

# Nasal Epithelium Potential Difference at High Altitude (4,559 m)

## Evidence for Secretion

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Hypoxia inhibits activity and expression of ion transport proteins of cultured lung alveolar epithelial cells. Here we tested, whether *in vivo* hypoxia at high altitude (4,559 m) also inhibits lung ion transport. Transepithelial nasal potentials (NP) were determined as a surrogate measure of lung ion transport activity before and during the stay at altitude. In normoxia, total NP was approximately 20% higher in control subjects than in susceptibles to high-altitude pulmonary edema, but there was no difference between groups in amiloride-inhibitable NPs. At high altitude total NP increased 250% in both groups, whereas amiloride-sensitive NP decreased in control subjects only (−80%), and the chloride ion (Cl<sup>−</sup>)-sensitive portion of NP almost doubled. Because many mountaineers suffer from nasal dryness at high altitude, a control study was performed in normobaric hypoxia (12% oxygen, 6 hours) at a controlled humidity of 50%. In this study, no change in total NP or its amiloride- and Cl<sup>−</sup>-sensitive portions was observed. The increased Cl<sup>−</sup> secretion at high altitude but no such change in normobaric hypoxia suggests that nasal dryness may stimulate local active Cl<sup>−</sup> and fluid secretion in the upper respiratory tract. It is therefore uncertain whether similar changes also occur at the alveolar epithelium.

**Keywords:** hypoxia; nasal potential; sodium ion transport; chloride ion secretion; nasal dryness

Active sodium ion (Na<sup>+</sup>) and water reabsorption is essential in maintaining alveolar lining fluid as thin as possible to allow rapid diffusion of respiratory gases, which is of critical importance in situations of low inspired oxygen (O<sub>2</sub>). Trans-epithelial Na<sup>+</sup> reabsorption generates the osmotic driving force for removal of alveolar fluid (1, 2). It is well documented that hypoxia inhibits Na<sup>+</sup> transport in cultured alveolar epithelial cells (3, 4–6) by decreasing activity and expression of transport proteins such as Na/potassium adenosine triphosphatase (ATPase), epithelial Na channel and Na/potassium/2Cl cotransport (NKCC) (4, 7, 8).

Exposure to hypoxia at altitudes above 3,000 m may cause high-altitude pulmonary edema (HAPE) with a high recurrence rate in those who had developed HAPE on past occasions (9). Alveolar edema occurs when fluid filtration exceeds the rate of fluid removal by active reabsorption and when

the capacity of fluid removal from alveolar space is limited (10). Exaggerated pulmonary hypertension, which increases fluid filtration into the interstitial and alveolar space (for review see Reference 9) is thought to be the main cause of HAPE. However, a decreased capacity for the removal of alveolar fluid might contribute to the persistence of alveolar edema. This notion is supported by results obtained in mice genetically engineered to express a reduced number of epithelial Na channels, in which exposure to hypoxia causes mild pulmonary edema (11, 12). Indirect evidence for a similar situation in mountaineers has recently been presented by Sartori and coworkers (13), who reported decreased potential differences and a decreased Na<sup>+</sup> transport activity of the nasal mucosa in HAPE-susceptibles.

Nasal potential measurement is an established tool to evaluate ion transport activity in airway epithelia (14). It has also been used to interpret alveolar epithelial function (13). Because alveolar transport activity cannot be assessed directly, in this study the nasal potential (NP) difference was measured to ascertain whether hypoxic inhibition of alveolar ion transport also occurs in the human lung *in vivo* and whether any evidence can be derived that might link hypoxic modulation of ion transport to HAPE. It was also of interest whether these differences in ion transport activity between HAPE-susceptibles and nonsusceptible control subjects exist not only in normoxia (13) but also in hypoxia. Preliminary results of these studies have been published in abstract form (15, 16).

## METHODS

Twenty-two nonacclimatized mountaineers who had never experienced HAPE during previous exposures to comparable altitudes (control subjects; 40.5 ± 8.6 years; 4 women, 8 men) and mountaineers with a history of HAPE (HAPE-susceptibles; 42.4 ± 8.4 years; 3 women, 7 men) participated in this high-altitude study after written informed consent (see also Reference 17). The study protocol was approved by the Ethics Committee of the University of Zürich, Switzerland and the University of Heidelberg, Germany. All control subjects remained well at altitude, 10 subjects developed HAPE, which was assessed by chest radiography (TRS; Siemens, Stockholm, Sweden) and clinical evaluation as described elsewhere (17).

