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High altitude impairs nasal transepithelial sodium transport in HAPE-prone subjects

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High altitude impairs nasal transepithelial sodium transport in HAPE-prone subjects. C. Sartori, H. Duplain, M. Lepori, M. Egli, M. Maggiorini, P. Nicod, U. Scherrer. ©ERS Journals Ltd 2004.

ABSTRACT: High-altitude pulmonary oedema (HAPE) occurs in predisposed individuals at altitudes >2,500 m. Defective alveolar fluid clearance secondary to a constitutive impairment of the respiratory transepithelial sodium transport contributes to its pathogenesis. Hypoxia impairs the transepithelial sodium transport in alveolar epithelial type II cells *in vitro*. If this impairment is also present *in vivo*, high-altitude exposure could aggravate the constitutive defect in sodium transport in HAPE-prone subjects, and thereby further facilitate pulmonary oedema.

Therefore, the aim of the current study was to measure the nasal potential difference (PD) in 21 HAPE-prone and 29 HAPE-resistant subjects at low altitude and 30 h after arrival at high altitude (4,559 m).

High-altitude exposure significantly decreased the mean±SD nasal PD in HAPE-prone (18.0±6.2 *versus* 12.5±6.8 mV) but not in HAPE-resistant subjects (25.6±9.4 *versus* 22.9±9.2 mV). This altitude-induced decrease was not associated with an altered amiloride-sensitive fraction, but was associated with a significantly lower amiloride-insensitive fraction of the nasal PD.

These findings provide evidence *in vivo* that an environmental factor may impair respiratory transepithelial sodium transport in humans. They are consistent with the concept that in high-altitude pulmonary oedema-susceptible subjects, the combination of a constitutive and an acquired defect in this transport mechanism facilitates the development of pulmonary oedema during high-altitude exposure.

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High-altitude pulmonary oedema (HAPE) is a life-threatening condition that occurs in predisposed but otherwise healthy individuals at altitudes >2,500 m. Augmented alveolar fluid flooding related to exaggerated hypoxic pulmonary vasoconstriction plays an important role in its pathogenesis, secondary to endothelial dysfunction and sympathetic overactivity [1–3]. However, recent observations indicate that this mechanism may not be sufficient to cause high-altitude pulmonary oedema [4].

Active sodium transport across the alveolar epithelium plays an important role in keeping the lungs free of fluid [5, 6]. In alveolar epithelial cells, sodium enters the apical membrane primarily through the amiloride-sensitive cation channels (mainly ENaC), and is then transported across the basolateral membrane into the interstitium by the ouabain-inhibitable Na-K-ATPase [5–8].

A genetic impairment of the transepithelial sodium transport mechanism facilitates pulmonary oedema in transgenic mice [9, 10] and possibly also in humans, as suggested by HAPE-prone subjects who have a smaller nasal potential difference (PD) (an indirect marker of vectorial sodium transport in the distal airways) [11] than mountaineers resistant to this condition [12]. Consistent with this concept, prophylactic stimulation of this transport mechanism with the β_2-adrenergic agonist salmeterol, at a dose that stimulates respiratory sodium transport *in vitro* [8] and increases alveolar fluid clearance *in vivo* [13], decreased the incidence of HAPE in highly susceptible subjects [12]. Hypoxia, a condition universally associated with high-altitude exposure, inhibits transepithelial sodium transport in alveolar epithelial type II cells *in vitro* [14, 15], in the lungs *ex vivo* [16] and in rats *in vivo* [17]. If this impairment is also present in humans, high-altitude exposure could aggravate the pre-existing defect in sodium transport and thereby facilitate pulmonary oedema. To test this hypothesis, the nasal PD was measured in HAPE-prone and -resistant subjects at low altitude and 30 h after arrival at high altitude (4,559 m). To gain further insight, the effects of amiloride superfusion on nasal PD were also studied in these subjects.

