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Authors: Sartori C, Allemann Y, Duplain H, Lepori M, Egli M, Lipp E, Hutter D, Turini P, Hugli O, Cook S, Nicod P, Scherrer U

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SALMETEROL FOR THE PREVENTION OF HIGH-ALTITUDE PULMONARY EDEMA

CLAUDIO SARTORI, M.D., YVES ALLEMANN, M.D., HERVÉ DUPLAIN, M.D., MATTIA LEPORI, M.D., MARC EGLI, M.D., ERNST LIPP, M.D., DAMIAN HUTTER, M.D., PIERRE TURINI, M.D., OLIVIER HUGLI, M.D., STÉPHANE COOK, M.D., PASCAL NICOD, M.D., AND URS SCHERRER, M.D.

ABSTRACT

Background Pulmonary edema results from a persistent imbalance between forces that drive water into the air space and the physiologic mechanisms that remove it. Among the latter, the absorption of liquid driven by active alveolar transepithelial sodium transport has an important role; a defect of this mechanism may predispose patients to pulmonary edema. Beta-adrenergic agonists up-regulate the clearance of alveolar fluid and attenuate pulmonary edema in animal models.

Methods In a double-blind, randomized, placebo-controlled study, we assessed the effects of prophylactic inhalation of the beta-adrenergic agonist salmeterol on the incidence of pulmonary edema during exposure to high altitudes (4559 m, reached in less than 22 hours) in 37 subjects who were susceptible to high-altitude pulmonary edema. We also measured the nasal transepithelial potential difference, a marker of the transepithelial sodium and water transport in the distal airways, in 33 mountaineers who were prone to high-altitude pulmonary edema and 33 mountaineers who were resistant to this condition.

Results Prophylactic inhalation of salmeterol decreased the incidence of high-altitude pulmonary edema in susceptible subjects by more than 50 percent, from 74 percent with placebo to 33 percent ($P=0.02$). The nasal potential-difference value under low-altitude conditions was more than 30 percent lower in the subjects who were susceptible to high-altitude pulmonary edema than in those who were not susceptible ($P<0.001$).

Conclusions Prophylactic inhalation of a beta-adrenergic agonist reduces the risk of high-altitude pulmonary edema. Sodium-dependent absorption of liquid from the airways may be defective in patients who are susceptible to high-altitude pulmonary edema. These findings support the concept that sodium-driven clearance of alveolar fluid may have a pathogenic role in pulmonary edema in humans and therefore represent an appropriate target for therapy. (N Engl J Med 2002;346:1631-6.)

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PULMONARY edema is a life-threatening condition that results from a persistent imbalance between the forces that drive water into the air space in the alveoli and the physiologic mechanisms that remove it.¹ For many years, it was believed that Starling forces and lymphatic drainage accounted entirely for the removal of excess intralveolar fluid, but it is now clear that an osmotic gradient created by vectorial transepithelial sodium transport plays an important part. Sodium enters the apical membrane of alveolar epithelial cells mainly through amiloride-sensitive cation channels and is transported across the basolateral membrane by ouabain-inhibitable $\text{Na}^+/\text{K}^+-\text{ATPase}$.²

In mice, deletion of the α subunit of the amiloride-sensitive epithelial sodium channel leads to neonatal death because of failure to clear the liquid from the lungs³; experimentally induced dysfunction of this channel impairs the clearance of alveolar fluid and predisposes mice to pulmonary edema.⁴ Beta-adrenergic agonists increase vectorial sodium transport *in vitro*,⁵ enhance the clearance of alveolar fluid in the resected human lung⁶ and in several species of animals,⁷⁻¹⁰ and accelerate the resolution of pulmonary edema in animal models of lung injury.¹¹⁻¹⁵ However, the effects of beta-adrenergic agonists in the treatment of pulmonary edema in humans have not been assessed, and information demonstrating the importance of this vectorial sodium transport in the development of and recovery from pulmonary edema in humans is sparse and indirect.^{16,17}

