Alveolar Flooding at High Altitude: Failure of Reabsorption?

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Na-driven fluid reabsorption prevents alveolar fluid accumulation. Hypoxia augments fluid filtration by hemodynamic effects and inhibits Na reabsorption in cultured cells. A combination of both effects in vivo causes alveolar flooding, edema, thickening of the diffusion barrier for oxygen, and hypoxemia, a life-threatening situation for mountaineers in remote high-altitude mountain ranges.

A large percentage of mountaineers suffer from acute mountain sickness when they rapidly ascend to high altitudes. Typical symptoms are headache, insomnia, anorexia, and nausea (1). Less common are high-altitude pulmonary edema (HAPE), a noncardiogenic form of pulmonary edema. Its incidence varies between 0.2% in a general mountaineering population but increases up to 15% due to lack of acclimatization when the ascent is too fast. The incidence can increase to almost 70% in mountaineers who had previous episodes of HAPE, which indicates a predisposition for this disease (1).

The clinical picture of mountaineers suffering from HAPE is quite dramatic. Dyspnea, cough, gurgling in the chest, and pink, frothy sputum are observed. At an altitude of 4,559 m, such as at the Capanna Regina Margherita in the Monte Rosa mountain range at the Swiss-Italian border, arterial PO2 typically is ~45 mmHg and arterial SO2 is >75% (16). In HAPE, arterial PO2 can decrease to values <30 mmHg, causing arterial SO2 to drop to <60%. Systolic pulmonary artery pressures of >90 mmHg can be found by Doppler echocardiography (16).

Three mechanisms have been discussed as the cause of HAPE. They are indicated in Fig. 1, which gives an overview of the structures involved in alveolar fluid balance. Lung water in the interstitium and/or the alveolar space increases 1) when the hydrostatic pressure in lung capillaries is increased due to (inhomogeneous) arterial and/or venous hypoxic vasconstriction, causing augmented filtration and even rupture of the alveolar barrier (Fig. 1, left, a), 2) when the permeability of the alveolar wall (capillary endothelium and/or alveolar epithelium) is increased due to inflammatory processes (Fig. 1, left, b), and 3) in the case of alveolar edema, when the rate of alveolar fluid reabsorption across the alveolar epithelium is insufficient to match fluid filtration into the alveolar space (Fig. 1, left, c) (1). HAPE can be prevented or treated when mountaineers descend to low altitudes, when they receive oxygen, or when pulmonary capillary pressure is lowered, e.g., with nifedipine (1). Once subjects return to normoxic conditions, edema is rapidly reabsorbed.

Alveolar fluid balance

The layer of alveolar lining fluid is kept thin to allow proper diffusion of respiratory gases. Fluid can get into the alveolar space by filtration through occasional leaks at the alveolar-bronchiolar interface and by secretion in terminal bronchi.

Alveolar epithelial cells are responsible for fluid removal from the alveolar space. It has been known for a long time that cultured alveolar type II (ATII) cells, which cover ~5% of the alveolar surface and which are in charge of surfactant secretion and alveolar repair, also have a high transepithelial Na transport capacity (8). Only recently has the presence of transporters involved in transepithelial Na transport also been demonstrated in alveolar type I cells, which form a very thin cell layer that covers ~95% of the alveolar surface (8). The relative contribution to Na and water reabsorption is not yet known.

Removal of alveolar fluid is strictly coupled to the transport of Na. As in other reabsorptive epithelia, Na enters the cell via various Na transporters in the apical plasma membrane and is extruded by basolaterally located Na/K pumps (Fig. 1). The major portion of apical Na entry seems to be mediated by amiloride-inhibitable pathways, most likely epithelial Na channels (ENaC) and nonselective Na- and K-permeable cation channels (7). Other means of apical Na entry seem to be mediated by amiloride-sensitive Na uptake, and of Na-K-2Cl cotransport. The importance of ENaC has been demonstrated on a knockout mouse model (3), where the α-subunit of the ENaC has been removed. αENaC knockout mice die shortly after birth due to their inability to clear the lung of fluid contained in the alveoli during intrauterine life (3).

Na and water reabsorption across the alveolar epithelium can be stimulated by β-adrenergic agonists and by glucocorticoids (7, 8), both of which increase the rate of amiloride-sensitive apical Na entry, probably by insertion of endogenous ENaC, by upregulation of ENaC expression, and, in the case of β-adrenergic agents, also by stimulation of Cl transport (6).

