Autonomic cardiovascular regulation in subjects with acute mountain sickness

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ACUTE MOUNTAIN SICKNESS (AMS) is a complex syndrome characterized by headache, gastrointestinal symptoms, weakness, insomnia, and certain neurological signs, including ataxia and changes in mental status (1). It may occur in subjects ascending to >2,500 m and is reported in 53% of those at >4,000-m altitude (6, 22).

AMS is generally harmless and transient but may occasionally progress to the more serious life-threatening cerebral and pulmonary forms of mountain sickness, i.e., high-altitude cerebral and pulmonary edema (1, 6).

The exact mechanism causing AMS is unknown, although the prevailing hypothesis points to a process within the central nervous system (1), possibly an altered adaptation to the neurohumoral and hemodynamic adjustments during hypoxia (8). A marked increase in peripheral sympathetic activity is a common feature of mountain sickness (4, 11) and has also been suggested to contribute to the genesis of high-altitude pulmonary edema (4). Whether autonomic hyperactivation may play a role in the genesis of AMS is not known.

The autonomic nervous system plays a role in the modulation of the oscillatory behavior of the cardiovascular system (23, 32a). Spectral analysis of variability in the R-R interval is a recognized tool that allows quantification of the oscillatory components, which in short-term recordings appear mainly organized into two frequency bands: low-frequency (LF, ~0.1 Hz) and high-frequency (HF, >0.15 Hz) respiratory bands. Although the HF rhythm primarily reflects the respiratory-driven vagal modulation of sinus rhythm (32a), the nonrespiratory LF rhythm appears to have a widespread neural genesis (26) and, in normalized units (NU), apparently mainly reflects the sympathetic modulation of the heart (23, 26, 32a), as well as the baroreflex responsiveness to the beat-to-beat variations in arterial blood pressure (BP) (30). During exposure to high altitude, R-R variability is reduced with a relative increase in the LF component (2, 12, 13), suggesting an increased sympathetic modulation of the sinus node in response to hypobaric hypoxia. Little is known about whether this pattern is influenced and/or modified by AMS. One study showed that AMS induced by early exposure to simulated altitude is accompanied by increased LF-to-HF ratio of R-R variability (21). Studies conducted on site (i.e., high altitude) and in response to more prolonged exposures are lacking.

In the present study, we have evaluated whether subjects with AMS at high altitude have signs of autonomic dysfunction compared with subjects without AMS. We also sought to verify whether cardiovascular autonomic variables at baseline and in response to acute hypoxia at low altitude might help identify subjects with AMS.

METHODS

Population

Forty-one nonacclimatized healthy mountaineers (10 women and 31 men, age 37 ± 10 yr) participated in the study after reaching the research laboratory in the Cappanna Regina Margherita at 4,559-m altitude on Monte Rosa in the Italian Alps. Only mountaineers who

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reached the top within 22 h were enrolled. Subjects ascended from 1,200 to 3,200 m by cable car, slept one night at 3,647 m, and reached the research station on the following morning.

A subset of 21 subjects repeated the evaluation at low altitude (320 m), at the Salvatore Maugeri Foundation, after 3 mo.

All subjects agreed to participate in the study, which was approved by the Institutional Ethics Committee.

Data Collection

High altitude. Subjects were evaluated 2–4 h after reaching the research laboratory. The evaluation consisted of a medical history and physical examination, including arterial O₂ saturation by pulse oximetry and arterial BP measurements. A 12-lead ECG (Esatoe Biomedica P80, Marquette) and a posterior-anterior chest radiograph (Euroastre Miniblock 100/30) were also obtained to verify the possible appearance of cardiac or pulmonary abnormalities in association with AMS.

Subjects were scored according to the Lake Louise AMS scoring system, which includes a self-reported questionnaire related to the presence and severity of symptoms and a clinical assessment (29). The Lake Louise score was obtained by adding the score of the clinical section to the self-reported questionnaire. AMS was defined by a score ≥3 (29).

