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INHALED NITRIC OXIDE FOR HIGH-ALTITUDE PULMONARY EDEMA

Urs Scherrer, M.D., Laurent Vollenweider, M.D., Alain Delabays, M.D., Milos Savcic, M.D.,
Urs Eichenberger, M.D., Gian-Reto Kleger, M.D., Antonin Fikrle, M.D., Peter E. Ballmer, M.D.,
Pascal Nicod, M.D., and Peter Bärtsch, M.D.

Abstract *Background.* Pulmonary hypertension is a hallmark of high-altitude pulmonary edema and may contribute to its pathogenesis. When administered by inhalation, nitric oxide, an endothelium-derived relaxing factor, attenuates the pulmonary vasoconstriction produced by short-term hypoxia.

Methods. We studied the effects of inhaled nitric oxide on pulmonary-artery pressure and arterial oxygenation in 18 mountaineers prone to high-altitude pulmonary edema and 18 mountaineers resistant to this condition in a high-altitude laboratory (altitude, 4559 m). We also obtained lung-perfusion scans before and during nitric oxide inhalation to gain further insight into the mechanism of action of nitric oxide.

Results. In the high-altitude laboratory, subjects prone to high-altitude pulmonary edema had more pronounced pulmonary hypertension and hypoxemia than subjects resistant to high-altitude pulmonary edema. Arterial oxygen saturation was inversely related to the severity of pulmonary hypertension ($r = -0.50$, $P = 0.002$). In subjects prone to high-altitude pulmonary edema, the inhalation of nitric oxide (40 ppm for 15 minutes) produced a decrease in mean ($\pm SD$) systolic pulmonary-artery pressure that was three times larger than the decrease in subjects resistant to such edema (25.9 ± 8.9 vs. 8.7 ± 4.8 mm Hg, $P < 0.001$). Inhaled nitric oxide improved arterial oxygenation in the 10 subjects who had radiographic evidence of pulmonary edema (arterial oxygen saturation increased from 67 ± 10 to 73 ± 12 percent, $P = 0.047$), whereas it worsened oxygenation in subjects resistant to high-altitude pulmonary edema. The nitric oxide–induced improvement in arterial oxygenation in subjects with high-altitude pulmonary edema was accompanied by a shift in blood flow in the lung away from edematous segments and toward nonedematous segments.

Conclusions. The inhalation of nitric oxide improves arterial oxygenation in high-altitude pulmonary edema, and this beneficial effect may be related to its favorable action on the distribution of blood flow in the lungs. A defect in nitric oxide synthesis may contribute to high-altitude pulmonary edema. (N Engl J Med 1996;334:624-9.)

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H IGH-ALTITUDE pulmonary edema is a life-threatening condition[1] characterized by marked pulmonary vasoconstriction.[2-6] Even though the exact underlying mechanisms of high-altitude pulmonary edema are incompletely understood, pulmonary hypertension is thought to play an important part.[3,7-9] On the basis of the hypothesis that in this condition pulmonary arteriolar vasoconstriction is heterogeneous, leading to areas of hypoperfusion and hyperperfusion, a decrease in pulmonary-artery pressure may be beneficial in two ways. A reduction of capillary pressure in overperfused areas may reduce the formation of edema, whereas augmentation of perfusion in previously underperfused areas, where gas exchange is not impaired, may improve oxygenation.

When administered by inhalation, nitric oxide, an endothelium-derived relaxing factor synthesized locally by the endothelium from the amino acid L-arginine,[10,11] attenuates the pulmonary vasoconstriction produced by short-term hypoxia.[12,13] We hypothesized that lowering pulmonary-artery pressure by administering nitric oxide may improve oxygenation in persons with high-altitude pulmonary edema. We therefore studied the effects of inhaled nitric oxide on pulmonary-artery pressure and arterial oxygenation in mountaineers susceptible to high-altitude pulmonary edema and those resistant to such edema after the subjects had ascended rapidly to a high altitude (4559 m). To gain further insight into the effects of nitric oxide administration, we performed lung-perfusion scans before and during the inhalation of nitric oxide at high altitude. We also examined the effects of nitric oxide inhalation on arterial oxygenation during short-term hypoxia at low altitude.

