B-type natriuretic peptide, vascular endothelial growth factor, endothelin-1, and nitric oxide synthase in chronic mountain sickness

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The pathogenesis of chronic mountain sickness (CMS) may involve vasoactive peptides. The aim of this study was to investigate associations between CMS and levels of B-type natriuretic peptide (BNP), vascular endothelial growth factor (VEGF), endothelin-1 (ET-1), and endothelial nitric oxide synthase (eNOS). A total of 24 patients with CMS and 50 control subjects residing at 4,300 m participated in this study. Mean pulmonary arterial pressure (mPAP) was measured by echocardiography. Serum BNP, VEGF, ET-1, and eNOS were measured. Receiver operator characteristic curves to assess the balance of sensitivity and specificity for CMS were constructed. As a result, patients with CMS had significantly greater mPAP compared with controls and had lower arterial O2 saturation (SaO2). Both BNP and ET-1 correlated positively with mPAP and negatively with SaO2, whereas serum VEGF levels were inversely correlated with SaO2; eNOS correlated negatively with mPAP and positively with SaO2. Median concentrations of BNP were greater in patients with CMS compared with those without CMS: 369 pg/ml [interquartile range (IQR) = 336–431] vs. 243 pg/ml (IQR = 216–279); P < 0.001. Similarly, concentrations of VEGF [543 pg/ml (IQR = 446–546) vs. 243 pg/ml (IQR = 216–279); P < 0.001] and ET-1 [14.7 pg/ml (IQR = 12.5–17.9) vs. 11.1 pg/ml (IQR = 8.7–13.9); P = 0.05] were higher in those with CMS compared with those without, whereas eNOS levels were lower in those with CMS [8.9 pg/ml (IQR 7.59–10.8) vs. 11.2 pg/ml (9.13–13.1); P < 0.001]. The areas under the receiver operator characteristic curves for diagnosis of CMS were 0.91, 0.93, 0.77, and 0.74 for BNP, VEGF, ET-1, and eNOS, respectively. In age- and biomarker-adjusted logistic regression, BNP and VEGF were positively predictive of CMS, whereas eNOS was inversely predictive. In conclusion, severe chronic hypoxemia and consequent pulmonary hypertension in patients with CMS may stimulate release of natriuretic peptides and angiogenic cytokines. These vasoactive peptides may play an important role in the pathogenesis and clinical expression of CMS and may indicate potential prognostic factors in CMS that could serve as targets for therapeutic trials or clinical decision making.

CHRONIC MOUNTAIN SICKNESS (CMS) is characterized by hypoxemia, excessive polycythemia, and pulmonary hypertension. The prevalence of CMS is greater in men than in women, rises with increasing altitude equally in both sexes, and is lower in Tibetan natives compared with Han Chinese or Peruvians (22). Increasing age, nocturnal oxygen desaturation, and obesity have proven to be additional risk factors in the development of this syndrome. High-altitude hypoxia is an etiologic key to the development of this disease, but the exact mechanisms underlying the pathogenesis are not fully understood.

B-type natriuretic peptide (BNP) is a cardiac neurohormone, secreted from cardiac myocytes in response to volume and pressure overload; BNP may be a useful biochemical marker for cardiac failure (5, 10). BNP levels may be elevated in association with pulmonary hypertension in patients with chronic lung disease and primary pulmonary hypertension, whereas another described trigger for BNP is hypoxia. However, there are no reports of studies concerning BNP and its association with CMS. Vascular endothelial growth factor (VEGF) is a hypoxia-induced protein that can increase vascular permeability and may contribute to the development of acute mountain sickness by increasing cerebral capillary permeability (28), yet its role in CMS is undefined. Endothelin-1 (ET-1) and endothelial nitric oxide (NO) synthase (eNOS) are a pair of antagonistic peptides present in endothelial cells, and the balance between NO and ET-1 may contribute to an altered vasomotor function on the pulmonary vasculature (4, 8), and its role in the pathogenesis of CMS is also yet to be defined.

The aim of this study was to evaluate the associations between CMS, particularly high-altitude pulmonary hypertension and concentrations of BNP, VEGF, ET-1, and eNOS, to enhance an understanding of the relationship between chronic high-altitude hypoxia and vasoactive peptides. Our hypothesis was that the excessive chronic hypoxemia in patients with CMS would be associated with increased BNP, ET-1, and lowered eNOS, which together may contribute to pulmonary hypertension and overload of the right ventricle; thus, the vasoactive peptides would be associated with the presence and severity of CMS.