Methods

From June 1997 to August 2000, 21 mountaineers (six females, 15 males, age (mean±SD) 36±8 yrs) who had had at least one radiographically documented HAPE within the previous 5 yrs, and 29 mountaineers (10 females, 19 males, age 31±6 yrs) who, despite repeated alpine-style climbing to peaks >4,000 m had never developed symptoms of HAPE or acute mountain sickness, were studied. The experimental protocols were approved by the institutional review board for human investigation and all subjects provided written informed consent.

Measurement of transepithelial sodium transport (nasal epithelial potential difference)

The nasal PD was measured using a recording bridge (Ringer-filled polyethylene tubing) inserted under the inferior turbinate, the location where the respiratory epithelium closely resembles the one in the distal airways [11, 18]. The intranasal recording bridge and a subcutaneous reference bridge (agar/Ringer-filled sterile 21-gauge needle) were linked by matched electrodes (Dri-Ref; World Precision Instruments Inc. Sarasota, FL, USA) to a high-impedance voltmeter (ISOMIL; World Precision Instruments). Throughout the measurement, the recording bridge was perfused with isothermic (37°C) Ringer solution (0.2 mL·min^{-1}). The PD was measured at five distinct sites on both sides by advancing or retracting the recording bridge in 0.5-cm intervals from the anterior to the posterior site and *vice versa*. The PD was expressed in absolute values as mean PD (the average of the five measurements obtained on each side). To determine the specific contribution of amiloride-sensitive sodium transport, the effect of amiloride superfusion on nasal PD was measured. To this end, the site with the highest stable PD was revisited. Once a stable PD recording was obtained, amiloride (1×10^{-4} M) was superfused at a rate of 5 mL·min^{-1} for 3 min *via* a second catheter [11, 18].

Study design

One to 4 weeks after a baseline measurement at 580 m (barometric pressure, 94.7 KPa (710 mmHg)), the subjects ascended within a period of <24 h from 1,130 to 4,559 m (Capanna Regina Margherita; barometric pressure, 58.7 KPa (440 mmHg)). The ascent consisted of the following: transport by cable car to an altitude of 3,200 m; a 1.5 h climb to an altitude of 3,611 m, where the subjects stayed overnight; and, on the next morning, a 4.5 h climb to the high-altitude research laboratory at 4,559 m. The subjects then spent 2 days and 2 nights in this laboratory.

Nasal epithelial PD was measured 30 h after arrival at the laboratory and, to determine the time-course of the high-altitude-induced changes in a subgroup of 14 HAPE-prone and eight HAPE-resistant subjects, it was also measured 6–8 h after their arrival at 4,559 m.

On the morning before the descent, or earlier when clinical signs of HAPE-developed, postero-anterior chest radiographs were obtained and the oxygen saturation of haemoglobin was measured (with a pulse oximeter attached to the fingertip). Chest radiographs were obtained in all subjects with the use of a mobile unit (Transportable Radiographic system; Siemens, Stockholm, Sweden) with a fixed target-to-film distance of 140 cm at 133 kV and 4–6 mA·s^{-1}. The radiographs were analysed according to previously described criteria [19] by a radiologist who was unaware of the subjects clinical history. Briefly, with the mediastinum used as the vertical axis and the hila as the horizontal axis, four areas of the lung were assessed separately for the presence of oedema. Each of the four areas were scored as follows: normal parenchyma was given a score of 0; areas with questionable pathological findings, 1; sections where <50% was affected by interstitial disease, 2; sections where >50% was affected by nonconfluent interstitial disease, 3; and areas of alveolar, partly confluent disease, 4. With the maximal possible score being 16, any radiograph in which at least one quadrant of a lung had a score of $\geqslant 2$ was considered to be positive for HAPE.

Statistical analysis

Statistical analyses were performed using paired or unpaired two-tailed t-tests for comparisons of single variables, as appropriate. Unless otherwise indicated, data are given as means±SD. A p-value <0.05 was considered statistically significant.

Results

At low altitude, the mean nasal PD was significantly lower ($p<0.01$), and its amiloride-sensitive fraction was significantly smaller ($p=0.01$), in HAPE-prone than in HAPE-resistant subjects (table 1).