METHODS

Subjects and Study Design

We studied 18 mountaineers (3 women and 15 men; mean [$\pm SD$] age, 42 ± 11 years) who had had radiographically documented high-altitude pulmonary edema within the previous four years. Another 18 mountaineers (5 women and 13 men; mean age, 42 ± 10 years) with a history of repeated alpine-style climbing to peaks above 4000 m and no symptoms of high-altitude pulmonary edema or acute mountain sickness served as controls. One to four weeks after a base-line examination at 580 m (barometric pressure, 710 mm Hg), the subjects ascended in groups of two or three from 1130 m to 4559 m (barometric pressure, 440 mm Hg) within a period of 22 hours. The ascent consisted of transport by cable car to an altitude of 3200 m; a 1½-hour climb to an altitude of 3611 m, where the subjects stayed overnight; and, on the next morning, a 4½-hour climb to the high-altitude research laboratory at Capanna Regina Margherita (Fig. 1). The subjects then spent two days and two nights at this hut. Two hours after their arrival, each morning on their two-day stay, and whenever symptoms suggestive of high-altitude pulmonary edema developed, the subjects were examined by the same observer using the Lake Louise acute mountain sickness scoring system.[14] Briefly, the subject was asked five questions about the following symptoms: headache; gastrointestinal upset; fatigue, weakness, or both; dizziness, lightheadedness, or both; and difficulty sleeping. The subject was then assessed clinically for three symptoms — namely, a change in mental status, ataxia, and peripheral edema. The response to each of the eight items was rated with a 4-point scale in which a score of 0 indicated no symptoms, 1 mild symptoms, 2 moderate symptoms, and 3 severe symptoms. The mountain-sickness score is the sum of the scores for the eight items. The experimental protocol was approved by

Figure 1. The High-Altitude Research Laboratory at Capanna Regina Margherita.
The laboratory is located at the Swiss–Italian border at an altitude of 4559 m.

the institutional review board on human investigation, and all subjects provided written informed consent.

Mixing, Administration, and Monitoring of Inspired Gas

During the study the subject was supine and wore a face mask connected to a non-rebreathing circuit consisting of a gas-delivery system with a 30-liter reservoir bag. The inspired gas was room air at high altitude and a mixture of 10 percent oxygen and 90 percent nitrogen (to induce hypoxia) at low altitude. Volumetrically calibrated flowmeters were used to obtain the desired nitric oxide concentration (40 ppm); nitric oxide mixed with nitrogen at a fixed concentration (1000 ppm of nitric oxide in pure nitrogen) was substituted in a ratio of 0.8 to 19.2 for the inspired gas. Replacement of 4 percent of the inhaled air with nitric oxide in nitrogen decreased the partial pressure of oxygen by 3.7 and 2.8 mm Hg at high and low altitudes, respectively. At low altitude, the concentration of nitric oxide in the inspired air was monitored with a chemiluminescence analyzer (model CLD 700, Eco Physics, Dürnten, Switzerland).

Analysis of Blood Gas and End-Expiratory Gas

The fraction of inspired oxygen, minute ventilation, end-tidal oxygen and carbon dioxide concentrations, and hemoglobin oxygen saturation (measured with a pulse oximeter attached to a fingertip) were recorded continuously (Capnomac Ultima, Datex, Helsinki, Finland). Before each test this device (which adjusts the measurements automatically in response to changes in atmospheric pressure and temperature) was calibrated with two known gases containing 21 percent oxygen and 0 percent carbon dioxide and 55 percent oxygen and 5.01 percent carbon dioxide, respectively. In a subgroup of 10 subjects prone to high-altitude pulmonary edema and 13 subjects resistant to such edema, end-expiratory air and arterialized blood from an ear lobe were sampled simultaneously. Both samples were analyzed immediately to determine the partial pressures of arterial oxygen and carbon dioxide (model 278 blood gas system, Ciba–Corning Diagnostics, Dietlikon, Switzerland). End-expiratory gas analysis is assumed to provide an estimate of alveolar gas composition. The differ-

ence between the end-expiratory partial pressure of oxygen and the end-expiratory partial pressure of arterial oxygen is therefore referred to as the alveolar–arterial oxygen difference.