Prealtitude measurements were performed in Zürich, Switzerland (490 m; low altitude [LA]). Subjects ascended from Alagna, Italy (1,100 m), spent one night in the Capanna Gnifetti (3,600 m), and climbed to the Capanna Regina Margherita (4,559 m) on the next morning. Measurements at 4,559 m were made within 3 hours after arrival (M1) and on the morning of the second day, 18 hours after arrival (M2) (17).

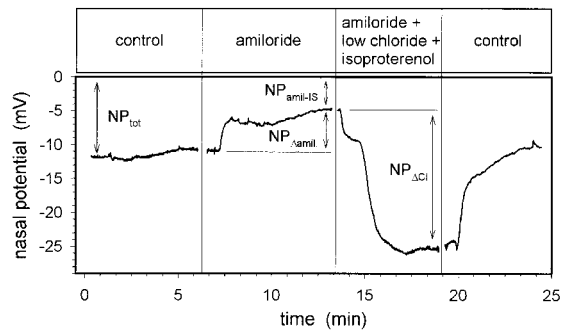
Due to the unexpected results of the transepithelial NP measurements at 4,559 m, a control study was performed in Heidelberg (105 m). Seventeen male subjects (26.7 ± 3.6 years), after giving written informed consent, were exposed to 6 hours of normobaric hypoxia (12% O<sub>2</sub>;

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**Figure 1.** Protocol for recording of the nasal potential (NP) difference. NP was measured as described in METHODS. The figure shows a typical tracing (subject N.U.; Zürich) indicating the experimental protocol. Control indicates the superfusion of the nasal mucosa with Ringer solution. Amiloride was applied at a concentration of 100  $\mu$ M. Low chloride indicates that the Ringer chloride ion ( $\text{Cl}^-$ ) concentration has been lowered to 5 mM by replacement with gluconate. Isoproterenol was added to a final concentration of 10  $\mu$ M.  $\text{NP}_{\text{tot}}$  = total NP difference at the end of the perfusion with Ringer;  $\text{NP}_{\Delta\text{amil}}$  = difference between  $\text{NP}_{\text{tot}}$  and NP after addition of amiloride;  $\text{NP}_{\text{amil-IS}}$  = NP after perfusion with Ringer containing amiloride;  $\text{NP}_{\Delta\text{Cl}}$  = difference between NP in presence of amiloride and NP after switching to low-Cl medium containing amiloride and isoproterenol.

corresponding to an altitude of 4,500 m) in a room equipped with an air-conditioning system controlling the  $\text{O}_2$  concentration by admixing nitrogen. The study protocol was approved by the Ethics Committee of the Medical Faculty, University of Heidelberg, Germany. Measurements were performed 1 hour before exposure to hypoxia as well as after 1 and 6 hours in hypoxia. Control measurements were also performed in normoxia 2 to 3 days before hypoxic exposure. One subject dropped out due to severe symptoms of mountain sickness. Four other subjects reported moderate to severe headaches and nausea but completed the study.

In both studies,  $\text{O}_2$  saturation was monitored by pulse oximetry (Biox 3700; Ohmeda, Denver, CO). Arterial blood samples were analyzed for pH,  $\text{Pco}_2$ ,  $\text{Po}_2$  and  $\text{O}_2$  saturation in the high-altitude study only (model 278 Ciba-Corning Diagnostics Analyzer and Co-oximeter; Ciba-Corning, Dietlikon, Switzerland).

Nasal potential differences were determined according to Knowles and coworkers (14) and Middleton and coworkers (18). Subjects were seated comfortably in chair with their head leaning on a headrest. An umbilical vessel catheter (Sherwood Medical, Tullamore, Ireland) cut to a length of approximately 20 cm was placed on the nasal mucosa for superfusion (100  $\mu$ l/minute) with the measuring electrode (WPI, Berlin, Germany) in line. An intravenous infusion line connected with the reference electrode was placed into an antecubital vein and perfused with Ringer solution (100  $\mu$ l/minute). The potential difference was measured with a high-impedance mV-meter (W. Nagel, Munich, Germany) and recorded on a computer.

