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Prevention and Treatment of High-Altitude Pulmonary Edema

Marco Maggiorini*

Intensive Care Unit, Department of Internal Medicine, University Hospital, Rämistrasse 100, CH-8091 Zurich, Switzerland

Abstract We distinguish two forms of high altitude illness, a cerebral form called acute mountain sickness and a pulmonary form called high-altitude pulmonary edema (HAPE). Individual susceptibility is the most important determinant for the occurrence of HAPE. The hallmark of HAPE is an excessively elevated pulmonary artery pressure (mean pressure 36-51 mm Hg), caused by an inhomogeneous hypoxic pulmonary vasoconstriction which leads to an elevated pulmonary capillary pressure and protein content as well as red blood cell-rich edema fluid. Furthermore, decreased fluid clearance from the alveoli may contribute to this noncardiogenic pulmonary edema. Immediate descent or supplemental oxygen and nifedipine or sildenafil are recommended until descent is possible. Susceptible individuals can prevent HAPE by slow ascent, average gain of altitude not exceeding 300 m/d above an altitude of 2500 m. If progressive high altitude acclimatization would not be possible, prophylaxis with nifedipine or tadalafil for long sojourns at high altitude or dexamethasone for a short stay of less then 5 days should be recommended. (Prog Cardiovasc Dis 2010;52:500-506)

Keywords: High-altitude pulmonary edema; Capillary pressure; Hypoxic pulmonary vasoconstriction; Trans-epithelial Na transport; Nifedipine; Sildenafil; Tadalafil; Dexamethasone

High-altitude pulmonary edema (HAPE) presents within 2 to 5 days after arrival at high altitude.[1-3] It is rarely observed below altitudes of 2500 to 3000 m and after 1 week of acclimatization at a particular altitude. Early symptoms of HAPE include exertion dyspnea, cough, and suddenly reduced exercise performance. As pulmonary edema progresses, orthopnea, breathlessness at rest, and gurgling in the chest develop, cough worsens and pink frothy sputum reveals overt pulmonary edema.[1-3] Râles are discrete at the beginning, typically located over the middle lung fields.[1-3] Chest radiographs and computed tomographic scans of early HAPE show a patchy, peripheral distribution of edema.[4] In advanced cases of HAPE observed at the altitude of 4559m arterial P_{O_2} usually drops below 35 mm Hg. In the early stage of HAPE bronchoalveolar lavage (BAL) reveals a protein- and red blood cell–rich edema fluid without signs of inflammation,[5] whereas in a more advanced stage, proinflammatory mediators and granulocytes add to the initial changes.[3,6]

Hemodynamic measurements in HAPE indicate that the development of pulmonary hypertension within hours after rapid exposure to high altitude is a hallmark of this disease. Characteristically, mean pulmonary artery pressure in HAPE ranges between 36 and 51 mm Hg.[1,7-11] Using the arterial occlusion method,[11] which is likely to measure pressures in vessels close to 100 μm in diameter,[12] we demonstrated that the pulmonary capillary pressure is elevated in HAPE, being on average 22 mm Hg (range, 20-26 mm Hg).[11] An impaired nitric oxide production in the lungs is probably the leading underlying mechanism of elevated pulmonary artery pressure in these individuals[5,13,14]; BAL performed in HAPE-susceptible adults within a day after ascent to 4559 m revealed elevated red blood cell counts and serum-derived protein

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* Address reprint requests to Marco Maggiorini, Intensive Care Unit, Department of Internal Medicine, University Hospital, Rämistrasse 100, CH-8091 Zürich, Switzerland.

E-mail address: klinmax@usz.unizh.ch.

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Abbreviations and Acronyms

AMS = Acute mountain sickness

BAL = bronchoalveolar lavage

ENaC = amiloride-sensitive Na-channels

HAPE = High-altitude pulmonary edema

concentration in BAL fluid, but the number of alveolar macrophages/μL and neutrophiles/μL, and the concentration of proinflammatory mediators, interleukin-1, tumor necrosis factor α, interleukin-8, thromboxane, prostaglandin E_2 and leukotriene B4 were not increased. Thus, HAPE in its early stage is a high-pressure-mediated permeability type of pulmonary edema.

In addition, it was found that hypoxia inhibits nasal epithelial Na-transport in both HAPE-resistant and susceptible mountaineers[15,16] and that, at low altitude, compared to those HAPE-resistant, HAPE-susceptible adults present with a lower activity of the amiloride-sensitive Na-channels (ENaC),[15-17] suggesting a possible contribution of alveolar epithelial cells ENaC to the pathophysiology of HAPE.

