic rationale for their use in the treatment of HAPE. While reports document their use for this purpose (9) and the author personally has used sildenafil to rapidly resolve mild HAPE on Mount McKinley, no systematic prospective studies have evaluated the potential benefit of phosphodiesterase inhibitors in HAPE treatment. Similarly, the use of beta-agonists such as salmeterol or albuterol has been reported in the literature, but there are no data to support this treatment modality. Although the use of diuretics has been documented (1), they also play no role in the treatment of HAPE, especially since many patients with this condition concurrently are volume depleted. Improved gas exchange, but not improved outcomes, was noted in HAPE patients using expiratory positive airway pressure (EPAP) in a single small study (23). EPAP or continuous positive airway pressure (CPAP) may be considered as an adjunct to oxygen therapy in the hospital setting but is impractical for use in the austere, high-altitude environment.

Treatment options for HAPE are summarized and graded in Table 3.

After evacuation to a lower altitude, hospitalization may be indicated for severe HAPE cases. Treatment consists of bed rest and oxygen supplementation to keep saturations greater than 90%. Pharmacotherapy or ventilatory support is rarely necessary, and rapid recovery is the rule. Discharge criteria include resolution of clinical dyspnea, arterial

Table 2.
HAPE prevention strategies.

Intervention	Grade	Route	Dosage
Gradual ascent	1C	N/A	N/A
Nifedipine	1A	PO	30 mg SR every 12 h or 20 mg SR every 8 h
Dexamethasone	1C	PO	4 mg every 6 h
Tadalafil	1C	PO	10 mg twice daily
Sildenafil	1C	PO	50 mg every 8 h
Salmeterol	2B	INH	125 μg twice daily[a]

Grade based on ACCP classification of clinical evidence for guidelines.

[a] Only used in combination with oral agents, rather than as monotherapy.

N/A, not applicable; PO, oral; INH, inhaled; SR, sustained release.

Table 3.
HAPE treatment strategies.

Intervention	Grade	Route	Dosage
Descent	1A	N/A	N/A
Supplemental oxygen	1B	NC/FM	Sufficient to keep S_PO_2 >90%
Portable hyperbaric chamber	1B	N/A	N/A
Nifedipine	1C	PO	30-mg SR every 12 h or[a] 20-mg SR every 8 h
CPAP	2B	N/A	N/A
Phosphodiesterase inhibitors	2C	PO	Varies
Beta-agonists	2C	INH/NEB	Varies

Grade based on ACCP classification of clinical evidence for guidelines.

[a] Only as adjunctive therapy or when descent is not feasible and O_2/hyperbaric chamber is unavailable.

N/A, not applicable; NC, nasal cannula; FM, face mask; PO, oral; SR, sustained release; INH, inhaled; NEB, nebulized.

partial pressure of oxygen greater than 60 mm Hg or saturation greater than 90% on room air, and radiographic improvement of pulmonary edema (11). Normalization of blood gas values is not required because respiratory alkalosis persists for days in at least partially acclimatized individuals descending from high altitude.

Advising Patients Considering Travel to High Altitude

Individuals who plan to travel to high altitude should be educated about the importance of gradual ascent to reduce the risk of HAPE and other high-altitude illness. Medical history should be reviewed for previous episodes of HAPE. Occurrence of HAPE at relatively low altitude or multiple previous episodes of HAPE warrant an echocardiogram to evaluate for pulmonary hypertension and cardiac abnormalities, such as patent foramen ovale or atrial septal defect, as well as lung function tests to evaluate for underlying conditions such as obstructive pulmonary disease. One recommended approach is that persons with mean pulmonary artery pressures greater than 35 mm Hg or systolic pulmonary artery pressures greater than 50 mm Hg should avoid sojourns to altitudes greater than 2,500 m (approximately 8,200 ft) and ensure the availability of supplemental oxygen and/or nifedipine prophylaxis if such travel must be undertaken (11,14). Since the inflammation associated with respiratory infections may predispose to alveolar capillary leaks and the development of pulmonary edema, patients with such illnesses should be counseled to avoid high altitude until fully recovered (8).

If significant concern exists for the potential of HAPE in an individual determined to ascend to high altitude, Doppler echocardiography in the setting of exercise in a hypoxic chamber may be useful. An exaggerated rise in systolic pulmonary artery pressure is suggestive of HAPE susceptibility and may warrant the use of prophylactic medications (17).

Conclusions

Inadequate acclimatization remains the most significant risk factor for developing HAPE. Clinicians advising individuals, who are preparing to travel to high altitude, should provide education about the importance of making a slow graded ascent. In addition, they should identify the presence of HAPE risk factors and prescribe chemoprophylaxis to those who are at high risk but insist on high-altitude travel. Nifedipine continues to be the prophylactic drug of choice, based on the quality of available clinical evidence and extensive experience with its use. Phosphodiesterase inhibitors, such as tadalafil or sildenafil, are highly promising alternatives, but larger randomized, controlled trials are needed in order to recommend them as primary agents.

Immediate descent and administration of supplemental oxygen to raise saturation levels above 90% continue to be the definitive treatments for HAPE. The use of portable hyperbaric chambers may be an effective temporizing measure, when descent and oxygen administration are impossible. Nifedipine may be considered as an adjunctive treatment but must not be used as monotherapy, unless descent, supplemental oxygen provision, and the use of portable hyperbaric chambers are not feasible.

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