Autonomic cardiovascular function was assessed by analysis of R-R interval and BP variability. Ten-minute recordings of ECG, respiration, and continuous BP were made in the supine position, after 20 min of rest in the same position. The recording system consisted of a bedside monitor (model HP78354A, Hewlett-Packard) providing a three-lead ECG and respiratory signals by the impedance method. BP was measured by finger probe plethysmography (Finapres model 2300, Ohmeda). Data were stored for subsequent analysis.

Low altitude. At low altitude, subjects underwent physical examination, ECG, and autonomic function assessment as described above. The autonomic assessment was performed at rest (baseline) and during short-term hypoxic hypoxia with a 12% O₂-in-N₂ gas mixture (4), which the subjects breathed by mouth from a 120-liter reservoir bag. At 20 min after instrumentation, the subjects were exposed to 15 min of hypoxic gas, the first 5 min serving to reach a steady state.

Data Analysis

Cardiovascular variability was analyzed in the time and frequency domains (23, 32a). Power spectrum analysis was applied to R-R variability. The LF and HF components of R-R variability were calculated in absolute values (LFRR and HFRR) and as normalized units (LFRRNU and HFRRNU), which were obtained by dividing the power of each spectral peak by total variance, from which the very-LF values were considered. The LF component of the R-R variability in normal sinus rhythm and allowing classification into LF (0.04 – 0.15 Hz) and HF (0.15 – 0.5 Hz) bands. The LF and HF components of R-R variability were standardized by multiplying them by 100 (23). The LF-to-HF ratio was also considered.

The LF component of the SBP variability (LFSBP) was used to evaluate the presence of interaction. P ≤ 0.05 was considered significant.

RESULTS

High Altitude

Seventeen subjects (41%) had AMS, as indicated by a Lake Louise score ≥3 (range 3–8). Headache and difficulty sleeping were the most frequent symptoms of AMS (67% and 72%, respectively), followed by gastrointestinal symptoms (33%), fatigue and dizziness (both 28%), and ataxia (5%)

There was no difference in the time of evaluation of subjects with and without AMS. The incidence of AMS between men and women was not statistically different (Table 1). Symptomatic subjects were older and more frequently had a previous history of AMS. No subjects showed ECG evidence of myocardial ischemia or arrhythmias at high altitude. Five subjects showed right-axis deviation with clockwise rotation, and three subjects showed left-axis deviation. However, these findings did not correlate with the presence of AMS. In eight subjects, including five with AMS, pulmonary auscultation showed mild rales in the absence of any radiographic signs of pulmonary edema.

Subjects with AMS tended to have a lower O₂ saturation than those without AMS (Table 1). The two groups had similar R-R interval, arterial BP, and R-R variance. LFRR tended to be lower and HFRR tended to be higher in subjects with AMS than in those without AMS [P = not significant (NS)]. LFRRNU was significantly lower (P = 0.001) and HFRRNU was signifi-

Table 1. Demographic, clinical, and autonomic characteristics at high altitude in subjects with and without AMS