In a double-blind, placebo-controlled study, we tested whether the prophylactic inhalation of the beta-adrenergic agonist salmeterol at a dose shown to stimulate the clearance of alveolar fluid¹⁸ decreases the incidence of pulmonary edema during exposure to high altitudes in subjects who are prone to high-altitude pulmonary edema. We also measured the nasal transepithelial potential difference (a marker of the transepithelial sodium and water transport in the distal air-

From the Department of Internal Medicine (C.S., H.D., M.L., M.E., P.T., O.H., S.C., P.N., U.S.) and the Botnar Center for Clinical Research (C.S., H.D., M.L., M.E., P.T., O.H., S.C., U.S.), Centre Hospitalier Universitaire Vaudois, Lausanne; and the Swiss Cardiovascular Center, University Hospital, Bern (Y.A., E.L., D.H.) — both in Switzerland. Address reprint requests to Dr. Scherrer at the Department of Internal Medicine, BH 10.642, Centre Hospitalier Universitaire Vaudois, CH-1011 Lausanne, Switzerland, or at urs.scherrer@chuv.hospvd.ch.

ways)¹⁹⁻²² at low altitude in subjects who were prone to high-altitude pulmonary edema, subjects who were resistant to this condition, and subjects who had had transient perinatal pulmonary hypertension.

METHODS

Study Subjects

Between June 1999 and July 2001, we studied 51 mountaineers who had had at least one radiographically documented episode of high-altitude pulmonary edema within the previous four years, 33 control subjects who had repeatedly engaged in alpine-style climbing to peaks higher than 4000 m with no symptoms of high-altitude pulmonary edema or acute mountain sickness, and 7 subjects with a history of transient perinatal pulmonary hypertension. The experimental protocols were approved by the institutional review board for human investigations at the Centre Hospitalier Universitaire Vaudois, and all subjects provided written informed consent.

Studies at High Altitude

Thirty-seven subjects who were prone to high-altitude pulmonary edema participated in the studies conducted at high altitude. One to four weeks after a base-line physical examination at an altitude of 580 m (barometric pressure, 710 mm Hg), the subjects ascended in less than 22 hours from 1130 m to 4559 m (barometric pressure, 440 mm Hg). The subjects were taken by cable car to an altitude of 3200 m; they then climbed for 1½ hours to an altitude of 3611 m, where they stayed overnight; the next morning, they climbed for an additional 4½ hours to the high-altitude research laboratory at Capanna Regina Margherita in Italy. The subjects then spent two days and two nights at this laboratory. On each of the two mornings, they were examined by the same observer, who used the Lake Louise acute-mountain-sickness scoring system (range of possible scores, 0 to 24, with higher scores indicating greater disease).²³

Thirty to 36 hours after each subject arrived, we estimated the systolic pulmonary-artery pressure (by echocardiography). On the morning before the descent, posteroanterior chest radiographs were obtained, and we measured the oxygen saturation of the hemoglobin (with a pulse oximeter attached to the fingertip) and the partial pressure of arterial oxygen and carbon dioxide (in samples of blood obtained from the radial artery). In subjects in whom clinical signs and symptoms of high-altitude pulmonary edema developed, chest radiographs and measurements of pulmonary-artery pressure and blood gases were obtained when the symptoms appeared, and the study was terminated and the subjects were treated and evacuated to low altitude.

Drug Administration

The subjects were instructed to use a pressurized metered-dose inhaler connected to a spacer (Volumatic, Glaxo Wellcome) and, after stratification according to the number of previous episodes of high-altitude pulmonary edema, were randomly assigned to inhale either 125 µg of salmeterol (Serevent, Glaxo Wellcome) or placebo every 12 hours. The administration started on the morning of the day before the subjects began the ascent to high altitude and was continued until the end of the study.

Echocardiography

To estimate systolic pulmonary-artery pressure, echocardiographic recordings were obtained with a real-time, phased-array sector scanner (model 5500, Hewlett-Packard) with an integrated color Doppler system and a transducer containing crystal sets for imaging (2.5 to 4.0 MHz) and for continuous-wave Doppler recording (1.9 MHz). The recordings were stored on SVHS videotape for analysis by an investigator who was unaware of the treatment-group assign-

ments. All reported values represent the mean of at least three measurements.