The total NP ( $\text{NP}_{\text{tot}}$ ) was measured during superfusion with Ringer solution.  $\text{Na}^+$  transport was assessed as the change in potential in presence of apical amiloride (100  $\mu$ M;  $\text{NP}_{\Delta\text{amil}}$ ),  $\text{NP}_{\text{amil-IS}}$  is the residual potential in presence of amiloride. Chloride ion ( $\text{Cl}^-$ ) transport ( $\text{NP}_{\Delta\text{Cl}}$ ) was measured as the change in potential by superfusion with a medium containing 100  $\mu$ M amiloride and 10  $\mu$ M isoproterenol, whereas in the Ringer solution all except 5 mM  $\text{Cl}^-$  was replaced with gluconate. Figure 1 shows a typical tracing.

Concentrations of norepinephrine and epinephrine were measured by HPLC according to Weicker and coworkers (19) in plasma from samples obtained after subjects rested for 20 minutes.

Transepithelial NP differences are shown as positive values (mean values  $\pm$  SD). Comparison between groups and between normoxia and hypoxia was performed by two-way analysis of variance for repeated measures. A p value of less than 0.05 indicates statistical significance.

**TABLE 1. ARTERIAL BLOOD GASES AND OXYGEN SATURATION BEFORE ASCENT, 3 HOURS AFTER ARRIVAL, AND THE MORNING AFTER ARRIVAL AT THE CAPANNA REGINA MARGHERITA**

	LA*	M1†	M2‡
Control subjects			
pHa	7.413 $\pm$ 0.026	7.485 $\pm$ 0.026‡	7.500 $\pm$ 0.048‡
$\text{Pa}_{\text{CO}_2}$ , mm Hg	36.8 $\pm$ 2.9	26.1 $\pm$ 3.4‡	24.4 $\pm$ 5.2‡
$\text{Pa}_{\text{O}_2}$ , mm Hg	89.0 $\pm$ 8.1	39.7 $\pm$ 4.0‡	40.9 $\pm$ 4.8‡
$\text{Sa}_{\text{O}_2}$ , %	94.9 $\pm$ 6.1	77.1 $\pm$ 5.8‡	79.2 $\pm$ 5.3‡
HAPE			
pHa	7.401 $\pm$ 0.020	7.483 $\pm$ 0.019‡	7.490 $\pm$ 0.025‡
$\text{Pco}_2$ , mm Hg	38.7 $\pm$ 2.2	27.2 $\pm$ 4.3‡	25.7 $\pm$ 3.8‡
$\text{Pa}_{\text{O}_2}$ , mm Hg	85.5 $\pm$ 6.7	31.6 $\pm$ 3.0‡§	31.1 $\pm$ 2.7‡§
$\text{Sa}_{\text{O}_2}$ , %	97.1 $\pm$ 0.8	62.9 $\pm$ 7.0‡§	59.5 $\pm$ 8.5‡§

Definition of abbreviations: HAPE = high-altitude pulmonary edema; LA = low altitude; M1 = Margherita measurement 1; M2 = Margherita measurement 2; pHa = arterial pH.

Results are mean values  $\pm$  SD.

\* Measurements taken at 490 m.

† Measurements taken at 3 hours after arrival at 4,559 m.

‡ Indicates  $p < 0.05$  compared to prealtitude.

§ Indicates  $p < 0.05$  between control subjects and HAPE-susceptible subjects.

|| Measurements taken at the morning after arrival at 4,559 m.

