

## High-altitude Pulmonary Oedema – Novel Risk Factors, Treatment and Prevention

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### Abstract

High-altitude pulmonary oedema (HAPE) is a non-cardiogenic form of pulmonary oedema usually occurring 36–72 hours after arrival at altitudes >2,500–3,000 m in otherwise healthy individuals. Individual predisposition is the most important risk factor for HAPE. In some cases, this might be related to foetal programming of pulmonary vascular dysfunction involving epigenetic mechanisms. Excessive non-homogenous hypoxic pulmonary vasoconstriction related to impaired pulmonary nitric oxide synthesis is the major mechanism. Moreover, defective alveolar fluid clearance related to impaired transepithelial respiratory salt and water transport also has a role. Immediate descent is the treatment of choice. If descent is not possible, low flow oxygen or a hyperbaric chamber can be used. If oxygen is unavailable, drugs that lower the pulmonary artery pressure should be administered. If neurologic symptoms develop, dexamethasone should also be added. HAPE can be prevented by slow, graded ascent (i.e., an increase in the average sleeping altitude >2,500 m by <400 m/day). Individuals who are susceptible to HAPE can prevent its reoccurrence by prophylaxis with dexamethasone or nifedipine.

### Keywords

High-altitude pulmonary oedema, prevention, treatment, hypoxic pulmonary hypertension, alveolar fluid clearance, foetal programming

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Pulmonary oedema results from a persistent imbalance between forces that drive water into the airspace of the lung and the biological mechanisms needed for its removal.<sup>1,2</sup> There is evidence that some degree of asymptomatic alveolar fluid accumulation might represent a normal phenomenon in healthy humans shortly after arrival at high altitude.<sup>3,4</sup> In some subjects, however, more severe lung fluid accumulation occurs and life-threatening high-altitude pulmonary oedema (HAPE) develops.

After a rapid ascent to 4,559 m in the Alps, approximately 10 % of mountaineers develop HAPE. This incidence increases to 60–70 % in mountaineers who had suffered from HAPE before (HAPE-prone subjects), demonstrating individual susceptibility to be the most important determinant of HAPE. HAPE usually develops between 36 and 72 hours after arrival at high altitude. It is rarely observed at altitudes <2,500 m and after more than five days spent at the same altitude. The initial symptoms are exaggerated dyspnea on exertion and cough. As the disease progresses, dyspnea worsens, the cough can become productive and fever often develops.<sup>5,6</sup> A discrepancy between mild signs at pulmonary auscultation (discrete rales) and severe clinical symptoms is often observed.

### Pathophysiology

Extensive and easily accessible reviews on the pathophysiology of HAPE have recently been published.<sup>7–10</sup> Briefly, HAPE results from the conjunction of defective pulmonary vascular function, leading to uneven exaggerated hypoxic pulmonary vasoconstriction<sup>11</sup> and, in turn,

capillary leaking, as well as defective alveolar fluid clearance related to defective respiratory transepithelial sodium and water transport. In HAPE-prone mountaineers, average systolic pulmonary artery pressure after rapid ascent to 4,559 m is typically approximately 70 mmHg; lung perfusion scans have provided direct evidence for uneven perfusion with overperfusion of lung regions with radiological evidence of pulmonary oedema.<sup>12</sup> Bronchoalveolar lavage early after arrival at high altitude revealed increased erythrocyte counts and large molecular weight proteins, demonstrating capillary leaking in HAPE-prone subjects.<sup>13</sup> Defective pulmonary nitric oxide (NO) production is a central mechanism underpinning exaggerated hypoxic pulmonary vasoconstriction in HAPE-prone subjects. Moreover, and possibly related to decreased NO bioavailability, exaggerated vasoconstriction induced by sympathetic overactivity<sup>14</sup> and increased endothelin-1 synthesis also have a role.<sup>15</sup> Finally, the prevalence of a patent foramen ovale (PFO) is markedly increased in HAPE-prone subjects.<sup>16</sup> By leading to exaggerated hypoxemia, right-to-left shunting across a PFO can further facilitate exaggerated hypoxic pulmonary hypertension in HAPE-prone subjects. Although these observations show the pathophysiological importance of pulmonary hypertension in this setting, in a recent study on foetal/perinatal programming of pulmonary vascular dysfunction in humans (see below), we found that exaggerated pulmonary hypertension per se is not always sufficient to trigger HAPE, and that additional mechanisms have a role.<sup>17</sup>