<table>
<thead>
<tr>
<th></th>
<th>Without AMS (n = 24)</th>
<th>With AMS (n = 17)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>34 ± 2</td>
<td>43 ± 2</td>
<td>0.007</td>
</tr>
<tr>
<td>Gender, F/M</td>
<td>4/20</td>
<td>6/11</td>
<td></td>
</tr>
<tr>
<td>History of AMS</td>
<td>1</td>
<td>7</td>
<td>0.04</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>125 ± 3</td>
<td>121 ± 4</td>
<td></td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>79 ± 2</td>
<td>77 ± 2</td>
<td></td>
</tr>
<tr>
<td>MFBp, mmHg</td>
<td>94 ± 2</td>
<td>91 ± 3</td>
<td></td>
</tr>
<tr>
<td>Sao₂, %</td>
<td>80 ± 1</td>
<td>78 ± 1</td>
<td></td>
</tr>
<tr>
<td>Mean R-R, ms</td>
<td>751 ± 29</td>
<td>722 ± 24</td>
<td></td>
</tr>
<tr>
<td>Variance R-R, ms²</td>
<td>1,026 ± 226</td>
<td>896 ± 494</td>
<td></td>
</tr>
<tr>
<td>LF, ms²</td>
<td>436 ± 103</td>
<td>288 ± 98</td>
<td></td>
</tr>
<tr>
<td>HF, ms²</td>
<td>102 ± 37</td>
<td>157 ± 43</td>
<td></td>
</tr>
<tr>
<td>LFRRNU</td>
<td>73 ± 5</td>
<td>43 ± 7</td>
<td>0.001</td>
</tr>
<tr>
<td>HFRRNU</td>
<td>16 ± 3</td>
<td>31 ± 7</td>
<td>0.02</td>
</tr>
<tr>
<td>LF/HF</td>
<td>8.3 ± 1.4</td>
<td>3.4 ± 1.3</td>
<td>0.052</td>
</tr>
<tr>
<td>LFRR, mmHg²</td>
<td>5.2 ± 1.2</td>
<td>12.2 ± 2.8</td>
<td>0.016</td>
</tr>
<tr>
<td>Respiratory frequency, Hz</td>
<td>0.302 ± 0.02</td>
<td>0.283 ± 0.02</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE. AMS, acute mountain sickness; F, female; M, male; SBP, DBP, and MBP, systolic, diastolic, and mean blood pressure; Sao₂, arterial O₂ saturation; R-R, R-R interval; LF and HF, low and high frequency; LFRRNU and HFRRNU, LF and HF components of R-R variability in normalized units; LFSSBP, LF component of SBP.
significantly higher ($P = 0.02$) in subjects with AMS than in those without AMS. The LF-to-HF ratio was lower in subjects with AMS ($P = 0.052$). By contrast, the LF component of SBP (LFSBP) was higher in subjects with AMS than in those without AMS ($P = 0.016$).

The Lake Louise score correlated directly with age and LFSBP and inversely with LFRRNU (Fig. 1) after adjustment for age. No correlation was found between age and LFRRNU. Figure 2 shows the autospectra of cardiovascular variability and respiration in a subject with particularly severe AMS and a subject without AMS. In the subject with AMS, the markedly reduced $O_2$ saturation was accompanied by important tachycardia and absence of LF components in R-R variability.

**Baseline Data and Changes From Baseline to High Altitude**

Twenty-one subjects (5 women and 16 men, 38 ± 12 yr) completed the protocol at low altitude. This cohort was highly representative of the original cohort of 41 subjects (Table 2). Nine subjects (43%) had AMS at high altitude. Subjects with AMS had significantly higher SBP and mean BP, but not diastolic BP, than those without AMS: SBP = 127 ± 3 vs. 118 ± 2 mmHg ($P = 0.02$), mean BP = 97 ± 5 vs. 91 ± 5 mmHg ($P = 0.02$), and diastolic BP = 82 ± 2 vs. 78 ± 2 mmHg ($P = \text{NS}$). Baseline mean BP correlated with AMS score at high altitude after adjustment for age ($R = 0.5, P = 0.03$), although age did not correlate with AMS score after adjustment for mean BP.