Systolic pulmonary-artery pressure was calculated from the pressure gradient between the right ventricle and the right atrium, measured with continuous-wave Doppler echocardiography, and the clinically determined mean jugular venous pressure.²⁴ Color Doppler echocardiography was used to locate the tricuspid-regurgitation jet. The maximal velocity was then determined by careful application of the continuous-wave sampler on the regurgitation jet. To calculate the transtricuspid pressure gradient, a modified Bernoulli equation was used, in which transtricuspid pressure equaled four times the square of the peak tricuspid-jet velocity. Systolic pulmonary-artery pressure estimates obtained by echocardiography and measurements obtained by pulmonary-artery catheterization are closely correlated.²⁵

Radiography

Posteroanterior chest radiographs were obtained in all subjects with the use of a mobile unit (TRS, Siemens) with a fixed target-to-film distance of 140 cm at 133 kV and 4 to 6 mA per second. The radiographs were analyzed according to previously described criteria²⁴ by a radiologist who was unaware of the subject's 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 edema. The scoring system was as follows: normal parenchyma, 0; areas with questionable pathological findings, 1; sections of which less than 50 percent was affected by interstitial disease, 2; sections of which more than 50 percent was affected by nonconfluent interstitial disease, 3; areas of alveolar, partly confluent disease, 4. Any radiograph in which at least one quadrant of a lung had a score of 2 or higher was considered to be positive for high-altitude pulmonary edema.

Measurement of Transepithelial Sodium Transport at Low Altitude

A group of 33 mountaineers who were prone to high-altitude pulmonary edema (19 of whom had also participated in the high-altitude studies; 6 women and 27 men; mean [±SD] age, 36±8 years), the 33 control subjects (13 women and 20 men; mean age, 34±9 years), and the 7 subjects with a history of transient perinatal pulmonary hypertension (3 women and 4 men; mean age, 22±2 years) participated in this part of the study. The nasal transepithelial potential difference was measured with a recording bridge (polyethylene tubing filled with Ringer's solution) inserted under the inferior turbinate.^{19,20} The intranasal recording bridge and a subcutaneous reference bridge (a sterile 21-gauge needle filled with agar and Ringer's solution) were linked by matched electrodes (Dri-Ref, World Precision Instruments) to a high-impedance voltmeter (Isomil, World Precision Instruments). During the measuring process, the recording bridge was perfused with isothermic (37°C) Ringer's solution (at a rate of 0.2 ml per minute). The difference in potential was measured at five distinct sites in each nostril by advancing or retracting the recording bridge by 0.5-cm intervals from the anterior to the posterior site, and vice versa. The potential difference was expressed in absolute values as the mean potential difference (the average of the five measurements obtained on each side). To determine the specific contribution of amiloride-sensitive sodium transport, we measured the effect of amiloride superfusion (floating amiloride over the nasal epithelium) on the nasal transepithelial potential difference at the site with the highest stable potential difference. Once a stable recording of potential difference had been obtained, amiloride (10⁻⁴ mol per liter) was superfused at a rate of 5 ml per minute for three minutes through a second catheter.¹⁹⁻²¹

Statistical Analysis

Statistical analyses were performed with JMP statistical software (SAS Institute) and involved paired or unpaired two-tailed

t-tests for comparisons of single variables, as appropriate. Fisher's exact test was used to compare the effects of salmeterol on the incidence of pulmonary edema with those of placebo. Relations between variables were analyzed by calculating the Pearson product-moment correlation coefficients. A P value of less than 0.05 was considered to indicate statistical significance. Unless otherwise indicated, data are given as means \pm SD.

RESULTS

Studies at High Altitude

The characteristics of the 37 subjects studied at high altitude are shown in Table 1. Two subjects in the placebo group but none in the salmeterol group had spent time above 3000 m during the two months preceding the study. Eleven of the subjects in the placebo group and 14 of those in the salmeterol group had had more than one episode of high-altitude pulmonary edema. One subject in the placebo group and two in the salmeterol group reported tremor, nocturnal palpitations, or both. The mean heart rate was similar in the two groups.