METHODS

Subjects. The research protocol was approved by the human subject protection committee at the Medical College of Qinghai University. Informed consent was obtained from each subject.

Twenty-four patients with CMS (16 Han Chinese and 8 Tibetans; mean age, 42 ± 3 years; and 50 control subjects (10 Han Chinese and 14 Tibetans; mean age, 39 ± 14 years) participated in this study, performed in Maduo County of Qinghai province, altitude 4,300 m. The Han subjects were born at lowland or moderate altitude and had resided at high altitude for 10.4 ± 5.6 years. Six Tibetans with CMS were born at an altitude of 2,300 m and had lived in Maduo at an altitude of 4,300 m for the preceding 15 to 20 years. Most Tibetans in the control...
group were nomads and permanently lived at altitudes of 4,500 to 5,000 m. Body mass index was calculated as weight in kilograms divided by the square of height in meters (kg/m²). None of the participants had a history of respiratory or cardiovascular disease, such as chronic obstructive pulmonary disease, pulmonary infection, asthma, shunt, valvular disease, congenital heart disease, or hypertensive heart disease.

Assessment of CMS. Each participant completed a CMS self-report questionnaire. The evaluation tool used was the Qinghai CMS score (14), established during the World Congress in 2004. The questionnaire criteria included headache, dizziness, breathlessness, palpitations, sleep disturbance, cyanosis, tinnitus, paresthesias, and venous dilatation. Each criteria was graded on a scale from 0 to 3, with 0 representing no symptoms; 1, mild symptom; 2, moderate symptoms; and 3, severe symptoms. Hemoglobin (Hb) concentration was represented as non-CMS. The evaluation tool used was the Qinghai CMS score (14), established during the World Congress in 2004.

Blood sampling and assay. Blood samples were drawn from all participants (n = 74) and analyzed for BNP, VEGF, eNOS, and ET-1. A 5-ml blood sample was drawn from the brachial vein, collected into a serum separator tube, and allowed to set for 15 min at 4°C before centrifugation (3,000 rpm for 10 min). The serum sample was stored in liquid nitrogen during transport to Xining for analysis.

Serum BNP was measured with a sandwich enzyme immunoassay (USCN Life and Technology, Missouri City, TX). The measurable range of the BNP assay was 5 to 1,200 pg/ml. The intra-assay and interassay of coefficients were 6.6 and 13%, respectively. Serum VEGF was measured with an enzyme-linked immunoassay kit (D&R system). The measurable range of the VEGF assay was 31.2 to 2,000 pg/ml. The intra-assay and interassay coefficients of variation were 6.7 and 8.8%, respectively. Serum levels of ET-1 were determined using a commercially available sandwich enzyme immunoassay kit (USCN Life and Technology). The measurable range of the ET-1 was 15.6 to 1,000 pg/ml. The intra-assay and interassay coefficients of variation were 5.6 and 11%, respectively. Serum levels of eNOS were determined using a commercially available sandwich enzyme immunoassay kit (USCN Life and Technology). The measurable range of the eNOS assay was 12 to 1,000 pg/ml. The intra-assay and interassay coefficients of variation were 6.6 and 12.5%, respectively.

Statistical analysis. Data are expressed as means ± SD or as medians with interquartile range in states of nonnormality as identified through the use of the Kolmogorov-Smirnov test. Comparisons of various parameters between the two groups were made by the Fisher protected least significant difference test at the 95% significant level, whereas nonnormal continuous variables were compared using the Wilcoxon's rank sum test. A Student’s unpaired t-test was used in comparing the CMS and control groups. A linear regression analysis was used to assess the correlation between variables; in states of nonnormality, log-transformed data were used for correlations. Following this, multivariable linear regression identified independent predictors of dependent continuous variables. Bonferroni correction was applied in the context of multiple comparisons. Receiver operator characteristic (ROC) curves (Analyze-it; Leeds, UK) examined the value of BNP, VEGF, and ET-1 for the diagnosis of CMS, with area under the curve established and expressed with 95% confidence intervals (CI). Finally, age and biomarker-adjusted logistic regression assessed independent associations between CMS and biomarkers and were expressed with odds ratios (OR) with 95% CI. A P value < 0.05 was held to represent significance. Statistics were done using SPSS software (version 13.0; Chicago, IL).

