Augmented Sympathetic Activation During Short-Term Hypoxia and High-Altitude Exposure in Subjects Susceptible to High-Altitude Pulmonary Edema

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Background—Pulmonary hypertension is a hallmark of high-altitude pulmonary edema and may contribute to its pathogenesis. Cardiovascular adjustments to hypoxia are mediated, at least in part, by the sympathetic nervous system, and sympathetic activation promotes pulmonary vasoconstriction and alveolar fluid flooding in experimental animals.

Methods and Results—We measured sympathetic nerve activity (using intraneural microelectrodes) in 8 mountaineers susceptible to high-altitude pulmonary edema and 7 mountaineers resistant to this condition during short-term hypoxic breathing at low altitude and at rest at a high-altitude laboratory (4559 m). We also measured systolic pulmonary artery pressure to examine the relationship between sympathetic activation and pulmonary vasoconstriction. In subjects prone to pulmonary edema, short-term hypoxic breathing at low altitude evoked comparable hypoxemia but a 2- to 3-times-larger increase in the rate of the sympathetic nerve discharge than in subjects resistant to edema (P<0.001). At high altitude, in subjects prone to edema, the increase in the mean±SE sympathetic firing rate was >2 times larger than in those resistant to edema (36±7 versus 15±4 bursts per minute, P<0.001) and preceded the development of lung edema. We observed a direct relationship between sympathetic nerve activity and pulmonary artery pressure measured at low and high altitude in the 2 groups (r=0.83, P<0.0001).

Conclusions—With the use of direct measurements of postganglionic sympathetic nerve discharge, these data provide the first evidence for an exaggerated sympathetic activation in subjects prone to high-altitude pulmonary edema both during short-term hypoxic breathing at low altitude and during actual high-altitude exposure. Sympathetic overactivation may contribute to high-altitude pulmonary edema. (Circulation. 1999;99:1713-1718.)

Key Words: edema, pulmonary hypertension, pulmonary nervous system, autonomic echocardiography

High-altitude pulmonary edema (HAPE) is a life-threatening condition characterized by augmented pulmonary vasoconstriction and pulmonary edema, pulmonary hypertension, and endothelial dysfunction.1–7 that is thought to play an important part in its pathogenesis. Although there is evidence that hypoxia stimulates pulmonary vasoconstriction,1–7 observations in animals and humans are consistent with the hypothesis that sympathetic activation may also play a role.7,9,10 In dogs, blockade of the stellate ganglion prevents pulmonary edema and lung injury evoked by intravenous infusion of oleic acid.10 In subjects suffering from HAPE, infusion of the α-adrenergic blocking agent phentolamine evokes significantly larger decreases in pulmonary artery pressure than infusion of nonspecific vasodilator drugs.7

It is well established that cardiovascular adjustments to hypoxemia are mediated, at least in part, by the sympathetic nervous system. In rabbits and cats, short-term hypoxia stimulates pulmonary and renal sympathetic nerve activity.11,12 In humans, plasma catecholamines, indirect markers of sympathetic activity, remained unchanged during short-term hypoxia but increased in some, but not other, studies during prolonged exposure to high altitude.13–17 In studies using direct microneurographic measurements of muscle sympathetic nerve activity (MSNA) in humans, brief and/or mild hypoxia caused little or no change in MSNA, whereas more sustained and severe hypoxia rather consistently stimulated sympathetic activity.15,16,18,19 Part of the discrepancy between norepinephrine plasma concentration and MSNA findings in these human studies could be related to the stimulation of norepinephrine clearance by hypoxia.20 Thus, although there is evidence that hypoxia stimulates postganglionic sympathetic nerve activity in humans, no
data are available at high altitude and in HAPE-susceptible subjects. We therefore measured sympathetic nerve activity in mountaineers susceptible to HAPE and in those resistant to such edema during short-term hypoxic breathing at low altitude and after the subjects had ascended rapidly to a high altitude (4559 m). We also measured systolic pulmonary artery pressure.

Methods

Subjects

We studied 8 mountaineers (2 women and 6 men; mean±SD age, 39±11 years) who had had radiographically documented HAPE within the previous 4 years. Another 7 mountaineers (7 men; mean age, 41±12 years) with a history of repeated alpine-style climbing to peaks >4000 m and no symptoms of HAPE or acute mountain sickness served as control subjects. One to 4 weeks after baseline examination at low-altitude (580 m; barometric pressure, 710 mm Hg), the subjects ascended in groups of 2 to 4 from 1130 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 day, a 4½-hour climb to the high-altitude research laboratory at Capanna Regina Margherita. The subjects spent 2 days and 2 nights at this hut. The experimental protocol was approved by the institutional review board on human investigation, and all subjects provided written informed consent.