Effects of hypoxia on alveolar Na transport

It has been shown on different models of cultured alveolar epithelial cells (SV40-transfected rat ATII cells, primary rat ATII cell monolayers, A549 cells of human alveolar origin) that exposure to hypoxia caused inhibition of the Na/K pump, of amiloride-sensitive Na uptake, and of Na-K-2Cl cotransport.
Reoxygenation of hypoxia-exposed cells restored the normal transport activity. Hypoxia-induced inhibition of transport was not due to cellular ATP depletion (6). The amount of mRNA and of plasma membrane-contained transport proteins also decreased in hypoxia (10, 19), which was paralleled by a decrease in overall protein synthesis (6). Tracer flux measurements of unidirectional 22Na and 86Rb uptake indicate that, at least in A549 cells, hypoxic transport inhibition occurs within ~30 min (6), which is much faster than the decrease in expression of Na transporters found in ATII cells (10). In Ussing chambers, transepithelial Na transport across primary cultured rat ATII cell monolayers is inhibited by exposure to hypoxia (5) at a rate that mirrors the decrease in expression of transporters (10). Transport inhibition by hypoxia was solely due to inhibition of apical amiloride-sensitive Na entry and a decreased capacity of Na/K pumps and ENaC (a functional measure of the number of copies of active transporters) (5). Amiloride-insensitive transport did not change, which indicates that intracellular Na remained constant in hypoxic ATII cells. Therefore, hypoxic inhibition of transepithelial transport must be due to a coordinate inhibition of amiloride-sensitive apical Na entry and basolateral Na/K pumps. Interestingly, transepithelial Na transport was stimulated by an increase in its amiloride-sensitive component and the expression of ENaC (12) when primary cultured fetal alveolar epithelial cells cultured at intrauterine (hypoxic) oxygenation levels (~3% O2) were switched to normoxic culture conditions. Together, these results indicate that activity and expression of transepithelial Na transport is directly controlled by oxygen and that hypoxia is associated with a low activity of Na transport of cultured alveolar epithelial cells.

In the isolated perfused lung, >50% of all fluid reabsorption was found to depend on amiloride-sensitive pathways, and transport can be stimulated by β-adrenergic agonists (5). Results on effects of hypoxia are controversial. Whereas some studies report no effects of anoxia and hypoxia on the reabsorption of fluid instilled into the lung, others found inhibition by hypoxia that was related to inhibition of Na reabsorption (17). Lung weight gain was accelerated when isolated ventilated and perfused rat lungs were exposed to hypoxia (17). Vivona et al. (17) found a decreased reabsorption of fluid instilled into nonventilated, nonperfused lungs of rats that were exposed to hypoxia. Hypoxic inhibition of fluid reabsorption was prevented when terbutaline was present in the instilled fluid (17). Neither hypoxic transport inhibition nor terbutaline stimulation of reabsorption were seen in the presence of amiloride, indicating that these effects depended on Na transport by ENaC. In the isolated, ventilated, and constant pressure-perfused rat lung, β-adrenergic agents did not prevent lung water accumulation (20). The weight gain of the hypoxic rat lungs was associated with the accumulation of significant amounts of albumin that originated from the perfusate, which indicates the presence of leaks of the alveolar barrier large enough to allow macromolecules to penetrate (20).

Hypoxic pulmonary edema has also been studied in vivo in animal models. Stelzner et al. (15) reported hypoxia-induced permeability edema in rats that could be prevented by treatment with glucocorticoids. Vivona et al. (17) also reported an increased wet-to-dry-weight ratio in rats exposed to hypoxia (8% O2), which Wodopia et al. (19) did not see at more moderate levels of hypoxia (10 to 14% O2). Lungs of αENaC knockout mice after partial gene recovery contained a decreased number of copies of ENaC (14). In contrast to the
αENaC knockout mice (3), these animals were able to clear alveolar fluid after birth. However, they developed pulmonary edema when exposed to hypoxia (8% O₂) for 72 h, whereas control mice did not (14).

The mechanisms that cause hypoxic inhibition of ion transport are not fully understood. Planes et al. (11) reported an increased Ca entry in hypoxic SV40-transformed ATII cells, which could not be confirmed in other types of alveolar epithelial cells. Reactive oxygen species and/or scavengers thought to be involved in oxygen sensing in a variety of cell types have no clear effect on alveolar epithelial cell transport since they affect different transport systems differently. In excitable, oxygen-sensitive cells such as the carotid body and in pulmonary vascular smooth muscle cells, hypoxia inhibits K channels. It is not known whether similar mechanisms exist in alveolar epithelial cells. The role of changes in intracellular Cl and/or cell volume are unclear. Changes in intracellular Cl might be caused by a possible oxygen-dependent activity of the cystic fibrosis transmembrane conductance regulator (CFTR), since a decreased activity of CFTR was observed in hypoxic MDCK cells (2). Other effects of decreased CFTR activity on alveolar Na transport in hypoxia are difficult to interpret because of the negative feedback between CFTR and ENaC and CFTR-mediated release of ATP, a known regulator of epithelial ion transport.