The current concepts for the prevention and treatment of HAPE are based on its pathophysiology and include progressive adaptation of the pulmonary circulation to the hypoxic environment (acclimatization), prevention and treatment of excessive hypoxic pulmonary vasoconstriction and improvement fluid clearance from the alveolar space (Fig 1).

Prevention

Slow ascent

Slow ascent is the major measure of prevention and is effective even in susceptible individuals. Indirect evidence came from the observation, that even subjects who developed HAPE more than once upon rapid ascent in the Alps successfully reached altitudes up to 7000 m when the average daily ascent rate above 2000 m does not

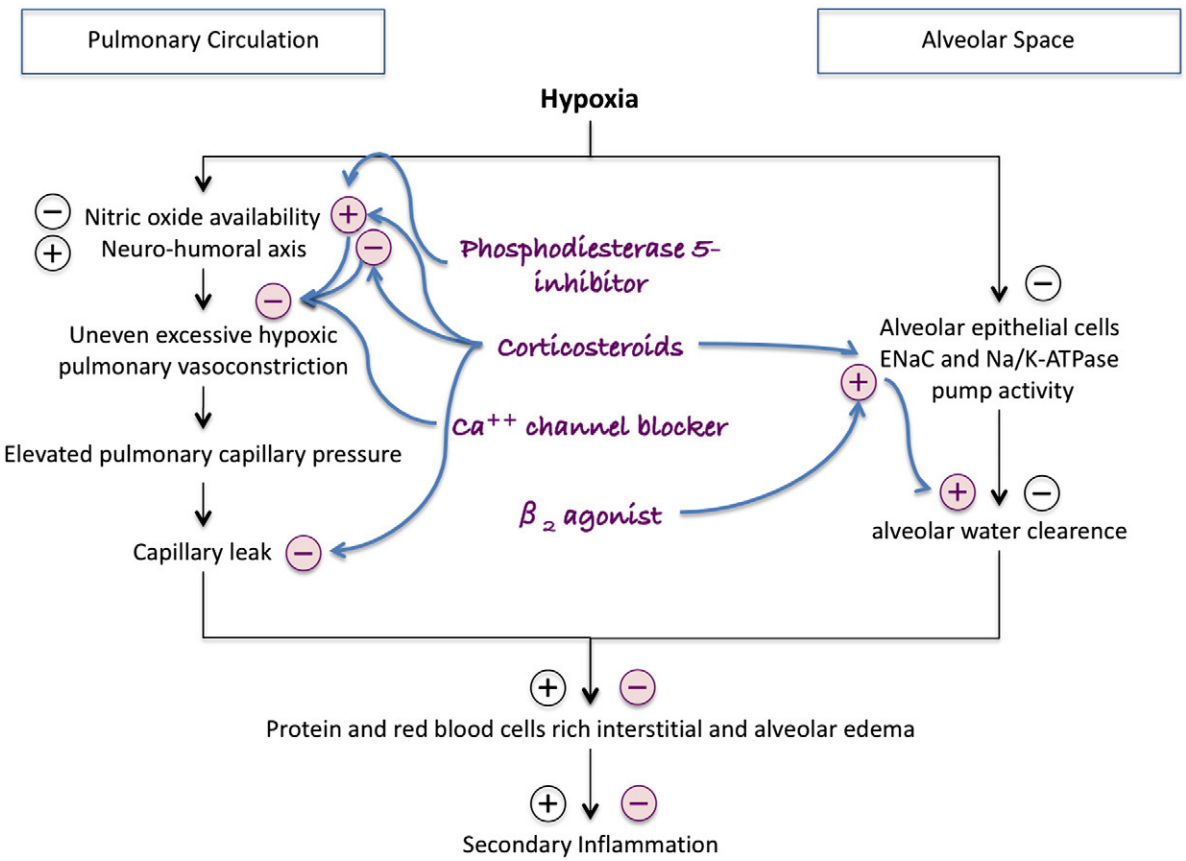

Fig 1. Action mechanisms of the different drugs used for prevention and treatment of high altitude pulmonary edema. Phosphodiesterase 5-inhibitors such as sildenafil and tadalafil increase nitric oxide availability in the pulmonary circulation leading to a decrease in pulmonary vascular tone; hence, pulmonary capillary pressure and fluid leakage in to the interstitial and alveolar space. Corticosteroids increase nitric oxide availability in the pulmonary circulation leading to a decrease in pulmonary vascular tone, decrease hypoxia associated neurohumoral activation and pulmonary capillary permeability, and enhance hypoxia-associated decrease in alveolar water clearance. β_2 agonists enhance alveolar water clearance by stimulating ENaC.