The comparison between baseline low and high altitude showed a tendency for greater $O_2$ desaturation in subjects with AMS (from 98 to 77%) than in those without AMS (from 99 to 82%; state effect: $F = 2.9, P = 0.05$; group × state interaction: $F = 3.9, P = 0.09$). Cardiovascular measures at baseline and high altitude in subjects with and without AMS are shown in Fig. 3. At baseline, mean R-R interval and cardiovascular variability measures were similar in the two groups of subjects with and without AMS. R-R interval and R-R variance decreased similarly in the two groups (Fig. 3; for both variables, group × state interaction: $P = \text{NS}$). LFRRNU increased significantly only in subjects without AMS ($P < 0.001$), although in subjects with AMS it did not change between baseline and high altitude (group × state interaction: $F = 6.97, P = 0.017$). HFRRNU decreased markedly in subjects without AMS and slightly in subjects with AMS (Fig. 3; group × state interaction: $F = 2.9, P = 0.1$). LFSBP was increased in both groups: slightly in subjects without AMS ($\sim 1$ mmHg$^2$) and more markedly in subjects with AMS ($\sim 5$ mmHg$^2$). However, no group × state interaction was observed ($F = 3.0, P = 0.09$).

**Short-Term Hypoxia at Low Altitude**

$O_2$ saturation did not differ between the two groups during short-term hypoxia at low altitude (84 ± 1.1 and 82 ± 1%, respectively, in subjects with and without AMS, $P = 0.24$). Cardiovascular variability parameters at baseline and during short-term hypoxia are shown in Fig. 4. In both groups, R-R interval (state effect: $F = 3.8, P < 0.0001$) and R-R variance (state effect: $F = 4.04, P = 0.058$) decreased from baseline to hypoxia (for both variables, state × group interaction: $P = \text{NS}$). LFRRNU showed a tendency for greater O2 desaturation in subjects with particularly severe AMS and a subject without AMS: SBP from 98 to 77% than in those without AMS (from 99 to 82%).

**DISCUSSION**

Our findings are as follows: 1) At high altitude, R-R variability decreased compared with low altitude in subjects with and without AMS, with a persistent relative predominance of the LF components of R-R variability. 2) Subjects with AMS
had an abnormal pattern of cardiovascular variability compared with subjects without AMS. For instance, AMS was accompanied by higher LFSBP but lower LFRRNU and higher HFRRNU. Compared with low altitude, LFRRNU was significantly increased in high altitude only in subjects without AMS.

Cardiovascular Variability and AMS

The effect of high altitude on the cardiovascular, respiratory, and cerebrovascular systems is complex and not fully understood. Increased sympathetic activity is a part of the integrated physiological response to a hypoxic stimulus (10, 31). In the present study, we observed, in association with acute hypobaric hypoxia, an increase in heart rate, a reduction in R-R variability, and a relative increase of LFRRNU in asymptomatic subjects, consistent with a sympathetic predominance in the neural inputs to the heart and in agreement with previous studies conducted at high altitude (2, 12, 13). Little is known about the effect of AMS on the autonomic cardiovascular regulation. Loeppky et al. (21) recently reported a higher LF-to-HF ratio in subjects with AMS after 6 h of simulated altitude, which suggests an increased cardiac sympathetic drive in association with AMS during early exposure to simulated altitude. In the present study, conducted in the field after 22 h of exposure to altitude, we observed a lower LF-to-HF ratio with lower LFRRNU.

Table 2. Demographic and high-altitude clinical and autonomic characteristics of the original cohort and the subgroup of subjects