General Procedures

Subjects were studied in the supine position. Heart rate (ECG), blood pressure (Finapres blood pressure monitor, Ohmeda), and efferent MSNA were recorded continuously on an electrocardiographic recorder and a TEAC R 71 tape recorder (TEAC Corp). The hemoglobin oxygen saturation (measured with a pulse oximeter attached to a fingertip) and the minute ventilation were recorded continuously (Capnomac Ultima, Datex). Respiratory excursions were monitored to detect inadvertent performance of a Valsalva maneuver or prolonged expiration because both maneuvers can markedly stimulate MSNA.

Recording of Sympathetic Nerve Activity

Details of the technique have been given elsewhere. In brief, multiunit recordings of postganglionic sympathetic nerve activity were obtained with unipolar tungsten microelectrodes inserted selectively into muscle nerve fascicles of the peroneal nerve. The neural signals were amplified 20 000 to 50 000 times, filtered (bandwidth, 700 to 2000 Hz), rectified, and integrated (time constant, 0.1 second) to obtain a mean voltage display of sympathetic activity. A recording of sympathetic activity was considered acceptable when it revealed spontaneous, pulse synchronous bursts of neural activity, with the largest bursts showing a minimal signal-to-noise ratio of 3:1. In each study, we documented that we were recording sympathetic outflow to skeletal muscle by demonstrating that the neural activity did not respond to arousal stimuli (loud noise) or a pinch of the skin but showed a characteristic biphasic response to the Valsalva maneuver. The recordings were all analyzed by the same observer who was unaware of the subject’s clinical history. The intraobserver and interobserver coefficients of variation of the mean in identifying bursts were <6% and <9%, respectively. Nerve traffic was expressed both as bursts per minute, an index of the frequency of the activity, and as bursts per minute times mean burst amplitude, an index of integrated (total) activity.

Doppler Echocardiography

To measure systolic pulmonary artery pressure, echocardiographic recordings were obtained with a real-time, phased-array sector scanner (model 2500, Hewlett-Packard Corp) with an integrated color Doppler system and a transducer-containing crystal set 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 ≥3 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. Color Doppler echocardiography was used to locate the tricuspid regurgitation jet. 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 equals 4 times the square of the tricuspid jet velocity. At this high-altitude laboratory, systolic pulmonary artery pressure measurements in 17 subjects obtained by echocardiography and by pulmonary artery catheterization were found to be closely correlated (r=0.87, P<0.001), and the mean±SD difference between echocardiographic and invasive pulmonary artery pressure measurements was 0.5±5.6 mm Hg.

Radiography

Each morning, posteroanterior chest radiographs were obtained with a mobile unit (TRS, Siemens) with a fixed target-to-film distance of 140 cm at 133 kV and 4 to 6 mAs. In subjects in whom clinical evidence of HAPE developed, additional radiographs were obtained when symptoms first appeared. The radiographs were analyzed according to previously described criteria by a radiologist who was unaware of the subject’s clinical history.

Experimental Protocols

Effects of Short-Term Hypoxic Breathing at Low Altitude

The subjects rested quietly for ≥30 minutes after instrumentation before breathing 4 gas mixtures sequentially for 20 minutes each: a control mixture with a fraction of inspired oxygen of 0.21 and 3 hypoxic mixtures with fractions of inspired oxygen of 0.14, 0.12, and 0.10, respectively. MSNA, hemoglobin oxygen saturation, and pulmonary artery pressure were recorded during the last 4 minutes of each period.

After all values had returned to their baseline levels, to assess the sympathetic responsiveness to a stimulus other than hypoxia, we used baroreceptor deactivation by the Valsalva maneuver and stimulation of cutaneous afferents by immersion of the hand in ice water for 2 minutes (cold pressor test).

Studies at High Altitude

The subjects were studied 18 to 24 hours after arrival at the hut. After instrumentation, they rested quietly for ≥15 minutes before MSNA and oxygenation were measured during another 15 minutes. In 2 subjects of each group, we did not succeed in obtaining a technically satisfactory recording of sympathetic nerve activity. Pulmonary artery pressure was measured 30 minutes after termination of the MSNA measurements. Immediately thereafter, subjects were examined by use of the Lake Louise Acute Mountain Sickness Scoring System.