Doppler Echocardiography

To measure systolic pulmonary-artery pressure, echocardiographic recordings were obtained with a real-time, phased-array sector scanner (model 1500, Hewlett–Packard, Andover, Mass.) with an integrated color Doppler system and a transducer containing crystal sets for imaging (2.5 MHz) and for continuous-wave Doppler recording (1.9 MHz). The recordings were stored on VHS videotape for analysis by an investigator who was unaware of the subject's clinical history. 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 with continuous-wave Doppler echocardiography and the clinically determined mean jugular venous pressure.[6] 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 tricuspid-jet velocity.

Systemic arterial pressure and heart rate were measured with a Finapres blood-pressure monitor (Ohmeda, Englewood, Colo.).

Lung-Perfusion Scintigraphy

Lung-perfusion scintigraphy was performed after the intravenous injection of macroaggregated albumin particles labeled with technetium-99m (radioactivity, 111 MBq and 444 MBq before and during nitric oxide inhalation, respectively) with a mobile scintillation camera (Trans-Cam, ADAC, Copenhagen, Denmark) with a divergent collimator and an acquisition matrix of 256 by 256 pixels. During nitric oxide inhalation but before scintigraphy was performed, the residual activity from the previous scan was determined and then subtracted. For quantitative analysis, posterior projections were used and each lung was divided into four contiguous horizontal regions.[15] For each region, the average im-

pulse rate per pixel was calculated by an investigator who was unaware of the subject's history. To assess the effects of nitric oxide inhalation on lung perfusion, the lung regions for each subject were categorized as edematous or nonedematous on the basis of radiographic findings.

Radiography

On the morning before descent, posteroanterior chest radiographs were obtained in all subjects with a mobile unit (TRS, Siemens, Stockholm, Sweden) with a fixed target-to-film distance of 140 cm at 133 kV and 4 to 6 mA·sec^{-1}. In subjects in whom clinical signs or symptoms of high-altitude pulmonary edema developed, additional radiographs were obtained when the symptoms first appeared. The radiographs were analyzed according to previously described criteria[16] 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 lung areas were assessed separately for the presence of edema. Normal parenchyma was given a score of 0; areas with questionable pathologic findings, 1; sections in which interstitial disease affected less than 50 percent of the area, 2; sections of nonconfluent interstitial disease affecting more than 50 percent of the area, 3; and areas of alveolar, partly confluent disease, 4. Any radiograph with at least one lung-quadrant score of 2 or more was considered to be positive for high-altitude pulmonary edema. To categorize lung-perfusion scans, each quadrant was subdivided horizontally and the resulting eight lung regions were assessed separately for the presence of edema.

Experimental Protocols

Effects of Nitric Oxide Inhalation at High Altitude

The subjects were studied in the supine position 18 to 36 hours after arriving at the hut. They rested quietly for at least 15 minutes before breathing two gas mixtures sequentially for 12 minutes each: room air (fraction of inspired oxygen, 0.21), which was used as the control, and room air supplemented with 40 ppm of nitric oxide (fraction of inspired oxygen, 0.20). In one subject resistant to high-altitude pulmonary edema it was not possible to administer nitric oxide for technical reasons. Respiratory responses, oxygenation, systemic arterial pressure, and heart rate were measured continuously, whereas pulmonary-artery pressure was measured during the last four minutes of breathing control air or nitric oxide.

Effects of Nitric Oxide Inhalation on Lung Perfusion at High Altitude

In four subjects with high-altitude pulmonary edema and two control subjects, we performed lung-perfusion scintigraphy immediately before and during the last minute of a 20-minute period of nitric oxide inhalation at high altitude.

Effects of Nitric Oxide Inhalation during Hypoxia at Low Altitude

Eight subjects prone to high-altitude pulmonary edema and six subjects resistant to this condition participated in this part of the study. The subjects rested quietly for 15 minutes before breathing three gas mixtures sequentially for 12 minutes each: a control mixture with a fraction of inspired oxygen of 0.21, a hypoxic mixture with a fraction of inspired oxygen of 0.10, and a hypoxic mixture with a fraction of inspired oxygen of 0.096 that contained 40 ppm of nitric oxide. Respiratory responses and oxygenation were recorded continuously, whereas pulmonary-artery pressure was measured during the last four minutes of each of the three periods.