In summary, immediate hypoxia causes rapid inhibition of transport activity by inactivation of transport proteins and/or by internalization of active transporters. When hypoxia persists, the expression of transporters is inhibited, probably by a general inhibition of protein synthesis (6), which also decreases the number of active transporters in the plasma membrane. Both the fast and the slow responses of hypoxic inhibition of transport seem to be directed toward the conservation of energy, since no ATP depletion could be detected in hypoxic cells (6) and hypoxia-exposed rats (19). It is not known whether transport inhibition and decreased expression of transporters are initiated by the same signaling cascade.

Lung fluid and ion transport in hypoxia in the human lung

Fluid reabsorption in the intact human lung can be determined by measuring the increase in the concentration of marker molecules contained in fluid instilled into the lung or by measuring the increase in protein content of edema fluid. In both cases, bronchoscopic and bronchoalveolar lavage techniques are required, which are difficult to perform and require local anesthesia of the upper respiratory tract. Therefore, results on human lung ion transport in vivo are sparse. Matthay et al. (9) have shown that an increase in the protein concentration of edema fluid indicative for the clearance of alveolar edema fluid was found in adult respiratory distress syndrome patients with a good clinical prognosis. In contrast, prognosis was bad when no signs of fluid clearance were

![Image](http://physiologyonline.physiology.org/)

**FIGURE 2.** Leaky alveolar epithelium renders fluid reabsorption ineffective and allows blood to enter the alveolar space. Compared with normal physiological conditions (A), when the alveolar barrier becomes leaky due to exaggerated pulmonary hypertension (B), any hydrostatic pressure gradient would force fluid into the alveolar space to generate alveolar edema. In this case, an osmotic gradient cannot be generated by active Na reabsorption and the reabsorption of filtered fluid is impossible. C: bronchoalveolar lavage fluid (BALF) from a mountaineer who suffered from high-altitude pulmonary edema (HAPE) in the Capanna Regina Margherita (4,559 m) was collected by bronchoscopy. In this study, BALF from HAPE susceptibles contained on average ~163 mg/dl protein and >70% of all cells in BALF were erythrocytes (16).
found (9), which indicates that an intact alveolar barrier is a requirement for edema clearance. No such studies were performed in hypoxic patients and in mountaineers at high altitude, although a certain degree of hypoxemia certainly existed in acute respiratory distress syndrome patients due to edema-induced disturbances of alveolar gas exchange.

Indirect evidence for lung ion transport activity might be obtained from measurements of the transepithelial potential across the nasal mucosa (nasal potential) on the basis of similarities in the expression of ENaC and Na/K pumps in airways and alveolar epithelium. In normoxia, total nasal potential as well as its amiloride-sensitive component were found to be lower in mountaineers susceptible to HAPE than in controls (13), which might indicate a deficiency in ENaC in these subjects. However, the number of copies of ENaC and its subunits seems to be high enough to maintain a normal alveolar fluid balance in normoxia. It has also been reported that in subjects exposed to hypoxia at high altitude (4,559 m) the amiloride-inhibitable portion of nasal potentials decreased in controls but not in mountaineers who developed HAPE (4). Similar to results on cultured alveolar epithelial cells, there was a decrease in the expression of Na/K pumps in airway epithelium of HAPE susceptibles but not in controls (4). If in vivo hypoxia caused transport inhibition similar to what has been shown in cultured alveolar epithelial cells, a critical threshold might be reached beyond which alveolar Na reabsorption becomes insufficient to drive the reabsorption of water. In mountaineers susceptible to HAPE, this effect might contribute to the formation of hypoxic pulmonary edema.