In subsequent studies, we then provided direct evidence for the importance of transepithelial respiratory sodium transport in

the pathogenesis of HAPE. In genetically engineered mice, defective respiratory sodium transport facilitates pulmonary oedema.<sup>18</sup> In HAPE-prone subjects, nasal potential difference, a proxy of transepithelial respiratory sodium transport, is decreased<sup>19</sup> and this defect is further aggravated at high altitude.<sup>20,21</sup> Beta-adrenergic agonists stimulate alveolar fluid clearance in *ex vivo* human and rat lungs.<sup>22</sup> Finally, and most importantly, pharmacological stimulation of this transport with the beta-adrenergic agonist salmeterol prevents HAPE in susceptible mountaineers.<sup>19</sup>

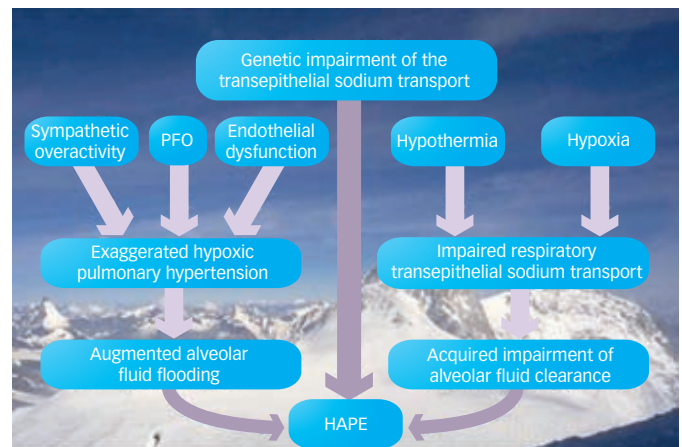
Based on these results, we suggested a new concept for the pathogenesis of HAPE (see *Figure 1*).

### Treatment of High-altitude Pulmonary Oedema

Rapid improvement of oxygenation is the treatment of choice. HAPE is therefore best managed by descent. When immediate descent is not possible, low flow oxygen (2–4 l/min) should be administered, if available. Alternatively, portable hyperbaric chambers (Gamow, USA; Certec, France), which are lighter to carry than are oxygen cylinders, can be used. However, there might be a rebound effect on stopping hyperbaria.

Other treatment options should never be considered as a substitute for rapid descent (or oxygen administration and/or hyperbaria), but should be used to improve the clinical condition to facilitate descent or when descent is impossible and oxygen and/or hyperbaric chambers are not available. Under these conditions, lowering pulmonary artery pressure with pharmacological agents is strongly recommended. Nifedipine (20 mg taken every six hours) improved symptoms, arterial oxygenation and radiographic appearance in a small group of mountaineers suffering from HAPE while remaining at 4,559 m.<sup>23</sup> Given that impaired NO bioavailability has a central role in the pathogenesis of HAPE, inhaled NO (40 ppm) has been successfully used to treat HAPE.<sup>24</sup> Despite strong evidence that, during normobaric and hypobaric hypoxia, phosphodiesterase 5 inhibitors increase NO bioavailability and decrease pulmonary-artery pressure,<sup>25</sup> there are no clinical trials on the use of these drugs for the treatment of HAPE; however, anecdotal data suggest that sildenafil is useful in this situation.<sup>26</sup> Interestingly, in this report, dexamethasone – a drug that, when administered alone, has no beneficial in the treatment of HAPE<sup>10</sup> – was co-administered for acute mountain sickness (AMS) symptoms and might have contributed by tightening pulmonary capillaries and stimulating alveolar fluid clearance. Moreover, dexamethasone might have prevented the exacerbation of AMS symptoms by sildenafil, a major problem associated with the use of these agents at high altitude.<sup>26</sup> Anecdotal reports suggest that lowering of pulmonary artery pressure with other pharmacological agents (e.g. hydralazine or phentolamine) also has beneficial effects in HAPE,<sup>27</sup> and there is evidence suggesting that alpha-adrenergic blockade is more potent in lowering pulmonary artery pressure than are other non-specific vasodilators. Although endothelin antagonists and prostacyclin analogues are effective for the treatment of pulmonary hypertension at low altitude and attenuate altitude-induced pulmonary hypertension,<sup>28</sup> there are no data on their potential usefulness for the treatment of HAPE. It is noteworthy that there is no place for the use of diuretics in the treatment of HAPE; not only do these drugs have no beneficial effects, but they can also cause serious adverse effects (i.e. severe arterial hypotension and shock) in already dehydrated subjects. Finally, it is currently unknown whether the combined regimen of bed rest, supplemental oxygen plus