Prophylactic inhalation of salmeterol decreased the incidence of pulmonary edema; 14 of the 19 subjects in the placebo group (74 percent) but only 6 of the 18 subjects in the salmeterol group (33 percent) had clinical and radiographic evidence of pulmonary edema ($P=0.02$). Moreover, the mean radiographic score was more than 2.5 times as high in the placebo group as in the salmeterol group ($P=0.006$).

The subjects in the placebo group had more marked hypoxemia and more pronounced mountain sickness than those in the salmeterol group. There was an inverse correlation between the acute-mountain-sickness score and both the arterial oxygen saturation ($r=-0.60$, $P<0.001$) and the partial pressure of oxygen in the arterial blood ($r=-0.66$, $P<0.001$). Pulmonary-artery pressure did not differ significantly between the two groups.

Studies at Low Altitude

The nasal transepithelial potential-difference measurement was 32 percent lower among the subjects who were prone to high-altitude pulmonary edema (17.2 ± 5.8 mV) than among the control subjects (25.4 ± 9.6 mV) or the subjects with a history of transient perinatal pulmonary hypertension (27.8 ± 9.7 mV, $P<0.001$ for both comparisons) (Fig. 1). There was no significant difference between the sexes in the nasal transepithelial potential difference (data not shown). Amiloride superfusion caused a significantly smaller decrease in the nasal transepithelial potential difference in the subjects who were prone to high-altitude pulmonary edema (-10.0 ± 4.6 mV) than in the control subjects (-15.3 ± 7.3 mV) or the subjects with a history of transient perinatal pulmonary hypertension (-14.4 ± 9.5 mV, $P<0.001$ for both com-

TABLE 1. CHARACTERISTICS OF THE 37 SUBJECTS STUDIED AT HIGH ALTITUDE.*

VARIABLE	SALMETEROL GROUP	PLACEBO GROUP	P VALUE
Age (yr)	49.6 \pm 10.2	46.0 \pm 12.6	NS
Sex (no.)			NS
Male	13	15	
Female	5	4	
No. of previous episodes†	2.4 \pm 1.0	1.9 \pm 1.1	NS
Heart rate (beats/min)	94.1 \pm 11.1	89.1 \pm 13.5	NS
Systolic pulmonary-artery pressure (mm Hg)	60.9 \pm 15.5	63.6 \pm 13.9	NS
Arterial oxygen saturation (%)	73.5 \pm 11.5	67.0 \pm 7.9	0.03
Partial pressure of arterial oxygen (mm Hg)	33.9 \pm 7.3	30.0 \pm 5.1	0.04
Partial pressure of arterial carbon dioxide (mm Hg)	22.4 \pm 1.8	22.0 \pm 1.5	NS
Radiographic score‡	2.1 \pm 3.1	5.4 \pm 4.0	0.006
Lake Louise acute-mountain-sickness score§	5.8 \pm 3.2	11.5 \pm 5.3	<0.001

*Plus-minus values are means \pm SD. NS denotes not significant.

†Data are the self-reported number of previous lifetime episodes of high-altitude pulmonary edema per climber.

‡In each radiograph, four lung areas were each scored as follows and averaged: normal parenchyma, scored as 0; areas with questionable findings, 1; interstitial disease affecting less than 50 percent of area, 2; nonconfluent interstitial disease affecting more than 50 percent of area, 3; areas of alveolar, partly confluent disease, 4.

§The range of possible scores is 1 to 24, with higher scores indicating more severe illness.²³

parisons). After amiloride superfusion, the nasal transepithelial potential difference in subjects who were prone to pulmonary edema (7.3 ± 5.2 mV) was no longer significantly different from that in control subjects (10.1 ± 6.8 mV).