<table>
<thead>
<tr>
<th></th>
<th>Original Cohort (n = 41)</th>
<th>Subgroup (n = 21)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>38 ± 2 (37)</td>
<td>38 ± 3 (36)</td>
<td>0.84</td>
</tr>
<tr>
<td>Gender, F/M</td>
<td>10/41</td>
<td>5/21</td>
<td>0.83</td>
</tr>
<tr>
<td>AMS, n</td>
<td>25 (40%)</td>
<td>9 (43%)</td>
<td>0.90</td>
</tr>
<tr>
<td>$\text{SaO}_2$, %</td>
<td>79 ± 1 (80)</td>
<td>79 ± 1.1 (80)</td>
<td>0.41</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>123 ± 2 (120)</td>
<td>124 ± 4 (18)</td>
<td>0.88</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>78 ± 2 (80)</td>
<td>77 ± 2 (78)</td>
<td>0.69</td>
</tr>
<tr>
<td>Mean R-R, ms</td>
<td>739 ± 19 (713)</td>
<td>747 ± 30 (756)</td>
<td>0.80</td>
</tr>
<tr>
<td>Variance R-R, ms²</td>
<td>973 ± 150 (656)</td>
<td>835 ± 150 (569)</td>
<td>0.73</td>
</tr>
<tr>
<td>LF, ms²</td>
<td>404 ± 77 (175)</td>
<td>313 ± 96 (153)</td>
<td>0.81</td>
</tr>
<tr>
<td>HF, ms²</td>
<td>135 ± 30 (40)</td>
<td>72 ± 24 (30)</td>
<td>0.18</td>
</tr>
<tr>
<td>LFRRNU</td>
<td>61 ± 5 (68)</td>
<td>64 ± 4 (67)</td>
<td>0.94</td>
</tr>
<tr>
<td>HFRRNU</td>
<td>22 ± 3 (19)</td>
<td>24 ± 3 (11)</td>
<td>0.89</td>
</tr>
<tr>
<td>LF-to-HF ratio</td>
<td>6.35 ± 1.2 (3.2)</td>
<td>6.8 ± 1.7 (6.4)</td>
<td>0.78</td>
</tr>
<tr>
<td>LFSBP, mmHg²</td>
<td>8.2 ± 71.5 (5.2)</td>
<td>8.9 ± 1.7 (6.5)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Values are means ± SE, with median in parentheses, unless otherwise noted. See Table 1 footnote for definition of abbreviations.

Fig. 2. Power spectra of R-R interval, systolic blood pressure (SBP), and respiration (Resp) at baseline at low and high altitude in subject 1 (without acute mountain sickness (AMS)) and subject 2 (with AMS). Subject 2, at high altitude, demonstrated more marked hypoxemia, lower R-R interval, and more markedly reduced R-R variance with a relatively blunted LF component of R-R variability than subject 1. PSD, power spectrum density; HF, high frequency; $\text{SaO}_2$, arterial O₂ saturation; mRR, mean R-R interval.
NU and higher HFRRNU in subjects with AMS, which may instead suggest a blunted sympathetic modulatory effect of the sinus node in this condition. Simulated vs. real altitude and a different proportion of women (64% in the study of Loeppky et al. vs. 25% in ours) might be factors in the differences observed in the two studies. Different duration of exposure to hypobaric hypoxia and/or of mountain sickness might also influence the autonomic response in subjects with AMS. In-

![Graphs showing autonomic changes from baseline (i.e., low altitude) to high altitude in subjects with and without AMS (ANOVA with repeated measures). R-R interval and R-R variance decreased similarly in both groups. LFRRNU increased at high altitude only in subjects without AMS. LFSSBP increased markedly in subjects with AMS and slightly in subjects without AMS.]

Fig. 3. Autonomic changes from baseline (i.e., low altitude) to high altitude in subjects with and without AMS (ANOVA with repeated measures). R-R interval and R-R variance decreased similarly in both groups. LFRRNU increased at high altitude only in subjects without AMS. LFSSBP increased markedly in subjects with AMS and slightly in subjects without AMS.
Indeed, in the study of Loepky et al. the LF-to-HF ratio, after the early peak at 6 h of exposure, was progressive reduced in the following hour. Whether this trend would have persisted to become smaller in subjects with AMS than in those without AMS with more prolonged exposure to altitude is not known.

Finally, environmental and/or cardiovascular effects of the previous exercise could have been implicated in the autonomic pattern observed in subjects with AMS in our study. However, subjects with and without AMS were studied in the same conditions and after a similar recovery time after exercise.