At high altitude, the difference in the nasal PD between the two groups was even larger than the one observed at low altitude, because altitude exposure further decreased the PD in HAPE-prone, but not in HAPE-resistant, subjects (fig. 1, table 1). In the subgroup of 14 HAPE-prone subjects in whom the nasal PD was measured twice, the values were already lower than at low altitude 6–8 h after arrival at the laboratory (19.5±7.2 *versus* 10.9±5.7 mV, $p<0.01$), and remained unchanged thereafter (9.5±7.0 mV). In HAPE-resistant subjects, nasal PD was comparable at all three time points (data not shown).

At high altitude, oxygen saturation was significantly lower in HAPE-prone than in HAPE-resistant subjects (72±7 *versus* 79±5%, $p<0.001$), and there was a positive relationship between the nasal PD and the arterial oxygen saturation ($r=0.33$, $p<0.05$, fig. 2).

High-altitude exposure did not alter the amiloride-sensitive fraction of the nasal PD, whereas it lowered the amiloride-insensitive fraction by ~30% ($p<0.05$) in the two groups (table 1, figs 3 and 4). Finally, at both altitudes, the amiloride-insensitive fraction was significantly smaller ($p<0.05$) in HAPE-prone than in HAPE-resistant subjects (table 1, fig. 4).

At high altitude, none of the subjects had clinical evidence of HAPE at the time of the PD measurement. Six to 16 h after the PD measurement, 13 out of the 21 HAPE-prone, but none of the 29 HAPE-resistant subjects, developed pulmonary oedema (the radiological score ranged 2–13; mean score 7.3±2.7 *versus* 0±0, affected *versus* nonaffected, $p<0.001$).

In the HAPE-prone subjects who actually developed pulmonary oedema, arterial oxygen saturation was lower than in those who did not develop HAPE, and nasal PD

Table 1. – Nasal potential difference (PD) at low and high altitude in 21 high-altitude pulmonary oedema (HAPE)-prone and 29 HAPE-resistant subjects

	Mean nasal PD mV		ΔAmiloride mV		Amiloride insensitive PD mV	
	580 m	4,559 m	580 m	4,559 m	580 m	4,559 m
HAPE-resistant	25.6±9.4	22.9±9.2	14.8±7.7	12.8±6.6	12.0±7.0	8.2±5.5$^{\#}$
HAPE-prone	18.0±6.2*	12.5±6.8*,$^{\#}$	10.0±5.1*	10.3±7.3	8.3±2.8*	5.3±3.1*,$^{\#}$

Data are expressed as mean±SD; PD: potential difference; *: $p<0.05$ HAPE-prone *versus* HAPE-resistant. $^{\#}$: $p<0.05$ 580 m *versus* 4,559 m.