## RESULTS

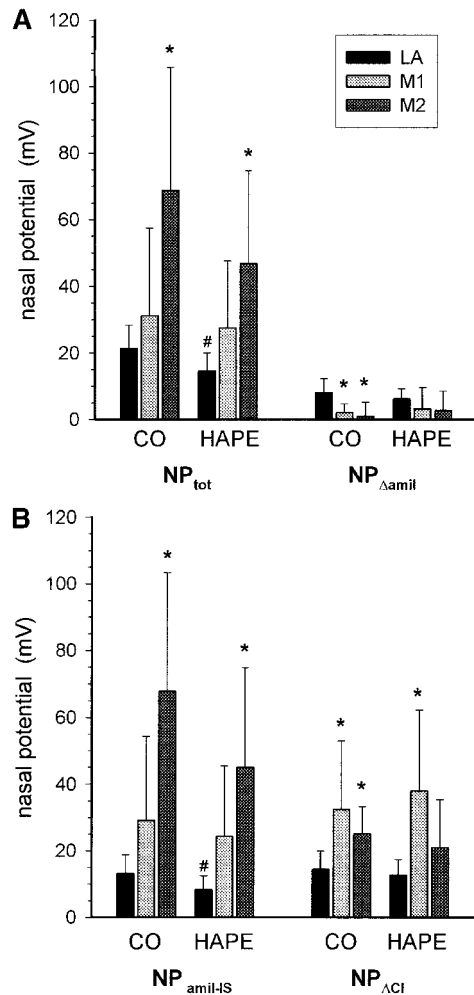
Blood gasses and  $\text{O}_2$  saturation show changes typical of exposure to high altitude. Results are listed in Table 1. In both groups there was a decrease in arterial  $\text{Pco}_2$  and a concomitant increase in arterial pH. Changes were not different between control subjects and HAPE-susceptibles. Arterial  $\text{Po}_2$  and  $\text{Sa}_{\text{O}_2}$  decreased significantly, and the change was more pronounced in HAPE-susceptibles.

### Nasal Potentials at High Altitude

Nasal potentials were measured to assess whether hypoxia at high altitude affects ion transport activity *in vivo* and to find any possible differences in transport activity between control subjects and subjects suffering from HAPE that might correlate with hypoxic edema formation. The results shown in Figure 2A indicate that in normoxia  $\text{NP}_{\text{tot}}$  was lower ( $-20\%$ ) in subjects suffering from HAPE than in control subjects. The lower potential might indicate a decreased basal reabsorptive transport activity in those subjects. In all subjects  $\text{NP}_{\text{tot}}$  increased at high altitude, but values in HAPE-susceptibles were always lower than in control subjects, although this difference was statistically not significant at altitude ( $p < 0.2$ ).

The amiloride-inhibitable portion of NP ( $\text{NP}_{\Delta\text{amil}}$ ) is a measure of apical Na uptake by epithelial cells mediated by transporters such as epithelial Na channels, nonselective cation channels, and Na/H exchange. In normoxia, there was no difference in  $\text{NP}_{\Delta\text{amil}}$  between control subjects and HAPE-susceptibles (Figure 2A). In control subjects, at high altitude  $\text{NP}_{\Delta\text{amil}}$  decreased significantly reaching nearly undetectable values the next day (M2). In HAPE-susceptibles no statistically significant decrease in  $\text{NP}_{\Delta\text{amil}}$  was found at high altitude.

Because the nasal epithelium is also capable of active  $\text{Cl}^-$ -driven fluid secretion, it was important to obtain a measure of  $\text{Cl}^-$  transport. Figure 2B shows that at low altitude  $\text{NP}_{\text{amil-IS}}$  was lower in HAPE-susceptibles than in control subjects. In both groups of subjects,  $\text{NP}_{\text{amil-IS}}$  increased on arrival at high altitude thus paralleling changes in  $\text{NP}_{\text{tot}}$ . No statistically significant difference was found at altitude. By generating a  $\text{Cl}^-$  gradient from blood to the apical surface by superfusion with a medium low in chloride in the presence of amiloride and isoproterenol to