Fig. 4. Autonomic changes from baseline to short-term hypoxia at low altitude in subjects with and without AMS (ANOVA with repeated measures). R-R interval and R-R variance decreased similarly in both groups. LF_RRNU slightly increased in both groups. LF_SBP markedly increased only in subjects with AMS and remained unchanged in subjects without AMS.
Therefore, exercise and environmental factors would not explain the differences in autonomic cardiovascular function that were observed in association with AMS in our study.

In our study, we observed particularly blunted LF_{RRNU} in the subjects with the most severe AMS, who also had more severe hypoxemia and tachycardia (Fig. 2), showing a pattern similar to that commonly observed in advanced heart failure (33). In heart failure, the oscillatory components of heart rate variability can be absent or extremely low in the power spectrum in the presence of a higher sympathetic drive (5, 33). A loss of sensitivity of the sinus node secondary to excessive sympathetic neurohumoral activity has been proposed to be one of the factors at the origin of reduced LF in heart failure (5). Increased neural and humoral sympathetic activities have been reported as features of established AMS (4, 11, 21). We may speculate that, as in heart failure, a loss of sensitivity of the sinus node secondary to excessive and more sustained sympathetic neurohumoral activity could explain the blunted LF_{RRNU} we observed in subjects with AMS. Episodes of interacting cardiovagal hyperactivity and generalized sympathetic hyperactivity, as represented by higher LF_{SBP}, cannot be excluded (23).

LF_{SBP} was higher in subjects with AMS than in those without AMS (Table 1). BP variability, and more specifically LF_{SBP}, is influenced by a multitude of physiological factors (17), which in the short-term include excitatory vasoconstrictive neural mechanisms, modulatory effects of baroreflex, and local effects of the nitric oxide system (16, 24, 27, 34). However, despite this composite origin, LF_{SBP} is commonly considered a marker of overall sympathetic influence to the vascular system (23). Therefore, enhanced LF_{SBP} in AMS may reflect overall an enhanced vascular sympathetic influence in this condition.

Hypoxia seems to add to the complexity of BP and BP variability regulation acting through neural and nonneural mechanisms (35) to induce vasoconstrictive α-mediated and vasodilatory β-mediated adrenergic mechanisms and, possibly, alterations in nitric oxide production. How all these mechanisms interact in inducing the observed increase in LF_{SBP} in AMS requires further investigations.

Age and AMS

We observed that subjects with AMS were slightly older than those without AMS, in agreement with a previous large study at the same altitude (22). Age correlated weakly, although significantly, with AMS score. By contrast, age and LF_{RRNU} showed no correlation. In addition, LF_{RRNU} correlated with AMS score also after adjustment for age, suggesting that age and autonomic function are independently associated with AMS.

Cardiovascular Variability at Low Altitude.

In a previous report by Rathat et al. (28), heart rate response to hypoxia in resting conditions did not predict the presence of AMS. We observed that also more sensitive indexes of R-R variability at low altitude were unable to identify subjects with AMS at baseline or during short-term hypoxia. Specifically, R-R variance, LF_{RRNU}, HF_{RRNU}, and LF-to-HF ratio at baseline and during short-term hypoxia were highly similar in the two groups (Fig. 4). A shorter duration of the exposure to hypoxia, a less profound degree of O2 desaturation, and/or a different ventilatory pattern at low altitude and high altitude (10, 25, 31) could account for the inability to elicit in AMS subjects during short-term hypoxia the same response observed at high altitude. Conversely, it could also be possible that subjects with AMS have preserved sympathetic cardiac modulation at rest and in response to hypoxia and that the LF_{RRNU} abnormalities observed at high altitude are secondary to established mountain sickness (7, 15).