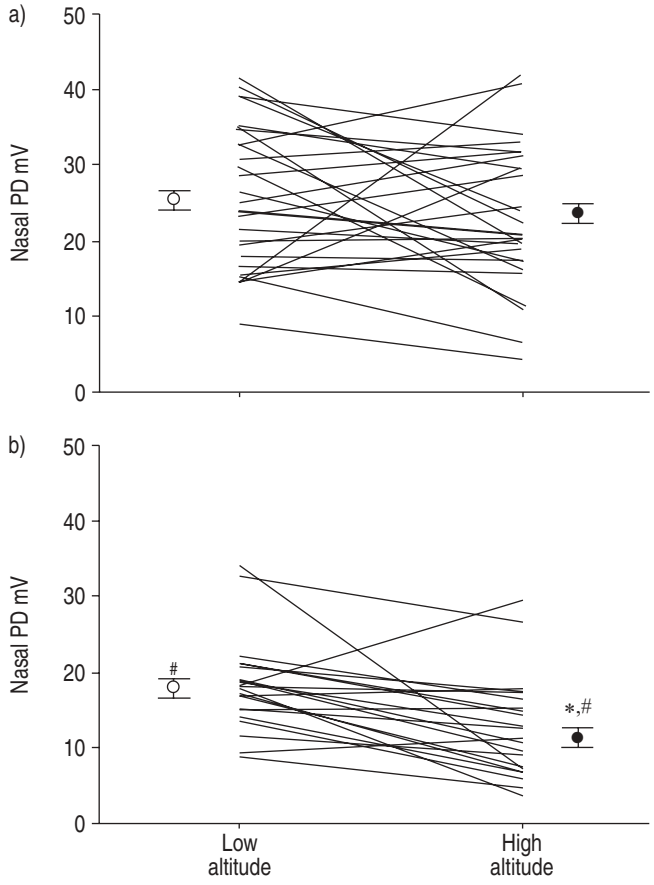

Fig. 1. – Individual and mean±SE nasal potential difference (PD) in a) 29 high-altitude pulmonary oedema (HAPE)-resistant and b) 21 HAPE-prone subjects at low altitude (580 m) and 30 h after arrival at high altitude (4,559 m). At low altitude, the mean nasal PD was significantly lower in HAPE-prone than in HAPE-resistant subjects. At high altitude, the difference between the two groups was even larger, because altitude exposure further decreased the PD in HAPE-prone, but not in HAPE-resistant subjects. *: $p<0.05$ *versus* low altitude; #: $p<0.05$ *versus* HAPE-resistant.

tended to be somewhat lower than in those who did not develop pulmonary oedema, both at low-altitude (16.5±3.1 *versus* 20.5±9.1 mV, p=0.25) and at high altitude (11.7±7.4

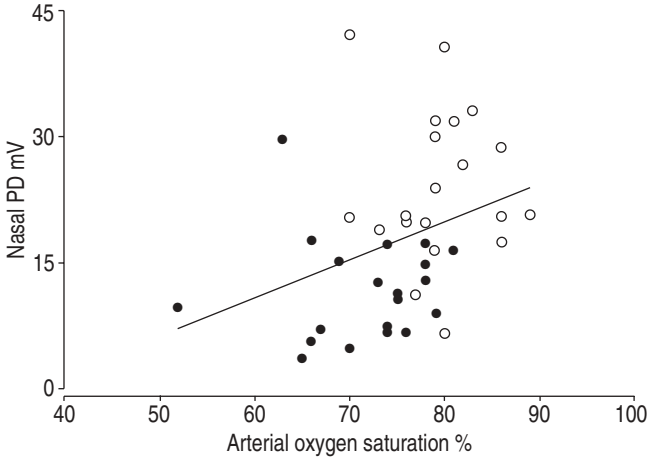

Fig. 2. – Correlation between nasal potential difference (PD) and oxygen saturation in high-altitude pulmonary oedema (HAPE)-resistant (○) and HAPE-prone (●) subjects at high altitude (r=0.33, $p<0.05$).

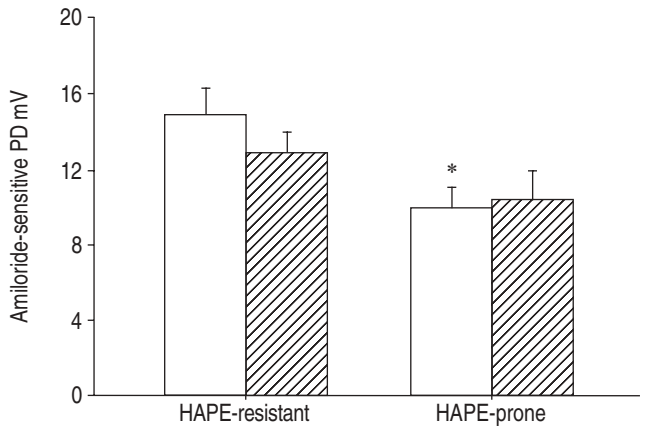

Fig. 3. – Amiloride-sensitive fraction of the nasal potential difference (PD) at low (□) and at high altitude (▨) in high-altitude pulmonary oedema (HAPE)-resistant and HAPE–prone subjects. *: $p<0.05$ *versus* HAPE-resistant.

versus 13.8±5.9 mV, p=0.47), but this difference did not reach statistical significance.