DISCUSSION

We found that prophylactic inhalation of salmeterol decreased the incidence of high-altitude pulmonary edema in susceptible subjects by more than 50 percent, from 74 percent with placebo to 33 percent. Several mechanisms could have contributed to this favorable effect. Enhancement of clearance of alveolar fluid may have played a part, since beta-adrenergic agonists up-regulate the clearance of alveolar fluid by stimulating transepithelial sodium transport²⁶ and attenuate alveolar flooding in animal models of lung injury (Fig. 2).¹¹⁻¹⁵ It is also possible that salmeterol, by improving alveolar ventilation and reducing alveolar hypoxia at high altitude, attenuates the hypoxia-induced impairment of alveolar absorption of sodium and fluid²⁷ in these subjects. Alternatively, salmeterol

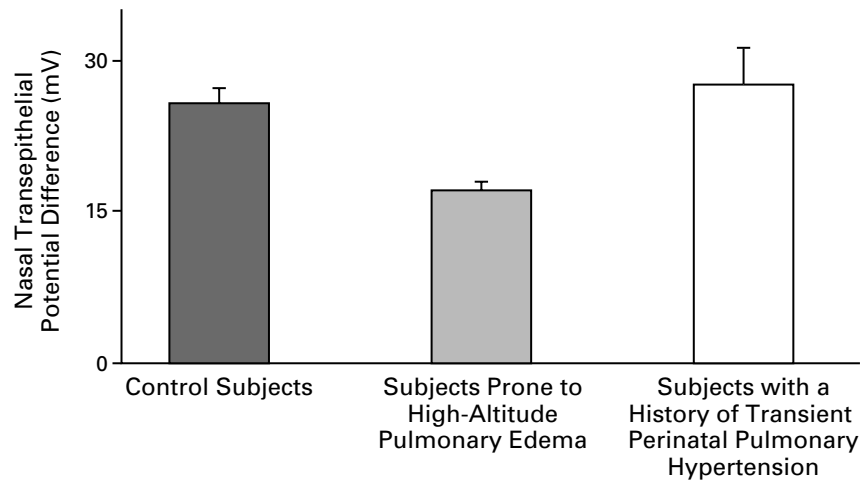


Figure 1. Mean Base-Line Bioelectrical Indexes of Nasal Transepithelial Sodium Transport. Thirty-three subjects who were prone to high-altitude pulmonary edema, 33 control subjects who were not susceptible to high-altitude pulmonary edema, and 7 adult subjects with a history of transient perinatal pulmonary hypertension were studied. $P < 0.001$ for the comparison between the subjects who were prone to high-altitude pulmonary edema and the control subjects. The I bars indicate the SE.