Statistical Analysis

Statistical analysis (JMP Statistical Software, SAS Institute) was performed with an ANOVA for comparisons between 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 value of P<0.05 was considered to indicate statistical significance. Unless otherwise indicated, data are expressed as mean±SE.

Results

Short-Term Hypoxic Breathing at Low Altitude

Figures 1 and 2 show that short-term hypoxic breathing caused an increase in MSNA burst frequency that was 2 to 3
times larger ($P<0.001$) in HAPE-susceptible than in HAPE-resistant subjects. In HAPE-prone subjects, MSNA burst frequency increased from $16\pm4$ to $40\pm4$ bursts per minute from baseline to the end of the hypoxic breathing (total activity increased from $343\pm78$ to $1043\pm148$ U), whereas in HAPE-resistant subjects, it increased only from $21\pm3$ to $33\pm4$ bursts per minute (total activity increased from $331\pm69$ to $558\pm98$ U). Moreover, in HAPE-prone subjects, MSNA increased significantly ($P=0.01$) during mild hypoxic breathing (fraction of the inspired oxygen, 0.14), whereas in HAPE-resistant subjects, this increase became significant only during the most severe hypoxic breathing used in these studies. Hypoxic breathing also evoked augmented pulmonary vasoconstriction in HAPE-prone subjects ($P<0.001$ versus HAPE resistant subjects; Figure 2). There was a direct correlation between sympathetic activity and systolic pulmonary artery pressure in these studies (burst rate, $r=0.55$, $P<0.001$; total activity, $r=0.48$, $P<0.001$). During the hypoxic breathing, hemoglobin oxygen saturation decreased gradually and similarly in both groups (Figure 2), whereas minute ventilation increased slightly but similarly in both groups; in HAPE-prone subjects, it increased from $9.2\pm0.6$ to $9.8\pm0.6$, $10.9\pm0.5$, and $11.2\pm0.6$ L/min during hypoxic breathing with fractions of inspired oxygen of 0.14, 0.12, and 0.10, respectively, in HAPE-resistant subjects, burst frequency increased by $36\pm7$ bursts per minute (from $16\pm3$ to $52\pm4$ bursts per minute), whereas in HAPE-resistant subjects, burst frequency increased by $15\pm4$ bursts per minute (from $21\pm4$ to $37\pm2$ bursts per minute).

Studies at High Altitude

After 24 to 36 hours at 4559 m, 4 of the 6 HAPE-prone subjects but none of the HAPE-resistant subjects had radiographic evidence of pulmonary edema (Table). All HAPE-prone subjects were studied before they had developed pulmonary edema. Compared with findings at low altitude, sympathetic nerve activity was augmented in both groups, but this increase was $>2$ times larger ($P<0.05$) in HAPE-prone than in HAPE-resistant subjects (Figure 3 and the Table). In HAPE-prone subjects, sympathetic burst frequency increased by $36\pm7$ bursts per minute (from $16\pm3$ to $52\pm4$ bursts per minute), whereas in HAPE-resistant subjects, burst frequency increased by $15\pm4$ bursts per minute (from $21\pm4$ to $37\pm2$ bursts per minute).

HAPE-prone subjects had more severe hypoxemia ($66\pm4\%$ versus $85\pm2\%$ arterial oxygen saturation, $P=0.002$) and more pronounced pulmonary hypertension ($71\pm3$ versus $45\pm3$ mm Hg, $P<0.001$) than control subjects. When both groups were taken together, there was an inverse correlation between MSNA and arterial oxygen saturation ($r=-0.81$, $P<0.001$).
Discussion

With the use of direct measurements of postganglionic sympathetic nerve discharge, these data provide the first evidence for an exaggerated sympathetic activation in subjects prone to HAPE both during short-term hypoxic breathing at low altitude and during actual high-altitude exposure. Short-term hypoxic breathing at low altitude evoked comparable hypoxemia but a 2-fold-larger increase in the rate of sympathetic nerve discharge in HAPE-prone than in HAPE-resistant subjects. Similarly, at high altitude, the sympathetic firing rate was 2 times higher in mountaineers prone to HAPE than in those resistant to such edema. Finally, we observed a direct relationship between sympathetic nerve activity and pulmonary artery pressure.