In subjects who actually developed pulmonary oedema, there was no correlation between the radiological score and the altitude-induced changes in nasal PD.

Discussion

The current authors have recently demonstrated that, in addition to augmented alveolar fluid flooding related to exaggerated pulmonary hypertension, the predisposition to HAPE is also associated with a constitutive defect in respiratory transepithelial sodium and water transport [12]. The current study shows that actual high-altitude exposure further aggravates this defect in HAPE-prone subjects. These findings provide the first evidence *in vivo* that an environmental factor, namely high-altitude exposure, impairs fluid absorption in the human lung. They are consistent with the new concept that, in HAPE-susceptible subjects, the combination of a constitutive and an environment-induced defect of alveolar fluid clearance facilitates pulmonary oedema during high-altitude exposure.

The nasal transepithelial PD has been used to quantify respiratory transepithelial sodium transport in patients with cystic fibrosis [11, 20–22], and to assess the effects of over- or

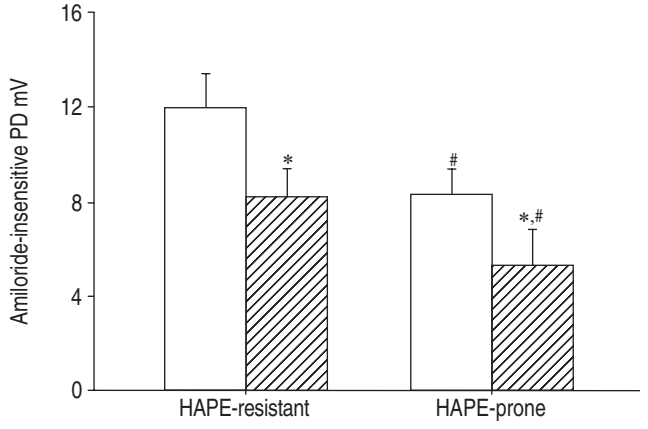

Fig. 4. – Amiloride-insensitive fraction of the nasal potential difference (PD) at low (□) and at high altitude (▨) in high altitude pulmonary oedema (HAPE)-resistant and HAPE-prone subjects. *: $p<0.05$ *versus* low altitude; #: $p<0.05$ *versus* HAPE-resistant.

under-expression of the amiloride-sensitive sodium channel on this transport mechanism [23, 24]. Nasal and airways epithelium exhibit similarities in membrane bioelectric properties and ion transport, suggesting that nasal PD may represent an estimate of vectorial sodium transport in the more distal airways [11]. The validity of this assumption is strengthened by the recent observation that, in mice with impaired function of the amiloride-sensitive sodium channel, nasal transepithelial PD closely reflects the impairment of the alveolar fluid clearance [9]. The present findings in humans *in vivo* are consistent with data showing that hypoxia impairs amiloride-sensitive and -insensitive sodium transport in alveolar epithelial type II cells *in vitro* [14, 25] and in the human lung *ex vivo* [16]. The altitude-induced decrease in transepithelial sodium transport does not appear to be related primarily to an impairment of the amiloride-sensitive sodium channel, since amiloride superfusion had comparable effects at low and high altitude.

In the alveolar cell, transepithelial sodium transport is dependent not only on its entry from the alveolar space into the cell through the sodium channels, but also on its extrusion into the interstitium *via* the Na-K-ATPase located in the basolateral membrane [5]. The present authors speculate that in the subjects in this study, the altitude-induced impairment of the transepithelial sodium transport was related to a defect in sodium extrusion. Consistent with this hypothesis, inhibition of the Na-K-ATPase by ouabain decreases nasal PD in the rat [26]. Moreover, in mice, Na-K-ATPase activity represents a potential limiting step in respiratory transepithelial sodium transport [10], and, in the rat, hypoxia decreases nasal PD [26], alveolar fluid clearance and Na-K-ATPase function [27]. However, since ENaC and Na-K-ATPase work in series, one would expect that impairment of Na-K-ATPase function increases intracellular sodium and, in turn, results in a reduced gradient for Na^+ entry. Therefore, if Na-K-ATPase and ENaC were the only sodium transport mechanisms, the amiloride-sensitive fraction of nasal PD should also have decreased. The fact that such a decrease was not detected suggests alterations in additional sodium transport mechanisms.