**Figure 1: A New Concept for the Pathogenesis of High-Altitude Pulmonary Oedema**



*Pulmonary oedema results from a persistent imbalance between the forces that drive water into the airspace and the biological mechanisms responsible for its removal. In high-altitude pulmonary oedema (HAPE)-prone subjects, alveolar fluid flooding is increased because of uneven exaggerated pulmonary vasoconstriction that is related, at least in part, to defective nitric oxide bioavailability and exaggerated sympathetic activation. Exaggerated pulmonary hypertension per se, however, is not sufficient to trigger HAPE. HAPE-prone subjects are also characterised by a defect of the respiratory transepithelial sodium and water transport, which, during high-altitude exposure, might be further impaired by environmental factors such as hypoxia and cold temperature. The conjunction of these pulmonary vascular endothelial and alveolar epithelial defects ultimately leads to HAPE. PFO = patent foramen ovale.*

administration of a pulmonary vasodilator drug is superior to bed rest and oxygen alone.

Beta-adrenergic agonists, such as salmeterol, stimulate transepithelial sodium transport and alveolar fluid clearance in experimental animal models.<sup>22</sup> In line with this concept, beta-adrenergic stimulation of respiratory transepithelial sodium transport was subsequently found to decrease extravascular lung water in patients with acute respiratory distress syndrome (ARDS),<sup>29</sup> to accelerate the resolution of pulmonary oedema after lung resection<sup>30</sup> and to have beneficial effects in the treatment of HAPE.<sup>31</sup>

### Prevention of High-altitude Pulmonary Oedema General Recommendations

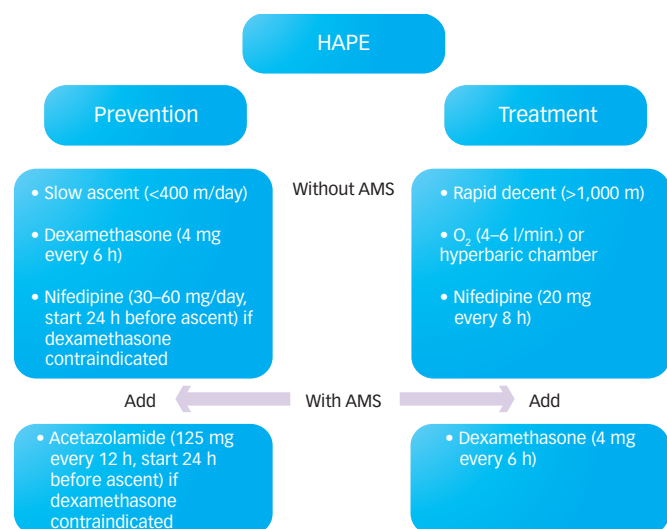
High-altitude illness occurs if there is a dysfunction in the adjustments made by an organism to the acute lowering of the arterial oxygen content. Three principal factors favour such dysfunction – individual susceptibility, rapidity of ascent and absolute altitude itself.<sup>32</sup> The major importance of slow ascent is demonstrated by the observation that mountaineers who repeatedly developed HAPE following rapid ascent to high altitude in the Alps successfully reached altitudes up to 7,000 m when the average daily ascent rate above 2,000 m did not exceed 400 m/day.<sup>26</sup> Besides these main determinants, additional factors, such as exposure to cold temperatures, heavy exercise, and recent or coexisting airway infection, might also facilitate the occurrence of HAPE.<sup>32</sup>

Even in the absence of a history of previous HAPE, observation of the following general principles might help to prevent altitude-related medical problems (see also *Figure 2*).

- Take sufficient time to acclimatise at an intermediate altitude of 2,500 m and avoid raising the average daily sleeping altitude by >400 m thereafter.

# High-Altitude Pulmonary Oedema

**Figure 2: Recommendations for Prevention and Treatment of High-Altitude Pulmonary Oedema**



AMS = acute mountain sickness; HAPE = high-altitude pulmonary oedema.

- A high carbohydrate diet increases the respiratory quotient and might improve oxygen use.
- Avoid alcohol and hypnotic drugs that might impair the hypoxic ventilatory response.
- When arriving at high altitude, avoid unnecessary exertion, because it potentiates the pulmonary vasoconstriction.
- Drink plenty of fluids during the stay at high altitude.