Table 2. Comparisons of various parameters between Han Chinese and Tibetans

<table>
<thead>
<tr>
<th></th>
<th>Han Chinese</th>
<th>Tibetans</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>28</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>39.7 ± 11.3</td>
<td>41.3 ± 13.7</td>
<td>0.469</td>
</tr>
<tr>
<td>Height, cm</td>
<td>160 ± 7.5</td>
<td>155 ± 7.5</td>
<td>0.053</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>67.6 ± 9.7</td>
<td>58.4 ± 9.3</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.29 ± 2.9</td>
<td>21.98 ± 2.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Hemoglobin, g/dl</td>
<td>19.4 ± 3.1</td>
<td>16.58 ± 1.7</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>78.75 ± 13.6</td>
<td>77.57 ± 13.9</td>
<td>0.270</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>86.75 ± 3.6</td>
<td>88.74 ± 3.3</td>
<td>0.017</td>
</tr>
<tr>
<td>BNP, pg/ml</td>
<td>326.44 ± 90.5</td>
<td>237.61 ± 73.3</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>VEGF, pg/ml</td>
<td>331.68 ± 95.2</td>
<td>252.95 ± 89.3</td>
<td>0.054</td>
</tr>
<tr>
<td>ET-1, pg/ml</td>
<td>13.26 ± 3.5</td>
<td>11.75 ± 3.2</td>
<td>0.063</td>
</tr>
<tr>
<td>NOS, pg/ml</td>
<td>9.5 ± 3.5</td>
<td>11.42 ± 3.1</td>
<td>0.052</td>
</tr>
<tr>
<td>mPAP, mmHg</td>
<td>25.33 ± 7.8</td>
<td>19.97 ± 7.4</td>
<td>0.004</td>
</tr>
<tr>
<td>RVEF, %</td>
<td>0.52 ± 0.9</td>
<td>0.54 ± 0.1</td>
<td>0.486</td>
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</table>

Values are means ± SD unless otherwise specified; N, number of subjects. BNP, B-type natriuretic peptide; ET-1, endothelin-1; NOS, nitric oxide synthase.
RESULTS

**General characteristics.** General characteristics of subjects with and without CMS are shown in Table 1. In this study, most of the subjects with CMS were Han Chinese and only four patients with CMS were natives. The results of the CMS scoring guideline indicated 7 subjects with mild, 11 with moderate, and 6 with severe illness. Table 2 shows the comparison of physiological characteristics between Han Chinese and Tibetans; the two groups were similar in terms of age, but the Han Chinese group had a higher Hb concentration, higher mPAP levels, and lower SaO2 than the Tibetans, though the small (but real) number of Tibetans with CMS reduces the power of this comparison.

**Diagnostic tests in CMS vs. non-CMS.** Table 1 shows that there were no significant differences in vital capacity, percentage of forced expiratory volume in 1 s, and maximal voluntary ventilation values between the two groups, suggesting that subjects with and without CMS were absent of chronic obstructive pulmonary disease. However, a significantly decreased mean forced expiratory flow during the first half of the forced vital capacity (25–75%) was observed in the CMS group, which reflects that the small airway resistance in subjects with CMS is slightly higher when compared with subjects without CMS; this condition at high altitude is very common, especially in the patients with CMS (24).

The mPAP in the CMS group (27.4 ± 6.5 mmHg) was significantly higher than in the control group (20.1 ± 7.5 mmHg; P < 0.001). There was no significant difference in right ventricular ejection fraction between the two groups.

**Correlations.** Significant correlations existed between BNP and VEGF (r = 0.341; P = 0.003), BNP and ET-1 (r = 0.404; P < 0.001), BNP and eNOS (r = −0.377; P = 0.001), VEGF and ET-1 (r = 0.273; P = 0.02), and ET-1 and eNOS (r = −0.294; P = 0.01). Concentrations of eNOS also inversely correlated with Hb (r = −0.297; P = 0.01). Figure 1 shows that BNP, VEGF, and ET-1 are highly positive correlated to mPAP, whereas the eNOS was inversely correlated.

In a multivariable linear regression analysis, predictors of BNP values included VEGF concentrations (β = 0.254; P = 0.01), mPAP (β = 0.289; P = 0.005), SaO2 measured from pulse oximetry (β = −0.184; P = 0.05), and the presence of CMS (β = 0.642; P < 0.001). Ethnic origin (Han Chinese vs. Tibetans), which reduces the power of this comparison.