Statistical Analysis

Statistical analysis (JMP statistical software, SAS Institute, Cary, N.C.) was performed with an analysis of variance or the Kruskal–Wallis test for comparisons between the groups and the two-tailed t-test or Mann–Whitney rank-sum statistic for single comparisons, as appropriate. Relations between variables were analyzed by calculating the Pearson product–moment correlation coefficients. A P value below 0.05 was considered to indicate statistical significance. Unless otherwise indicated, data are expressed as means ±SD.

RESULTS

After 18 to 36 hours at 4559 m, 10 of the 18 subjects prone to high-altitude pulmonary edema but none of the control subjects had radiographic evidence of pulmonary edema. All 10 of these subjects were studied while they had radiographic evidence of edema (radiographic score, 2 to 16; mean [±SD], 9.2±4.2). In the control group, symptoms of acute mountain sickness were absent in 12 subjects and minor in all but 3 (mountain-sickness score, 1 to 9; mean, 3.9±2.4), whereas most subjects prone to high-altitude pulmonary edema had high mountain-sickness scores (range, 3 to 12; mean, 7.5±2.7; P<0.001 for the comparison with controls).

Subjects prone to high-altitude pulmonary edema had more severe hypoxemia than controls and had more pro-

Table 1. Effects of Nitric Oxide Inhalation at High Altitude (4559 m).*

VARIABLE	HAPE-RESISTANT SUBJECTS (N = 17)		HAPE-PRONE SUBJECTS WITHOUT PULMONARY EDEMA (N = 8)		HAPE-PRONE SUBJECTS WITH PULMONARY EDEMA (N = 10)		P VALUE
	BASE LINE	NITRIC OXIDE INHALATION†	BASE LINE	NITRIC OXIDE INHALATION†	BASE LINE	NITRIC OXIDE INHALATION†	
Systolic pulmonary-artery pressure (mm Hg)	43±7	34±5	67±13	42±6‡	66±11	40±9‡	<0.001
Arterial oxygen saturation (%)	81±5	79±5	75±5	75±6	67±10	73±12§	0.005
End-tidal carbon dioxide concentration (mm Hg)	28±3	29±6	27±4	27±4	28±2	26±4	NS
Partial pressure of arterial oxygen (mm Hg)¶	46±5	44±3	45±3	43±4	36±6	41±8‖	0.003
Alveolar–arterial oxygen difference (mm Hg)¶	8±3	7±3	9±4	6±3**	15±4	11±3††	0.04

*Plus−minus values are means ±SD. The P values are for the comparisons of changes from base line between study groups. HAPE denotes high-altitude pulmonary edema, and NS not significant.

†Adding nitric oxide to the inhaled gas decreased the fraction of inspired oxygen from 0.21 to 0.20.

‡P<0.001 for the comparison with changes from base line in subjects resistant to high-altitude pulmonary edema.

§P=0.005 for the comparison with changes from base line in subjects resistant to high-altitude pulmonary edema.

¶Values are for 13 subjects resistant to high-altitude pulmonary edema, 5 subjects prone to such edema without radiographic evidence of pulmonary edema, and 5 subjects prone to such edema with radiographic evidence of pulmonary edema.

‖P=0.002 for the comparison with changes from base line in subjects resistant to high-altitude pulmonary edema.

**P=0.05 for the comparison with changes from base line in subjects resistant to high-altitude pulmonary edema.

††P=0.04 for the comparison with changes from base line in subjects resistant to high-altitude pulmonary edema.