## Prevention of exaggerated pulmonary hypertension

Pharmacological prevention of exaggerated pulmonary hypertension in HAPE-prone subjects reduces the incidence of pulmonary oedema during high-altitude exposure when slow ascent is not possible.<sup>33,34</sup>

Sustained release nifedipine (20 mg slow release three times daily) started on the day before ascent and continued during the first three to five days after ascent, significantly reduced the incidence of exaggerated pulmonary hypertension and pulmonary oedema in HAPE-prone subjects.<sup>26,33</sup> More recently, increasing NO bioavailability with the phosphodiesterase-5 inhibitor tadalafil had similar beneficial effects that came, however, at the cost of severe AMS in some of the participants.<sup>34</sup> Although dexamethasone has no beneficial effects in the treatment of HAPE<sup>10</sup>, when taken one day prior to ascent (but not if taken after the first night) at 4,559 m, a recent study showed that the drug prevented pulmonary hypertension and pulmonary oedema in HAPE-prone subjects.<sup>34</sup> The mechanism is unknown, but because dexamethasone prevents insulin- and alcohol-induced sympathetic activation in humans by a central neural mechanism,<sup>35,36</sup> it is tempting to speculate that its beneficial effects are related to the prevention of exaggerated hypoxia-induced sympathetic vasoconstriction in HAPE-prone subjects. Alternatively, stimulation of alveolar transepithelial sodium and water transport, and tightening of the pulmonary capillary endothelium by inhibition of hypoxia-induced inflammation, and improvement of surfactant production might also have a role.

## Stimulation of Transepithelial Sodium Transport and Alveolar Fluid Clearance

To examine the importance of defective respiratory sodium transport in the pathogenesis of HAPE, we studied whether pharmacological

stimulation of this transport decreases the incidence of HAPE in susceptible subjects. We found that prophylactic stimulation of this transport with salmeterol decreased the incidence of high-altitude pulmonary oedema in highly susceptible subjects by more than 50%.<sup>19</sup> Salmeterol appears to be slightly less effective than drugs that prevent exaggerated pulmonary hypertension (i.e. nifedipine, tadalafil and dexamethasone), suggesting that prevention of the excessive increase in pulmonary–artery pressure is possibly more effective than stimulation of alveolar fluid clearance. Whether the combination of a pulmonary vasodilator and a beta-adrenergic agonist has synergic effects in the prevention or HAPE has not yet been investigated.

Currently, and in the absence of contraindications (e.g., glucose intolerance), dexamethasone has possibly the most attractive profile, because it is also highly efficient for the prophylaxis of AMS that is often also present in patients suffering from HAPE.

## Prediction of HAPE susceptibility

Prediction of HAPE susceptibility in individuals without previous high-altitude exposure represents one of the most challenging problems in high-altitude medicine. Although a history of previous HAPE (see above) or AMS in adults<sup>37</sup> is highly valuable to predict the risk and take adequate preventive measures during future exposure, there currently exists no validated test or battery of tests at low altitude that can be used to predict the risk of high-altitude illness in healthy subjects with no previous exposure.

## Simulated Altitude Exposure

Pulmonary–artery pressure in HAPE-prone subjects is normal and not different from that of HAPE-resistant subjects at low altitude.<sup>38</sup> Based on this observation, studies have examined whether pulmonary–artery pressure responses to hypoxia, or whether hypoxia plus exercise can be used to identify individuals at risk for HAPE. A recent study examining HAPE-prone and HAPE-resistant mountaineers suggested that measurement of pulmonary–artery pressure during normoxic exercise or short-term exposure to hypoxia could be used to identify individuals at risk,<sup>38</sup> even though there existed an overlap in the pulmonary vascular responses between the two groups. This study suggested that the limit of a normal systolic pulmonary–artery pressure response to normoxic exercise or acute exposure to hypoxia (equivalent to an altitude of 4,500 m) was approximately 40 mmHg. Based on this study, in a recent small prospective trial, seven out of 29 subjects with a pulmonary–artery pressure >40 mmHg, but none of 24 individuals with a response <40 mmHg, developed HAPE during a two-night stay at 4,559 m. This suggests that a negative test (pulmonary artery systolic pressure [PASP]<40 mmHg) enables one to rule out HAPE (negative predictive value 97%) whereas a positive test has little predictive value (positive predictive value of 56%).<sup>39</sup> Whether the positive predictive value of this test could be increased by the combination of other measurements, such as the nasal potential difference<sup>20</sup> or the hypoxic ventilatory drive,<sup>40</sup> is not known.

## Genetic Predisposition

There is some evidence to suggest that, in some populations, endothelial NO synthase (eNOS) polymorphisms associated with impaired vascular NO synthesis contribute to HAPE susceptibility,<sup>41,42</sup> whereas eNOS polymorphisms associated with increased NO synthesis confer protection against HAPE.<sup>43</sup> However, these observations have no practical implications for the prediction of HAPE susceptibility in the general population so far.