![Fig. 1. Association of B-type natriuretic peptide (BNP; A), VEGF (B), endothelin-1 (ET-1; C), and endothelial nitric oxide synthase (eNOS; D) to mean pulmonary arterial hypertension (mPAP) in high-altitude residents. A direct positive correlation was seen between mPAP and BNP, VEGF, and ET-1, whereas a negative correlation existed with eNOS.](http://ajpheart.physiology.org/)

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\includegraphics[width=\textwidth]{Fig1}
\caption{Association of B-type natriuretic peptide (BNP; A), VEGF (B), endothelin-1 (ET-1; C), and endothelial nitric oxide synthase (eNOS; D) to mean pulmonary arterial hypertension (mPAP) in high-altitude residents. A direct positive correlation was seen between mPAP and BNP, VEGF, and ET-1, whereas a negative correlation existed with eNOS.}
\end{figure}
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Tibetan) was not a predictor of BNP concentrations in this adjusted model ($\beta = -0.096; P = 0.30$).

Independent predictors of VEGF values included Hb concentrations ($\beta = 0.402; P = 0.005$), right ventricular ejection fraction ($\beta = -0.247; P = 0.002$), BNP values ($\beta = 0.397; P < 0.001$), $SaO_2$ measured from pulse oximetry ($\beta = -0.313; P = 0.001$), and presence of CMS ($\beta = 0.419; P = 0.006$); in this adjusted model, ethnic origin did not predict VEGF values ($\beta = 0.039; P = 0.78$). Independent predictors of ET-1 concentrations included only mPAP ($\beta = 0.282; P = 0.02$) and the presence of CMS ($\beta = 0.294; P = 0.01$). Following adjustment, only mPAP predicted eNOS values ($\beta = -0.478; P < 0.001$). Ethnic extraction did not predict either ET-1 or eNOS concentrations in these models ($\beta = -0.214, P = 0.10$; and $\beta = 0.035, P = 0.74$, respectively).

**Biomarkers and diagnosis of CMS.** Serum BNP, VEGF, and ET-1 levels were significantly higher in the CMS group than in the controls, whereas eNOS values were lower in those with CMS compared with those without (Fig. 2). ROC analyses (Fig. 3) demonstrated an area under the curve of 0.91 (95% CI $0.83–0.98; P < 0.0001$) for BNP, 0.93 (95% CI $0.86–1.0; P < 0.0001$) for VEGF, 0.77 (95% CI $0.66–0.88; P < 0.0001$) for ET-1, and 0.74 (95% CI $0.63–0.86; P < 0.0001$) for eNOS. In addition, according to the definition of high-altitude pulmonary hypertension (mPAP $\geq 30$ mmHg) as defined by the Qinghai CMS consensus, 16 subjects (12 CMS, and 4 controls) were diagnosed with high-altitude pulmonary hypertension. When compared with those without high-altitude pulmonary hypertension, among these patients, there were only small differences in blood Hb levels (19.6 vs. 18.1 g/l; $P = 0.132$); however, patients with high-altitude pulmonary hypertension had higher median BNP (376 vs. 237 pg/ml; $P < 0.001$), VEGF (488 vs. 260 pg/ml; $P < 0.001$), and ET-1 (15.7 vs. 11.8 pg/ml; $P = 0.01$) concentrations, whereas eNOS concentrations were lower in those with high-altitude pulmonary hypertension compared with those without [7.64 pg/ml (interquartile range = 7.08–9.06) vs. 11.1 pg/ml (9.13–13.1); $P < 0.001$].

**Logistic regression analysis.** In a multivariable logistic regression analysis adjusted for age and biomarkers at ROC-optimal cut points (BNP $\geq 294$ pg/ml, VEGF $\geq 350$ pg/ml, ET-1 $\geq 13.0$ pg/ml, eNOS $< 11.0$ pg/ml), both BNP (OR = 65.3; 95% CI $6.0–705; P = 0.001$) and VEGF (OR = 43.0; 95% CI $4.1–455.8; P = 0.002$) remained independently

![Fig. 2. Concentrations of BNP (A), VEGF (B), ET-1 (C), and eNOS (D) as a function of the presence or absence of chronic mountain sickness (CMS) in subjects at an altitude of 4300 m. The CMS group showed significantly higher levels of each biomarker than did the non-CMS group. N, number of subjects.](http://www.ajpheart.org)
of these differences are not fully understood, our recent data on pulmonary vasoconstriction (1, 2). Although the mechanisms that activated PAP and low SaO2 and have associated elevated levels of biomarkers may contribute to the development of CMS. Our data suggest that patients with CMS have significantly higher concentrations of several important vasoactive peptides, including those with a putative role in the development of the disease.