The sympathetic nervous system is thought to play an important role in cardiovascular adjustments to hypoxia, and exaggerated pulmonary hypertension is a hallmark of HAPE. In these studies, the increase in pulmonary artery pressure was more pronounced in HAPE-prone subjects than in control subjects both during short-term hypoxic breathing at low altitude and at high altitude. Moreover, we found a direct relationship between sympathetic nerve activity and pulmonary artery pressure under both experimental conditions. Finally, in all HAPE-prone subjects, the exaggerated sympathetic activation at high altitude preceded the clinical symptoms and radiographic evidence of pulmonary edema. Taken together, these findings are consistent with the hypothesis that sympathetic activation may play a part in the exaggerated pulmonary vasoconstrictor response in HAPE-prone subjects. In line with this

![Figure 3](image-url)

**Figure 3.** Segments of representative nerve recordings in a HAPE-resistant and a HAPE-susceptible subject obtained at low and high altitude. On these mean voltage displays of MSNA, each peak represents a spontaneous burst of sympathetic nerve discharge.

![Figure 4](image-url)

**Figure 4.** Relationship between systolic pulmonary artery pressure and firing rate of sympathetic nerves (MSNA) measured at low (580 m) and high (4559 m) altitude in 6 HAPE-prone (□) and 5 HAPE-resistant subjects (●) ($r=0.83, P<0.001$).
hypothesis, phentolamine infusion evokes larger decreases in pulmonary artery pressure in HAPE-prone subjects than infusion of nonspecific vasodilator drugs.7

Studies in animals also indicate that sympathetic activation plays a role in the mediation of pulmonary vasoconstrictor responses. In anesthetized cats, hypoxia increases pulmonary sympathetic nerve activity and pulmonary artery pressure.12 In dogs, sympathetic activation by intracisternal administration of veratrine causes a massive increase pulmonary artery pressure and extravascular lung water,25 whereas sympathetic blockade attenuates the hypoxia-induced pulmonary vasoconstriction.26 In addition to its vasoconstrictor effect, sympathetic activation may augment the pulmonary transvascular fluid shift,25,27 an effect that is prevented by stellate ganglion blockade.10 Recent observations in humans suggest that a defect of nitric oxide synthesis may contribute to the exaggerated pulmonary hypertension in HAPE-prone subjects.1 In rabbits, nitric oxide synthase inhibition potentiates the pulmonary vasoconstrictor response to electrical stimulation of sympathetic nerves.28 Taken together, these observations could be consistent with the hypothesis that in HAPE-prone subjects, a defect in nitric oxide synthesis1 may potentiate the pulmonary vasoconstrictor response to the altitude-induced sympathetic overactivation.

At high altitude, hypoxemia was more severe in HAPE-prone than in HAPE-resistant subjects and may have contributed to the augmented sympathetic activation. The data at low altitude suggest, however, that this observation cannot be explained on the basis of more severe hypoxemia alone, because during short-term hypoxic breathing the sympathetic activation was exaggerated in HAPE-prone subjects even though hypoxemia was similar in the 2 groups. Ventilation attenuates the sympathetic response to hypoxia in humans.24 In the present studies, ventilation increased similarly during hypoxic breathing in both groups, indicating that differences in the hypoxia-induced sympathetic activation cannot be explained on the basis of differential inhibitory effects of ventilation. Our findings in HAPE-resistant subjects are consistent with earlier data showing that mild, short-term hypoxia causes little or no sympathetic activation in normal subjects.15,25 Finally, the exaggerated sympathetic responsiveness in HAPE-prone subjects appears to be specific for hypoxia (as evidenced by the normal responses to the cold pressor test and the Valsalva maneuver). It should be noted that in these studies, we measured sympathetic outflow targeted at the skeletal vasculature. One has to be cautious when extrapolating these findings to the pulmonary vascular bed. Further studies are needed to assess sympathetic responses targeted at the pulmonary vasculature and to establish causality between sympathetic activation and pulmonary vasoconstriction in such patients.

We do not know yet the exact mechanism by which high-altitude exposure leads to exaggerated pulmonary vasoconstriction in HAPE-prone subjects. What this study shows, however, is that in HAPE-prone subjects, both short-term and long-term exposure to hypoxia leads to exaggerated sympathetic vasoconstrictor activation, which is directly correlated with pulmonary artery pressure. We speculate that sympathetic overactivation could be one of the factors contributing to augmented pulmonary vasoconstriction and susceptibility to pulmonary edema at high altitude.

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References

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