Before Nitric Oxide Inhalation

A

Before Nitric Oxide Inhalation

B

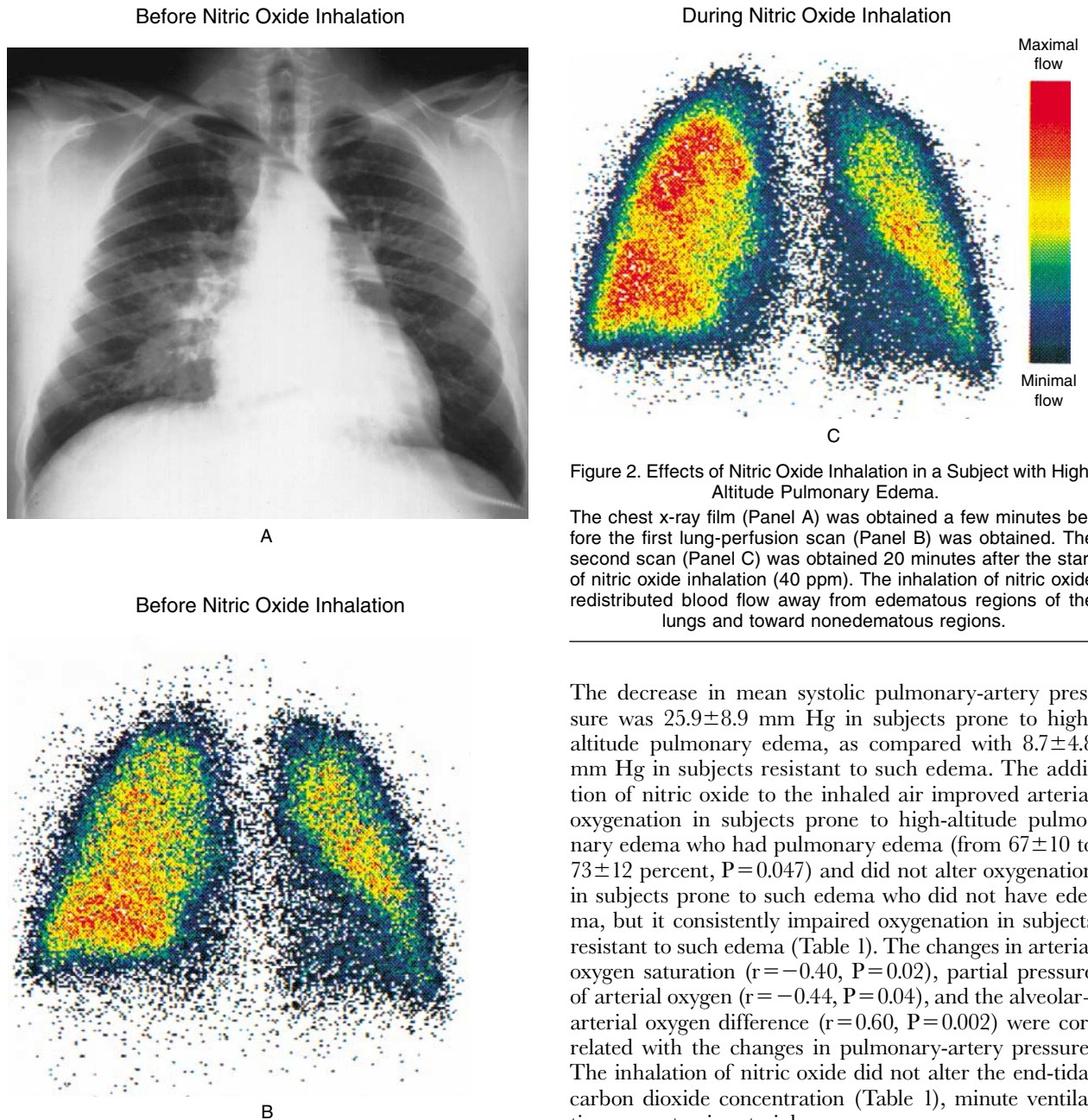During Nitric Oxide Inhalation

C

Figure 2. Effects of Nitric Oxide Inhalation in a Subject with High-Altitude Pulmonary Edema.

The chest x-ray film (Panel A) was obtained a few minutes before the first lung-perfusion scan (Panel B) was obtained. The second scan (Panel C) was obtained 20 minutes after the start of nitric oxide inhalation (40 ppm). The inhalation of nitric oxide redistributed blood flow away from edematous regions of the lungs and toward nonedematous regions.

nounced pulmonary hypertension (Table 1). There was an inverse correlation between arterial oxygen saturation and pulmonary-artery pressure (r=−0.50, P=0.002) and between the partial pressure of arterial oxygen and pulmonary-artery pressure (r=−0.48, P=0.003), whereas the alveolar–arterial oxygen difference was directly related to the pulmonary-artery pressure (r=0.55, P<0.001).

Effects of Nitric Oxide Inhalation at High Altitude

The inhalation of nitric oxide produced a decrease in pulmonary-artery pressure that was markedly greater in subjects prone to high-altitude pulmonary edema than in control subjects (Table 1), and the decrease in pulmonary-artery pressure was directly correlated with the severity of the pulmonary hypertension (r=0.89, P<0.001).