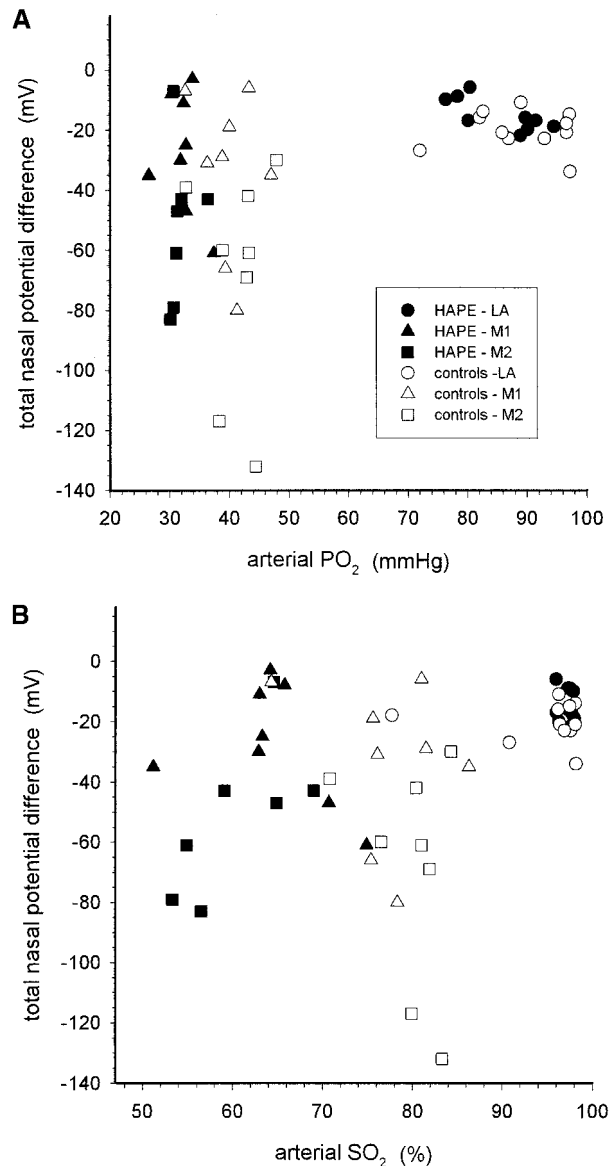
**Figure 2.** Changes in NP differences in control subjects and high-altitude pulmonary edema (HAPE)-susceptibles at 4,559 m. Total NP differences under control conditions (NP<sub>tot</sub>), amiloride-sensitive and insensitive (NP<sub>Δamil</sub> and NP<sub>Δamil-S</sub>, respectively), and chloride-sensitive NP (NP<sub>ΔCl</sub>) were measured at the time points described in the legend to Figure 1. Results are mean values  $\pm$  SD. \* Indicates p value less than 0.05 relative to values obtained in Zürich (490 m; LA). # Indicates difference between controls (CO) and subjects in whom HAPE was diagnosed at the Capanna Margherita (measurements on the day of arrival [M1] and on the next day [M2]).

stimulate Cl<sup>-</sup> transport to the apical surface, a Cl<sup>-</sup>-sensitive portion of the NP (NP<sub>ΔCl</sub>) can be measured. NP<sub>ΔCl</sub> therefore represents a measure of Cl transport capacity. Figure 2B indicates no difference in NP<sub>ΔCl</sub> between control subjects and HAPE-susceptibles in prealtitude tests and at the Capanna Margherita. In both groups, NP<sub>ΔCl</sub> increased two- to threefold on arrival at 4,559 m. NP<sub>ΔCl</sub> decreased ( $p < 0.1$ ) the next day at the Margherita hut but was still higher than the normoxic value.

It was of interest to determine whether changes in the trans-epithelial NP differences at altitude correlate with the level of oxygenation. Plots of NP<sub>tot</sub> as a function of arterial PO<sub>2</sub> (Figure 3A) and SaO<sub>2</sub> (Figure 3B) indicate that no correlations exist between these parameters. This is also true for NP<sub>Δamil</sub>, NP<sub>Δamil-S</sub>, and NP<sub>ΔCl</sub> (not shown).

#### Nasal Potentials in Normobaric Hypoxia

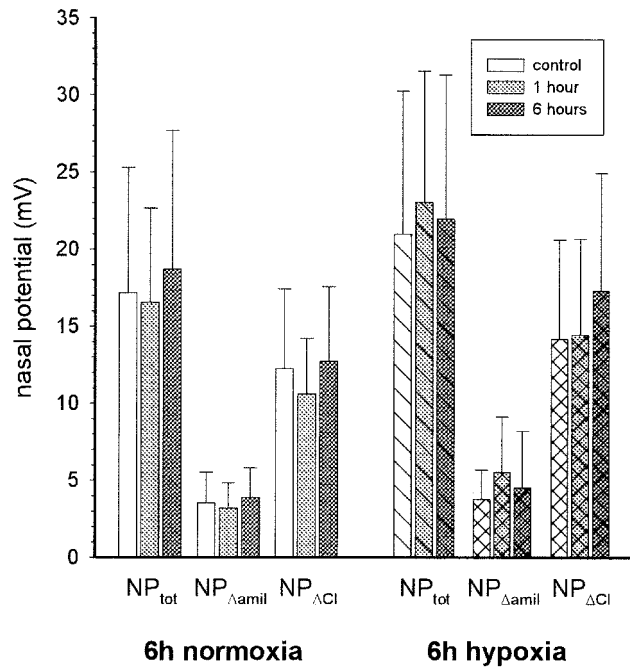
Nasal potentials were difficult to measure at high altitude. Many subjects reported dry, encrusted and even bloody noses most