It is well recognized that circulating BNP levels are elevated in conditions with ventricular volume and pressure overload, and the measurement of BNP is currently used as a routine test for the diagnosis of heart failure (5, 10). Additionally, however, reports also suggest the importance of BNP levels within the context of pulmonary artery hypertension with or without right ventricular dysfunction (12, 13), presumably released by the right ventricular myocardium in response to stretch. To the best of our knowledge, no research on levels of circulating BNP in relation to chronic high-altitude hypoxia and patients with CMS have been previously reported. Our results demonstrate that the patients with CMS had significantly higher concentration of BNP when compared with subjects without CMS, especially with those suffering from high-altitude pulmonary hypertension, showing the highest values.

VEGF, a key mediator of angiogenesis and a downstream product of the hypoxia response pathway, is upregulated in vascular smooth muscle and endothelial cells under hypoxic conditions, and studies (6, 9, 28) have shown that the circulating VEGF levels may significantly increase when sea level residents acutely ascend to a high altitude. Furthermore, studies suggest (16, 18) that the overproduction of VEGF in the lung attenuates the development of hypoxic pulmonary hypertension due, in part, to the protection of an endothelium-dependent function. Tissot van Patot et al. (28) reported that the subjects who developed acute mountain sickness had markedly higher levels of free plasma VEGF than control subjects and suggested that increased levels of VEGF at high altitude may contribute to the development of acute mountain sickness. We now show elevations of VEGF to also be independently associated with CMS. The pathophysiological consequence of increased VEGF production at a high altitude might contribute to vasoconstriction and new vessel formation along with the remodeling of pulmonary vessels, the proliferation of vascular smooth muscle cells, and the consequent loss of distal functional arteries; each of these changes is a potential contributor to the development of CMS (17, 18).

DISCUSSION

Important findings of this study are that patients with CMS have elevated BNP levels that are proportionate to their elevated PAP and low SaO2, and have associated elevated levels of VEGF and ET-1, which appear to be induced similarly by the presence and severity of CMS. Furthermore, those with CMS had lower concentrations of eNOS. Our data suggest that chronic hypoxia with consequent CMS may lead to higher circulating concentrations of these important vasoactive compounds, either as a direct result of hypoxia/CMS (VEGF, ET-1, eNOS) or as compensation to the concomitant pulmonary hypertension and cardiac changes that follow (BNP), and imply a potential role for the measurement of these peptides in the prognostic evaluation of patients with suspected CMS.

In the present study we found that Tibetans who lived permanently at Maduo (4300 m) had significantly lower levels of Hb, mPAP SaO2, and fewer developed CMS compared with Han Chinese. These findings are quite consistent with previous studies that Tibetans are characterized by a lower Hb concentration, decreased arterial O2 content, and lack of hypoxic pulmonary vasoconstriction (1, 2). Although the mechanisms of these differences are not fully understood, our recent data (26), as well as the studies from Yi et al. (30) and Beall et al. (3), indicated that genes in the hypoxic-inducible factor (HIF) oxygen-signaling pathway seem to have been subject to highly positive selection in Tibetans. These association studies demonstrated that the genes EPAS1 (HIF2α), EGLN1 (a regulator of HIF), and PPARA (a transcriptional target of HIF) are strongly associated with reduced Hb levels. Thus these studies provide additional evidence of genetic adaptation to high altitude in Tibetan highlanders.

CMS is a multifactorial disease caused by maladaptation to chronic exposure to a high-altitude hypoxic environment. The prevalence of the disease is significantly increased at high elevations and is lower in Tibetans (but not absent) than in Han lowlanders (1.2% compared with 5.6%) living in the Tibet autonomous region (23). Contributing factors to the development of CMS have included hypoventilation, sleep disorders, and obesity (15, 20, 27, 25), yet it remains unclear what might be the contribution of vasoactive peptides that underlie the development of CMS. Our data suggest that patients with CMS with consequent development of pulmonary hypertension have measurably higher concentrations of several important vasoactive peptides, including those with a putative role in the development of the disease.