The decrease in mean systolic pulmonary-artery pressure was 25.9±8.9 mm Hg in subjects prone to high-altitude pulmonary edema, as compared with 8.7±4.8 mm Hg in subjects resistant to such edema. The addition of nitric oxide to the inhaled air improved arterial oxygenation in subjects prone to high-altitude pulmonary edema who had pulmonary edema (from 67±10 to 73±12 percent, P=0.047) and did not alter oxygenation in subjects prone to such edema who did not have edema, but it consistently impaired oxygenation in subjects resistant to such edema (Table 1). The changes in arterial oxygen saturation (r=−0.40, P=0.02), partial pressure of arterial oxygen (r=−0.44, P=0.04), and the alveolar–arterial oxygen difference (r=0.60, P=0.002) were correlated with the changes in pulmonary-artery pressure. The inhalation of nitric oxide did not alter the end-tidal carbon dioxide concentration (Table 1), minute ventilation, or systemic arterial pressure.

Effects of Nitric Oxide Inhalation on Lung Perfusion at High Altitude

In all four subjects prone to high-altitude pulmonary edema who had pulmonary edema and whom we examined with lung-perfusion studies, the inhalation of nitric oxide at high altitude redistributed blood flow in the lungs away from edematous segments and toward nonedematous segments (Fig. 2). Before the inhalation of nitric oxide, the average activity per pixel was higher in edematous than in nonedematous lung segments (81±7 vs. 75±4 counts per pixel, P=0.07) in all four subjects. The inhalation of nitric oxide increased the average activity per pixel in the nonedematous lung segments by a factor of 4 as compared with the edematous lung segments (increase, 12±3 vs. 3±3 counts

per pixel, P=0.009), and in three of the four subjects the average activity per pixel became lower in edematous than in nonedematous lung segments (84±8 vs. 88±6 counts per pixel). During the inhalation of nitric oxide the pulmonary blood-flow ratio (the average activity per pixel of nonedematous lung regions divided by the average activity per pixel of edematous lung regions) increased by 13±6 percent (P=0.03). In the two control subjects studied, the inhalation of nitric oxide did not alter the distribution of blood flow in the lungs; the average activity per pixel increased similarly and homogeneously in both lungs (by 9±7 counts per pixel in the right lung and by 13±7 counts per pixel in the left lung).

Effects of Nitric Oxide Inhalation during Hypoxia at Low Altitude

The inhalation of a hypoxic gas mixture (fraction of inspired oxygen, 0.10) decreased arterial oxygen saturation and increased pulmonary-artery pressure to values that did not differ between the subjects who were prone to high-altitude pulmonary edema and those who were not (Table 2). In contrast to the situation at high altitude, lowering of pulmonary-artery pressure by nitric oxide inhalation did not improve oxygen saturation in subjects prone to high-altitude pulmonary edema, but it further decreased arterial oxygen saturation to a value that was similar to the one observed in subjects who were resistant to high-altitude pulmonary edema.

DISCUSSION

We found that in subjects with high-altitude pulmonary edema, the inhalation of nitric oxide produced a large decrease in pulmonary-artery pressure and rapidly improved arterial oxygenation, even though adding nitric oxide to the inhaled air slightly decreased the fraction of inspired oxygen. In contrast, in subjects resistant to high-altitude pulmonary edema, adding nitric oxide to the inhaled gas, although it also reduced the pulmonary-artery pressure, consistently impaired arterial oxygenation. These findings suggest that in high-altitude pulmonary edema, but not in high-altitude–induced pulmonary vasoconstriction alone, the inhalation of nitric oxide exerts beneficial effects on arterial oxygenation.