**Figure 3.** Lack of dependency of NP<sub>tot</sub> on arterial PO<sub>2</sub> and SaO<sub>2</sub>. Individual values of NP<sub>tot</sub> and arterial blood gases from Zürich (490 m; LA) and the Capanna Regina Margherita (M1, M2).

likely due to the dry air. To control for climate conditions in the Margherita hut other than decreased PO<sub>2</sub>, a different set of subjects in a separate study was exposed to normobaric hypoxia (12% O<sub>2</sub>) matching the degree of hypoxia experienced at the Capanna Margherita, but at a constant comfortable humidity of approximately 50%. The results of this study are summarized in Figure 4. The figure shows no clear diurnal variation in measured components of NP differences. In contrast to the high-altitude results, the 6-hours exposure to normobaric hypoxia did not alter NP<sub>tot</sub>, NP<sub>Δamil</sub>, and NP<sub>ΔCl</sub>.

Figure 5 summarizes the results of measurements of norepinephrine and epinephrine in normoxia and during normobaric hypoxia. On exposure to hypoxia for one hour plasma norepinephrine tended to increase ( $p < 0.064$ ), but levels were not different from the 1-hour time point on the control day (normoxia). There was no difference in normoxic values after 6 hours of normobaric hypoxia. Although plasma epinephrine was signifi-



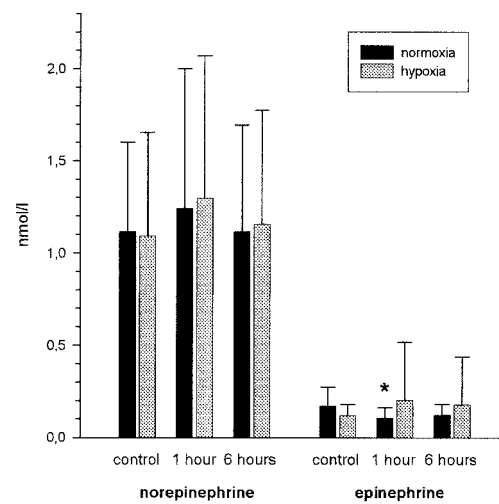
**Figure 4.** Nasal potential differences in normoxia and in normobaric hypoxia. Subjects were exposed to normobaric hypoxia (12% O<sub>2</sub>) for 6 hours. On the first day of the study, (6 hours normoxia) NP were measured in normoxia. On the second day, measurements were repeated after 1 hour and after 6 hours of exposure to normobaric hypoxia (12% O<sub>2</sub>). On both days, control measurements were made within approximately 90 minutes before entering the chamber. Measurements were performed as described in the *legend* to Figure 1. Results are mean values  $\pm$  SD from 17 subjects.

cantly decreased at the 1-hour time point on the control day, no statistically significant change was observed in hypoxia.

## DISCUSSION

This study was performed to determine whether differences in ion transport at the nasal epithelium exist between individuals susceptible and not susceptible to HAPE. Our results show a difference in NP<sub>tot</sub> but not in NP<sub>Δamil</sub> in normoxia between control subjects and HAPE-susceptibles. At high altitude, NP<sub>Δamil</sub> decreased significantly in control subjects only. In both groups, NP<sub>tot</sub>, NP<sub>Δamil-IS</sub> and NP<sub>ΔCl</sub> increased greatly at high altitude but not during shorter exposure to normobaric hypoxia indicating that this response may be dependent on other factors of the mountain environment such as the cold, dry air.

Alveolar fluid reabsorption cannot be assessed noninvasively in humans *in vivo*. On the basis of similarities in the expression of epithelial Na channels, Na/K-ATPase, and other ion transporters between nasal mucosa, airways, and alveolar epithelium, the potential difference across the nasal mucosa might reflect transport activity in the alveolar epithelium (20), although there seems to be some variation in the expression of subunits of epithelial Na channel along the respiratory tract (21). On the other hand, the nasal and alveolar epithelia are considerably different. The nasal epithelium is a composite tissue similar to airway epithelium, which, in addition to mucus secretion, has secretory and reabsorptive functions. In contrast, the adult alveolar epithelium, besides surfactant secretion by AII-cells, is thought to be strictly reabsorptive, and transport is mediated both by ATI- (22) and AII-cells (1).