Fig. 3. Receiver operator characteristic curves (depicting the balance of sensitivity and specificity) for BNP, VEGF, ET-1, and eNOS to diagnose CMS.

predictive of CMS diagnosis. Although ET-1 and eNOS values were significantly associated with CMS and were a significant predictor of CMS in the absence of BNP and VEGF values, both subsequently lost significance as predictors of CMS in the presence of BNP and VEGF in the final model. In addition, although the data in Table 2 suggest that Han Chinese as an ethnic group had higher Hb, PAP, and biomarkers when compared with Tibetans, once CMS was figured into the model, the differences are no longer significant. Thus we cannot determine whether there is an ethnic/genetic difference in vascular biomarkers in patients with CMS, but we can state strongly that the results in terms of CMS prediction are not biased by the ethnic difference in physiology or CMS frequency.
Both NO and ET-1 are produced locally by the vascular endothelium and modulate both pulmonary vascular reactivity and vascular smooth muscle cell proliferation. An alteration of the balance between NO and ET-1 may contribute to the development of pulmonary hypertension. Concentrations of serum eNOS levels in the CMS group were significantly lower than in the non-CMS group, and whereas ET-1 levels were higher, the multiple linear regression analysis indicated that the ratio of NOS to ET-1 was significantly negative correlated with mPAP ($r = -0.550$). It has been noted in previous studies (7) that Tibetans permanently living at a very high altitude tend to have lower PAP and higher plasma NO compared with newcomers to the altitude. Taken together, these data suggest that an increased PAP at high altitude may be associated with decreased NO and increased ET-1 availabilities. Mechanistically, endothelial injury secondary to increased pulmonary blood flow and/or pressure due to high-altitude hypoxia could at least in theory lead to impaired endothelium-dependent pulmonary relaxation, decreased eNOS expression, increased ET-1 expression, with resultant pulmonary hypertension (18,21).

What is needed now is a better understanding of what role(s) BNP, VEGF, ET-1, and eNOS play for the development of CMS. We suspect but cannot prove that the triggers for their release include the pathophysiological changes that humans undergo when ascending and staying at high altitude, including the formation of high-altitude pulmonary hypertension. Indeed, while we found a compelling partitioning of biomarker concentrations with CMS, considering patients merely on the basis of mPAP, we found among those diagnosed with high-altitude pulmonary hypertension the most radical elevations in BNP and ET-1, as well as the lowest concentrations of eNOS. In total, these results support the suggestion that hypoxia, leading to higher ET-1 levels and lower bioavailability of NO, contributes to the increased hypoxic vasoconstriction in the CMS group, whereas higher levels of BNP are an indicator of greater right ventricular load due to higher PAP.

As concentrations of BNP and VEGF were both independently predicted by the presence of CMS, both might be considered potentially useful for the diagnostic and, perhaps more importantly, prognostic evaluation of the patient with suspected CMS. Indeed, we have frequently observed during physical examination that many high-altitude residents, particularly patients with CMS, exhibit a ruddy or erythemic facial color, which we call “plateau red face.” This occurrence is more common in young women and may be associated with elevations in VEGF; in some cases, the mucosa and conjunctiva are markedly congested from the formation of abnormal new vessels, while the clubbing of fingers is also commonly observed. In this context, we suggest that BNP and VEGF measurement may be useful for a better understanding of the presence and pathophysiology of this most extreme manifestation of CMS.

Limitations. The limitations of our study include its small size and the limited echocardiographic data obtained. Nonetheless, the associations between biomarker concentrations and the presence and complications of CMS are compelling and suggest a new avenue of investigation for high-altitude medicine. It is important to acknowledge that the data we presented are correlative and do not prove cause and effect. We cannot determine with certainty whether factors like BNP, VEGF, ET-1, or eNOS play direct roles in the pathophysiology of CMS or rather are secondary to the disease process and reflect the severity of disease. Nevertheless, the data especially for BNP and VEGF are quite strikingly different in patients with CMS compared with controls that were strongly associated with the disease process. Future work will be required to determine the time course of elevation of these biomarkers in CMS and to evaluate whether they provide prognostic information that would be beneficial in guiding therapy; for example, whether patients with CMS could be safely treated at their home altitudes or should be more urgently recommended to descend. Lastly, the nature of the population in Madua resulted in a control group that was predominantly Tibetan and a patient group that was predominantly Han Chinese, resulting in a possible selection bias. However, the fact that differences in physiological parameters between ethnic groups disappeared when CMS was taken into account in our overall regression model gives us increased confidence that the differences between CMS and controls were more likely due to the disease itself and not the ethnic differences in biomarkers.

In conclusion, natriuretic and angiogenic peptides may modulate the adaptive response to chronic high-altitude exposure and serve as a marker of the severity of and perhaps pathophysiological trigger for CMS.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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