At high altitude, subjects prone to high-altitude pulmonary edema had more pronounced pulmonary vasoconstriction than did subjects resistant to such edema. During nitric oxide inhalation, however, pulmonary-artery pressure was similar in both groups because the nitric oxide–induced decrease in pressure was larger in the subjects prone to edema than in those resistant to edema. These observations are consistent with the hypothesis that a defect in nitric oxide–mediated pulmonary vasodilatation — a mechanism that may act as a brake on pulmonary vasoconstriction[17] — could contribute to susceptibility to high-altitude pulmonary edema. In line with

Table 2. Effects of Nitric Oxide Inhalation during Hypoxia at Low Altitude.*

VARIABLE	HAPE-PRONE SUBJECTS (N=8)			HAPE-RESISTANT SUBJECTS (N=6)		
	BASE LINE	NITRIC OXIDE INHALATION†	P VALUE	BASE LINE	NITRIC OXIDE INHALATION†	P VALUE
Systolic pulmonary-artery pressure (mm Hg)	54±10	31±2	<0.001	46±11	34±3	0.04
Arterial oxygen saturation (%)	67±6	62±7	0.03	67±7	62±6	0.03
End-tidal carbon dioxide concentration (mm Hg)	28±5	27±4	NS	27±4	27±4	NS

*The fraction of inspired oxygen was 0.10. Plus–minus values are means ±SD. The P values are for the comparisons with the base-line values. HAPE denotes high-altitude pulmonary edema, and NS not significant.

†Adding nitric oxide to the inhaled gas decreased the fraction of inspired oxygen from 0.10 to 0.096.

this concept, the inhibition of endothelium-dependent vasodilatation with N^G-monomethyl-L-arginine potentiates the pulmonary vasoconstrictor response to short-term hypoxia in dogs[18] and humans.[19] Alternatively, it has also been shown that inhibition of nitric oxide synthesis in cats and rats augments microvascular permeability in several vascular beds.[20] Bronchoalveolar lavage has revealed increased capillary permeability in subjects with high-altitude pulmonary edema.[21] It is possible that a defect in nitric oxide synthesis could contribute to increased vascular permeability in this condition.

Our results provide some mechanistic insight into nitric oxide–induced effects on pulmonary gas exchange. In subjects with high-altitude pulmonary edema, the inhalation of nitric oxide redistributed blood flow in the lungs away from edematous regions and toward nonedematous regions, thereby improving the matching of ventilation and perfusion and reducing the alveolar–arterial oxygen difference. The more pronounced vasodilatation in nonedematous as compared with edematous lung regions may be related either to the easier accessibility of nitric oxide to these highly ventilated (and nonedematous) areas or to augmented vasoconstriction in these regions, as suggested by the overperfusion hypothesis.[7,22] Our finding of a trend toward high perfusion in lung regions with radiographic evidence of edema could be consistent with this latter interpretation.

In subjects prone to high-altitude pulmonary edema who had no radiographic evidence of edema, the inhalation of nitric oxide decreased the alveolar–arterial oxygen difference (and did not impair arterial oxygen saturation), suggesting that such persons may already have had clinically relevant ventilation–perfusion mismatches that responded favorably to inhaled nitric oxide. In contrast, subjects resistant to high-altitude pulmonary edema did not seem to have relevant mismatches because the inhalation of nitric oxide did not alter the alveolar–arterial oxygen difference and impaired arterial oxygenation (this effect is attributable to the reduction of the partial pressure of oxygen by 3.7 mm Hg, caused by the replacement of 4 percent of the inhaled air by nitric oxide in nitrogen). This interpretation is strengthened by the present and previous[23] observations of the effects of nitric oxide inhalation on arterial oxygenation during short-term hypoxia at low altitude.

A decrease in pulmonary-artery pressure and improved oxygen saturation in subjects with high-altitude pulmonary edema have also been reported after the

administration of the vasodilator agents nifedipine,[5] hydralazine, and phentolamine.[24] In contrast to those agents, nitric oxide did not alter the systemic arterial pressure or the heart rate, suggesting that it dilates lung vessels selectively.[13] Although the exact mechanism by which systemic vasodilators exert their beneficial effects in high-altitude pulmonary edema needs to be elucidated, these findings support the concept that attenuation of pulmonary vasoconstriction, possibly in conjunction with a reduction in the ventilation–perfusion mismatch, plays an important part in both the treatment[5,24] and the prevention[6] of high-altitude pulmonary edema.