**Figure 5.** Plasma catecholamines in subjects exposed to normobaric hypoxia. Exposure to normobaric hypoxia (12% O<sub>2</sub>) and sampling times were the same as described in the legend to Figure 4. Measurements were performed as described in METHODS. Results are mean values  $\pm$  SD from 17 subjects. \*Indicates p values less than 0.05 relative to the respective control value.

## Total Nasal Epithelial Potential Difference

Secretion of Cl<sup>-</sup> and reabsorption of Na<sup>+</sup> across the nasal mucosa both generate an apical side negative transepithelial potential difference. Our results indicate that in normoxia the total transepithelial NP difference (NP<sub>tot</sub>) was smaller in mountaineers who developed HAPE later in the same study than in control subjects. This finding is in accordance with results reported by Sartori and coworkers (13). We could not confirm, however, the slightly decreased values of NP<sub>Δamil</sub> in HAPE-susceptibles in normoxia (13).

On ascent to high altitude, NP<sub>tot</sub> increases. Similar results have been found by Mason and coworkers on ascent to an altitude of 3,800 m (23). The highest values were found on the day of arrival at 4,559 m (M1). On the next day (M2) NP<sub>tot</sub> had increased further. The increase appears to be due to stimulated secretion of Cl<sup>-</sup> as indicated by the increase in NP<sub>Δamil-IS</sub> and NP<sub>ΔCl</sub>.

## Evidence for Stimulated Cl<sup>-</sup> Secretion in the Nasal Mucosa

The increased values of NP<sub>tot</sub> and of NP<sub>ΔCl</sub> at high altitude in the presence of a reduced NP<sub>Δamil</sub> indicate that Cl<sup>-</sup> and water secretion in the nasal mucosa were stimulated in mountaineers at high altitude. The increase in NP<sub>Δamil-IS</sub> supports this notion. Because amiloride blocks the major apical Na-uptake routes, in its presence the transepithelial potential should depend mainly on Cl<sup>-</sup> secretion. Increased secretion might have been the result of the nasal dryness that is a common complaint at high altitude because of the low water content of cold air. This interpretation is supported by results indicating increased secretion across the airway epithelium on breathing dry air (for review see Reference 24). To further evaluate this possibility we exposed subjects to normobaric hypoxia (12% O<sub>2</sub>), 20°C room temperature at a controlled humidity of 50%. In contrast to results at high altitude, 6 hours of normobaric hypoxia at a comfortable humidity did not affect NP. Therefore the increase in NP<sub>tot</sub> and NP<sub>ΔCl</sub> found in the Capanna Margherita seems to be specific to high altitude and not to hypoxia *per se* and might be interpreted as a compensatory mechanism to prevent drying of the nasal mucosa.

The question arises whether hypoxia-stimulated Cl<sup>-</sup> secretion

indicated by the altered transport activity of the nasal mucosa might also occur in the alveolar epithelium. Evidence comes from the fetal lung, whose distal lung epithelium secretes  $\text{Cl}^-$  and water (25) and functions at a level of oxygenation similar to that experienced by mountaineers at an altitude of 4,559 m. When fetal alveolar epithelial cells cultured at their physiological (intrauterine)  $\text{PO}_2$  of approximately 40 mm Hg are switched to 21%  $\text{O}_2$ , expression and activity of  $\text{Na}^+$  transporters are stimulated (6). Stimulation of  $\text{Na}^+$  transport by oxygenation can be reversed by exposure to hypoxia. However, it has not been demonstrated yet whether these maneuvers also alter  $\text{Cl}^-$  secretion. If exposure to high-altitude hypoxia inhibits  $\text{Na}^+$  reabsorption and at the same time stimulates  $\text{Cl}^-$  secretion by the alveolar epithelium, one might speculate that hypoxia might actually stimulate fluid secretion into the alveolar space and contribute to the formation of alveolar edema. However, adult alveolar epithelial cells lack the cAMP-activated  $\text{Cl}^-$  channels (26) that in airway epithelium mediate  $\text{Cl}^-$  secretion (2). Therefore, the surprising hypothesis of hypoxia-induced alveolar secretion requires experimental support. In a more general sense, these data suggest caution in extending the results from transport events in the nasal mucosa as measured by changes in potential difference to active ion transport at the alveolar level.