Subjects with AMS had higher resting blood pressure at low altitude and showed a significant increase in LF_{SBP} during short-term hypoxia, which by contrast remained stable in subjects without AMS (Fig. 4). LF_{RRNU} and LF_{SBP} behaved differently in subjects with AMS during hypoxia (Fig. 4), possibly reflecting different regulatory influences of chemoreceptors (primarily influencing the vascular system) and increased ventilation (primarily influencing heart function) in this condition (25). Hence, the enhanced LF_{SBP} during short-term hypoxia in subjects with AMS might be a reflection of an enhanced chemoreflex vasoconstrictor response to hypoxia. Enhanced peripheral sympathetic nerve activity in response to hypoxic breathing has been reported to characterize subjects prone to high-altitude pulmonary edema (4). Therefore, an exaggerated vasoconstrictor chemoreceptor reflex response to hypoxia seems to be a constant factor implicated in the maladaptation to high altitude resulting in mountain sickness.

We observed a correlation of resting blood pressure to severity of AMS. Larger studies are needed to clarify whether and at which level arterial BP may predict the development of AMS.

We also observed that resting blood pressure was correlated with the LF_{SBP} response to short-term hypoxia in a dose-response relation. Higher chemoreflex sympathetic nerve activity to the muscle vessels has been reported in borderline young hypertensive subjects (32), who also have a reduced tolerance to simulated altitude (19). Therefore, an exaggerated sympathetic chemoreflex response could be a factor in the increased susceptibility to AMS in subjects with higher (although still in the normal range) blood pressure. How an increased sympathetic activity might be implicated in the genesis of AMS remains to be clarified.

At high altitude, blood pressure was similar between the subjects with and without AMS. The reason for this apparent discrepancy is not clear. The blood pressure response to hypoxia results from the complex interaction between several factors, including the effects of chemoreflexes (vasoconstriction), hyperventilation (vasodilation), and central and peripheral (local) contrasting effects of hypoxia and hypocapnia (10, 25, 31, 35). Perhaps an increased sympathetic drive to the vasculature in subjects with AMS is counteracted by a local vasodilatory effect resulting from more severe hypoxia (25).

Limitations

The limitations of the study are as follows: 1) Subjects might have been studied too soon after a strong physical effort at high altitude to be considered at baseline at high altitude. However, this would not explain the differences in autonomic cardiovascular function that were observed in association with AMS. 2) Low-altitude evaluation was performed after the high-altitude evaluation. Long-term effects...
of AMS could have potentially affected the results obtained at low altitude. However, subjects were completely asymptomatic at the time of the evaluation, which was performed 3 mo later, during which no other exposure to high altitude had occurred. 3) Only half of the original cohort repeated the evaluation at low altitude. Low statistical power could explain the lack of statistically significant interaction in LF\textsubscript{RRI}NU during hypoxic test at low altitude and in LF\textsubscript{SBP} from low to high altitude. However, to our knowledge, our study population is the largest ever reported to address autonomic cardiovascular physiology at high altitude.

We conclude that autonomic cardiovascular function is altered in subjects with AMS. The degree of autonomic compromise appears to be related to the severity of symptoms.

A higher vasomotor response to hypoxia seems to identify subjects prone to develop AMS and suggests that an exaggerated chemoreflex sympathetic vascular response is potentially implicated in the genesis of AMS.

Clinical Implications

Morbidity and mortality are significant among visitors to high altitude. A survey of deaths from all causes among mountain hikers in the Alps showed that 30% of all deaths were sudden, that >50% occurred in men >60 yr of age, and that risk increased with degree of physical exertion (3). Coronary artery disease is believed to be the main cause of exercise-related deaths at high altitude (20). Depressed R-R variability predicts cardiac mortality after myocardial infarction (14). Blunted LF\textsubscript{RRI}NU in heart failure predicts sudden death (18). Therefore, the autonomic derangement that accompanies AMS could potentially increase the risk of life-threatening arrhythmias in predisposed subjects and could be an important cofactor in the cardiac deaths reported in older people at high altitude. The autonomic cardiovascular response to short-term hypoxia could represent a low-cost noninvasive test to help identify, among subjects with coronary artery disease, those who are at risk for AMS.

ACKNOWLEDGMENTS

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