One reason for susceptibility to HAPE might be a deficiency in ENaC. This notion is supported by the fact that prophylactic inhalation of β-adrenergic agents significantly decreased the incidence of HAPE by ~50% in HAPE susceptibles (13). β-Adrenergic agents are well-established stimulators of alveolar Na reabsorption (8) and might thus prevent fluid accumulation by increasing the rate of reabsorption. The proposed mechanism appears to be plausible in light of results by Vivona et al. (17), who found that alveolar application of terbutaline reversed the inhibition of reabsorption of fluid instilled into lungs of hypoxic rats. However, besides their well-established effect on stimulating Na reabsorption, β-adrenergic agents have several other modes of action that might contribute to the prevention of HAPE such as lowering pulmonary artery pressure and tightening of the alveolar barrier, which indicates that this subject needs further experimental evaluation. It must also be pointed out that all HAPE susceptibles studied so far respond with exaggerated pulmonary hypertension to hypoxia induced by breathing gas mixtures of low oxygen content for just a few minutes, whereas in nonsusceptibles only moderate pulmonary hypertension has been observed. This indicates that the hemodynamic component is a major determinant of HAPE susceptibility (1).

How might Na transport defects contribute to HAPE?

It has been shown repeatedly that the occurrence of HAPE is associated with exaggerated pulmonary hypertension (1). West et al. (18) presented histological evidence of capillary stress failure in overperfused normoxic rat lungs that caused leaks large enough to allow even red blood cells to enter the alveolar space. Swenson et al. (16) reported the presence of albumin and red blood cells in bronchoalveolar lavage fluid (BALF) of mountaineers in early HAPE at the Capanna Regina Margherita (4,559 m) (Fig. 2) and argued that filtration might be due to the extremely high values of pulmonary artery pressure found in these subjects. Also, mountaineers not susceptible to HAPE developed pulmonary hypertension, but their pulmonary artery pressures were considerably lower. BALF of those control subjects contained just a few red blood cells and much less protein, indicating some leakage in their lungs as well in hypoxia (16). In later stages of HAPE, leukocytes, high values of cytokines, and other markers of inflammation BALF (1) might indicate that in this state of HAPE increased pulmonary artery pressure and alveolar fluid accumulation might also be caused by increased permeability due to a secondary inflammatory process. These results indicate that the alveolar endothelium and epithelium might become leaky in hypoxia due to hemodynamic stress, which allows fluid to enter the alveolar space.

In late HAPE, this process is even enhanced when inflammation increases the permeability of the alveolar barrier. There is no doubt that alveolar water reabsorption is a requirement for normal gas exchange in normoxia and even more in hypoxia, when the diffusion gradient for oxygen decreases. The role of transepithelial transport in the pathogenesis of hypoxic edema remains unclear. It is obvious that alveolar reabsorption can only be effective when the barrier is intact, when leaks are transient, and when the rate of reabsorption is higher than the rate of leakage. Ion and water reabsorption, regardless of being stimulated or not, is inefficient when hydrostatic forces are so strong that large proteins and even erythrocytes are ejected into the alveolar space (Fig. 3).

Figure 3 summarizes scenarios of what might be happening during ascent to high altitude and when Na transport comes into play. As alveolar PO2 decreases with progressing ascent, hypoxia causes an increase in pulmonary capillary pressure that increases fluid filtration into the interstitial space (interstitial

![Figure 3](https://example.com/figure3.png)
tial edema) and into alveoli (alveolar edema). Exaggerated pulmonary hypertension leads directly to HAPE by flooding the interstitial and the alveolar spaces. However, when the increase in pulmonary capillary pressure is moderate the rate of fluid filtration into alveoli might still be balanced by fluid clearance driven by active Na reabsorption. Endogenous (or exogenously applied) β-adrenergic agents certainly support this mechanism by stimulating the reabsorption of Na. Hypoxia, however, also inhibits alveolar Na transport. In individuals with a high capacity of alveolar Na transport, transport activity, though decreased by hypoxia, might still be sufficient to drive the removal of water from the alveoli. Subsequently, sufficient oxygen diffusion and arterial PO2 are maintained. However, any preexisting defect in alveolar Na reabsorption in combination with hypoxic inhibition of Na transport might be detrimental since it blunts the removal of filtered fluid. In this case, a vicious circle begins, since now the layer of alveolar lining fluid thickens, which impairs oxygen diffusion, increases the degree of hypoxemia, augments pulmonary capillary pressure and filtration, further inhibits transport, and so forth. At this point, this circle can only be interrupted by preventing pulmonary vasoconstriction by oxygen or by drugs.

References


Corrigendum

In the February 2003 issue, the title of the review by Hug et al. (*News Physiol Sci* 18: 38–42, 2003) contained an error. The correct title is “CFTR and Bicarbonate Secretion by Epithelial Cells.”