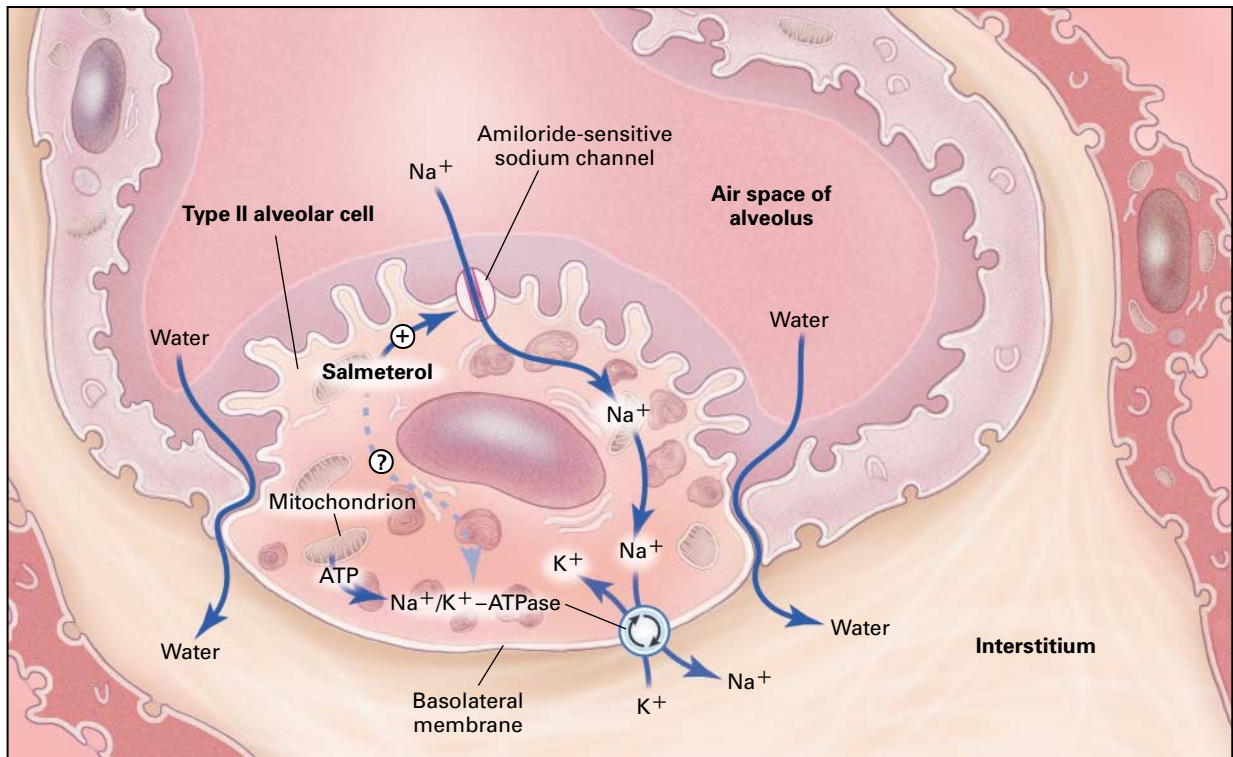


Figure 2. A Type II Alveolar Cell, Its Apical and Basal Sodium Channels, and the Possible Site of Action of Salmeterol. Sodium enters the apical membrane of alveolar cells mainly through amiloride-sensitive cation channels, such as the amiloride-sensitive epithelial sodium channel and the nonselective cation channel, and is then transported across the basolateral membrane into the interstitium by ouabain-inhibitable Na^+/K^+ -ATPase. Salmeterol is thought to increase transepithelial sodium transport primarily by stimulating its amiloride-sensitive component and possibly by increasing the activity of Na^+/K^+ -ATPase.

could act by protecting against the development of edema.

Prevention of pulmonary edema by the inhalation of salmeterol was not associated with an attenuation of altitude-induced pulmonary hypertension. This observation is consistent with the finding that the inhalation of salmeterol by sheep stimulates clearance of alveolar fluid without any detectable pulmonary hemodynamic effect.²⁸ It remains possible, however, that a hemodynamic action at the level of the pulmonary microcirculation, favorable effects on capillary permeability,²⁹ or both, may have contributed to the positive effect of salmeterol. Inhalation of salmeterol not only decreased the incidence of pulmonary edema, but also attenuated the symptoms of acute mountain sickness, an effect that appears to be related to the alleviation of hypoxemia.

The nasal transepithelial potential-difference value was 32 percent lower in the subjects who were prone to pulmonary edema than in the control subjects, suggesting a defect of transepithelial sodium and water transport that may be related, at least in part, to an impairment of its amiloride-sensitive fraction.^{30,31} We speculate that this defect of transepithelial sodium transport may facilitate the development of pulmonary edema in humans. This hypothesis is consistent with the finding that such a transport defect predisposes mice to exaggerated accumulation of pulmonary fluid during acute lung injury,³² whereas a normal transport function appears to protect humans from pulmonary edema in the face of exaggerated altitude-induced pulmonary hypertension (as evidenced by the results of studies in the subjects with a history of transient perinatal pulmonary hypertension).

In summary, the present studies demonstrate the clinical benefit of an inhaled beta-adrenergic agonist for reducing pulmonary edema in humans. Moreover, the results suggest that a predisposition to high-altitude pulmonary edema may be associated with defective sodium-dependent clearance of alveolar fluid. We speculate that in other disease states associated with augmented alveolar flooding and hypoxia, such as heart failure and the acute respiratory distress syndrome, a preexisting defect of respiratory sodium transport may facilitate the development of pulmonary edema or, by delaying its resolution, increase the incidence of related illness and death. Beta-adrenergic stimulation of the clearance of alveolar fluid may represent a novel therapeutic strategy to prevent such potentially fatal outcomes.

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