## Subpopulations at Risk for High-Altitude Pulmonary Oedema

Anatomical (congenital absence of the right pulmonary–artery, pulmonary–artery occlusion from granulomatous mediastinitis)<sup>44,45</sup> or functional (Down syndrome)<sup>46,47</sup> abnormalities that facilitate hypoxic pulmonary hypertension, are risk factors for developing HAPE even at relatively low altitude (1,500–2,500 m).

### Patent Foramen Ovale

At high altitude, HAPE-prone subjects display exaggerated hypoxemia before there is any evidence of alveolar fluid accumulation. We found that intracardiac right-to-left shunting contributes to this problem, because the prevalence of patent foramen ovale (PFO) is more than four times greater in HAPE-prone than in HAPE-resistant mountaineers.<sup>16</sup> We suggest that, in HAPE-prone patients, the acute hypoxic pulmonary vasoconstriction initiates a vicious cycle by causing right-to-left shunting across a PFO, which in turn aggravates hypoxemia. This results in reduced mixed venous oxygen tension, greater alveolar hypoxia and greater pulmonary hypertension.<sup>48</sup> In healthy adults, the prevalence of PFO is 20–25 %.<sup>49</sup> However, so far there is no information available whether, in this population, a PFO predisposes an individual to exaggerated hypoxic pulmonary hypertension and HAPE.

### Down Syndrome (Trisomy 21)

Circumstantial evidence suggests that individuals with Down syndrome are at risk for HAPE at relatively low altitude.<sup>46</sup> In line with this observation, Bolivian high-altitude natives with Down syndrome display sustained pulmonary hypertension at high altitude and appear to be at risk for re-entry HAPE (a particular form of HAPE occurring in high-altitude dwellers when returning from a sojourn at low altitude).<sup>47</sup>

## Foetal Programming of Hypoxic Pulmonary Hypertension

Epidemiological studies suggest that adverse events *in utero* predispose individuals to cardiovascular and metabolic disease in adulthood.<sup>50</sup> For example, preeclampsia is the most frequent complication of pregnancy. In mothers suffering from this problem, circulating vasculotoxic factors [e.g. free radicals, soluble fms-like tyrosine kinase 1 (sFlt-1), which binds placental growth factor (PlGF) and vascular endothelial growth factor (VEGF)] produced by the diseased placenta, induce vascular dysfunction and arterial hypertension.<sup>51–53</sup> We speculated that some of these factors might cross the placental

barrier and alter the regulation of vascular function in the fetus, which might predispose that individual to a pathological response later in life. To test this hypothesis, we measured pulmonary–artery pressure in offspring of mothers with preeclampsia born and permanently living at high altitude (La Paz, Bolivia, 3,600 m). We found that pulmonary–artery pressure was approximately 30 % higher in offspring of mothers with preeclampsia compared with control subjects living at the same altitude.<sup>54</sup> Vascular dysfunction was related to preeclampsia itself (rather than to a genetic anomaly predisposing the mother to preeclampsia and the offspring to vascular dysfunction), because vascular function was perfectly normal in siblings of offspring of preeclampsia who were born after a normal pregnancy. The preeclampsia-induced vascular dysfunction already has clinical consequences at a young age, as evidenced by pulmonary hypertension in approximately one third of these offspring of preeclampsia-affected mothers living at high altitude,<sup>54</sup> and by a high prevalence of re-entry HAPE. Studies in experimental animals suggest that the vascular dysfunction in offspring of preeclampsia is related to an epigenetic mechanism.<sup>55</sup> It is not yet known whether, among low-altitude residents, offspring of preeclampsia are at increased risk for classical HAPE.

## Conclusions

High-altitude pulmonary oedema HAPE is a non-cardiogenic form of pulmonary oedema usually occurring 36–72 hours after arrival at high altitude in otherwise healthy individuals. Individual predisposition is the most important risk factor for HAPE. Recent data suggest that, in some cases, pathological events during the foetal period involving epigenetic mechanisms contribute to this predisposition. Excessive non-homogenous hypoxic pulmonary vasoconstriction related to impaired pulmonary NO synthesis in conjunction with defective alveolar fluid clearance related to impaired transepithelial respiratory salt and water transport are the main underlying mechanisms. Immediate descent is the treatment of choice. If descent is not possible, low flow oxygen or a hyperbaric chamber can be used. If oxygen is unavailable, nifedipine (20 mg of extended release formulation every 8 hours) or other drugs known to lower pulmonary artery pressure should be administered. If neurological symptoms develop, dexamethasone should be added. HAPE can be prevented by slow, graded ascent (increase of the average sleeping altitude >2,500 m by <400 m/day). In individuals who are susceptible to HAPE, prophylaxis with dexamethasone or nifedipine, in addition to a slow ascent, can help to prevent its reoccurrence. ■

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