Amiloride-insensitive cation channels have been identified both on the apical and the basolateral side of rat alveolar epithelial type II cells. While their exact contribution to nasal PD and lung liquid clearance in humans remains to be established, it appears possible that altitude-induced dysfunction of such amiloride-insensitive cation channels could also contribute to the findings presented here.

Several mechanisms may impair transepithelial sodium transport at high altitude. In alveolar epithelial type II cells, hypoxia decreases Na-K-ATPase mRNA expression and activity [15]. It has been suggested that alveolar epithelial type II cells exposed to hypoxia may release a soluble factor that inhibits Na-K-ATPase activity [28]. Interestingly, high-altitude exposure stimulates the release of an endogenous digoxin-like factor, which may have inhibitory effects on transepithelial sodium transport [29]. Alternatively, hypoxia-induced oxidative stress may also inhibit sodium transport [30]. In the lung, sodium transporter trafficking, an important determinant of their function [31], may be impaired by hypoxia [32]. In addition to hypoxia, hypothermia also impairs sodium transport in the lung [33]. However, it appears unlikely that, in the present study, hypothermia played an important role, since the measurements were performed in a room kept at 18–20°C and, most importantly, isothermic solutions were used for the nasal superfusion experiments.

Two recent studies reported an altitude-induced increase in nasal PD in healthy subjects [34, 35]. This finding, which is in contrast with the current data and all the available *in vitro* and *in vivo* data on the effects of hypoxia on respiratory sodium transport [5, 15], has been attributed to nasal epithelial dryness-induced increase in chloride secretion [35], a phenomenon that has never been shown to occur at the alveolar level.

The discrepancy between the present and earlier reports could be related to the intranasal measurement site (inferior turbinate *versus* medial surface) [11, 18]. The PD measured across the nasal epithelium correlates closely with the one measured across the more distal airways only when measured under the inferior turbinate (protected epithelium constituted mainly of ciliated cells), but not when measured at other sites of the nasal mucosa (covered mainly by metaplastic squamous epithelium) [11]. It appears that in the two previous studies, no particular care was taken to locate the recording electrode in the inferior turbinate. Other technical differences in the experimental protocols for the nasal PD measurement (*e.g.* temperature control of the superfused solutions or averaged repeated *versus* one single measurement) could be additional factors contributing to the observed differences.

At high altitude, the nasal PD decreased significantly only in HAPE-prone subjects. This may be related to the more severe arterial hypoxaemia in these subjects, as suggested by the positive correlation between the oxygenation and nasal PD at high altitude. Alternatively, in addition to endothelial dysfunction and exaggerated arterial vasoconstriction [2], the altitude-induced impairment of the transepithelial sodium transport may represent a new example of a pathophysiological response to the lack of oxygen in HAPE-prone subjects.

In conclusion, it has been shown here that high-altitude exposure impairs nasal transepithelial sodium transport in high-altitude pulmonary oedema-prone subjects. Taken together with the authors previous data [12], these findings suggest that the conjunction of a constitutive and an acquired defect in this transport mechanism underlies susceptibility to high-altitude pulmonary oedema. The authors speculate that a similar defect could also be operational in other disease states associated with alveolar fluid flooding and hypoxia, such as heart failure and acute respiratory distress syndrome. β-Adrenergic stimulation of this transport mechanism [12] and correction of alveolar hypoxia may help to maintain/restore alveolar fluid clearance and accelerate the resolution of pulmonary oedema, and thereby decrease morbidity and mortality in these disease states.

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