REFERENCES

1. Houston CS. Acute pulmonary edema of high altitude. N Engl J Med 1960; 263:478-80.
2. Fred HL, Schmidt AM, Bates T, Hecht HH. Acute pulmonary edema of high altitude: clinical and physiologic observations. Circulation 1962;25:929-37.
3. Hackett PH, Roach RC. High altitude pulmonary edema. J Wilderness Med 1990;1:3-26.
4. Hultgren HN, Lopez CE, Lundberg E, Miller H. Physiologic studies of pulmonary edema at high altitude. Circulation 1964;29:393-408.
5. Oelz O, Maggiorini M, Ritter M, et al. Nifedipine for high altitude pulmonary oedema. Lancet 1989;2:1241-4.
6. Bärtsch P, Maggiorini M, Ritter M, Noti C, Vock P, Oelz O. Prevention of high-altitude pulmonary edema by nifedipine. N Engl J Med 1991;325:1284-9.
7. Hultgren HN. High altitude pulmonary edema. In: Staub NC, ed. Lung water and solute exchange. Vol. 7 of Lung biology in health and disease. New York: Marcel Dekker, 1978:437-69.
8. Schoene RB. Pulmonary edema at high altitude: review, pathophysiology, and update. Clin Chest Med 1985;6:491-507.
9. Staub NC. Pulmonary edema — hypoxia and overperfusion. N Engl J Med 1980;302:1085-7.
10. Palmer RMJ, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. Nature 1987;327:524-6.
11. Furchgott RF, Zawadski JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 1980;288:373-6.
12. Frostell CG, Fratacci M-D, Wain JC, Jones R, Zapol WM. Inhaled nitric oxide: a selective pulmonary vasodilator reversing hypoxic pulmonary vasoconstriction. Circulation 1991;83:2038-47. [Erratum, Circulation 1991;84:2212.]
13. Frostell CG, Blomqvist H, Hedenstierna G, Lundberg J, Zapol WM. Inhaled nitric oxide selectively reverses human hypoxic pulmonary vasoconstriction without causing systemic vasodilation. Anesthesiology 1993;78:427-35.
14. Roach RC, Bärtsch P, Hackett PH, Oelz O, Lake Louise AMS Scoring Consensus Committee. The Lake Louise acute mountain sickness scoring system. In: Sutton JR, Houston CS, Coates G, eds. Hypoxia and molecular medicine. Burlington, Vt.: Queen City Printers, 1993:272-4.
15. West JB. Distribution of gas and blood in the normal lungs. Br Med Bull 1963;19:53-8.
16. Vock P, Fretz C, Franciolli M, Bärtsch P. High-altitude pulmonary edema: findings at high-altitude chest radiography and physical examination. Radiology 1989;170:661-6.
17. Dinh-Xuan AT, Higenbottam TW, Clelland CA, et al. Impairment of endothelium-dependent pulmonary-artery relaxation in chronic obstructive lung disease. N Engl J Med 1991;324:1539-47.
18. Perrella MA, Edell ES, Krowka MJ, Cortese DA, Burnett JC Jr. Endothelium-derived relaxing factor in pulmonary and renal circulations during hypoxia. Am J Physiol 1992;263:R45-R50.
19. Blitzer ML, Loh E, Roddy M-A, Berryman JR, Stamler JS, Creager MA. Endothelium-derived nitric oxide regulates pulmonary and systemic vascular resistance during acute hypoxia in humans. Circulation 1994;90:I-295. abstract.
20. Kubes P. Nitric oxide-induced microvascular permeability alterations: a regulatory role for cGMP. Am J Physiol 1993;265:H1909-H1915.
21. Schoene RB, Swenson ER, Pizzo CJ, et al. The lung at high altitude: bronchoalveolar lavage in acute mountain sickness and pulmonary edema. J Appl Physiol 1988;64:2605-13.
22. West JB, Mathieu-Costello O. Stress failure of pulmonary capillaries: role in lung and heart disease. Lancet 1992;340:762-7.
23. Pison U, Lopez FA, Heidelmeyer CF, Rossaint R, Falke KJ. Inhaled nitric oxide reverses hypoxic pulmonary vasoconstriction without impairing gas exchange. J Appl Physiol 1993;74:1287-92.
24. Hackett PH, Roach RC, Hartig GS, Greene ER, Levine BD. The effect of vasodilators on pulmonary hemodynamics in high altitude pulmonary edema: a comparison. Int J Sports Med 1992;13:Suppl 1:S68-S71.

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