### Hypoxic Inhibition of $\text{Na}^+$ Transport

In primary alveolar epithelial cell monolayers from rat lungs hypoxia inhibits apical  $\text{Na}^+$  entry via amiloride-sensitive  $\text{Na}^+$  channels and basolateral Na/potassium ATPase (5). Because  $\text{Na}^+$  reabsorption is believed to generate the driving force for the reabsorption of water, these results indicate that the transepithelial transport of water is also inhibited in hypoxic alveolar epithelium. Vivona and coworkers (27) presented evidence of impaired lung fluid reabsorption in the nonperfused lungs of rats that were exposed to hypoxia before the measurement of fluid clearance. Also in rats, Tomlinson and coworkers (28) found that hypoxia decreased the transepithelial NP difference, which could be attributed to a decrease in transport via amiloride-sensitive  $\text{Na}^+$  transport pathways. Here we show for the first time *in vivo* data of humans exposed to high altitude that indicate that the amiloride-sensitive portion of the NP is inhibited at high altitude in healthy control subjects.

In mountaineers who developed HAPE, no statistically significant inhibition of  $\text{Na}^+$  transport ( $\text{NP}_{\Delta\text{amil}}$ ) was found at high altitude. However, there was a much greater variability in  $\text{NP}_{\Delta\text{amil}}$  in HAPE-susceptibles than in control subjects. In mountaineers with HAPE and/or acute mountain sickness a threefold increase in norepinephrine and a twofold increase in epinephrine and cortisol was found at 4,559 m (29) probably because of a greater increased degree of hypoxemia, whereas in control subjects epinephrine and cortisol did not increase and norepinephrine increased only twofold (30). Exercise even enhances this difference (29). Because stress hormones stimulate alveolar  $\text{Na}^+$  and water reabsorption in the lung (31–33), it is likely that in HAPE-susceptibles inhibition of  $\text{Na}^+$  transport is blunted by endogenous stress hormones. Experimental evidence in support of this hypothesis was obtained in lungs of hypoxic rats whose rate of alveolar clearance of instilled fluid was decreased but could be increased with terbutaline-mediated stimulation of amiloride-sensitive  $\text{Na}^+$  transport (27). Also, the recent finding of a reduction in HAPE incidence by salmeterol could be attributed to stimulated alveolar  $\text{Na}^+$  reabsorption (13). However, we have pointed that pharmacologic effects of  $\beta$  agonists on pulmonary hemodynamics and on endothelial and alveolar barrier function may be more likely to account for prevention of HAPE (34).

An inverse relation has been found between the cystic fibrosis transmembrane regulator, a major pathway for airway epithelial

$\text{Cl}^-$  secretion, and  $\text{Na}^+$  reabsorption (35, 36). It is therefore conceivable that the decrease in  $\text{NP}_{\Delta\text{amil}}$  of the nasal epithelium at high altitude is caused by the stimulation of  $\text{Cl}^-$  secretion, which is turned on to prevent drying of the nasal mucosa. Because neither epinephrine nor norepinephrine were increased in normobaric hypoxia, any blunting of hypoxic inhibition of  $\text{Na}^+$  transport by adrenergic stimulation can be ruled out. It is also unclear whether exercise during ascent stimulated secretion. Both an increase (37) and a decrease (38) of NP have been reported during exercise in normoxia.

In conclusion, our results indicate that an increased chloride secretion compensating for drying of the nasal mucosa underlies the increment in transepithelial NP at high altitude. Unchanged NP in normobaric hypoxia in a comfortably humid environment support this hypothesis. Therefore, the decrease in the amiloride-inhibitable portion of NP, although in accordance with hypoxic transport inhibition at the alveolar epithelium, appears to be due to inhibition of epithelial  $\text{Na}^+$  channels subsequent to the stimulation of  $\text{Cl}^-$  secretion rather than to hypoxia directly. These results suggest that changes in NP during high-altitude exposure occur as a specific response of the nasal mucosa to the environment at high altitude and, most likely, do not reflect processes at the alveolar epithelium.

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