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Relationship between Changes in Cerebral Blood Flow with Symptoms of Acute Mountain Sickness in Men Repeatedly Exposed to Simulated High Altitude

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Abstract

Objective: To study the relationship between changes in the cerebral blood flow (CBF) velocity with symptoms of acute mountain sickness (AMS) during simulated high altitude. **Research Design and Methods:** Mean middle arterial cerebral flow velocity (MCAv) was assessed by transcranial Doppler sonography in 8 healthy lowland male adults aged 20 - 24 yrs before and after 6 h and 48 h at simulated altitude corresponding to 4572 m. The same study was repeated three weeks later in the same subjects. End-tidal pCO_2 ($ETCO_2$) and arterial oxygen saturation (SaO_2) were measured by standardized procedures. AMS symptoms were recorded using the modified environmental symptoms questionnaire after 6 h and 48 h exposure to calculate the mean score of cerebral (AMS-C) symptoms. **Results:** Mean MCAv significantly increased with high altitude (HA) by 4% at 6 h HA and 24% at 48 h HA ($P < 0.05$) compared to sea-level values. We observed a substantial inter-subject variance in MCAv changes, especially in the first hours upon altitude exposure. Within first 2 days, we found a moderate positive correlation between MCAv with decreased $ETCO_2$ (mean ± SD 32 ± 4 mmHg; r = 0.47, $P < 0.05$), and a weak negative correlation of MCAv with a similar low SaO_2 (77% ± 8%; r = −0.43, $P < 0.05$). Five of the 10 original subjects developed symptoms of AMS; however, AMS-C scores decreased ($P = 0.08$) with increased duration of exposure (6 h HA 0.91 ± 1.09 *vs* 48 h HA 0.39 ± 0.40). No differences in AMS-C scores were observed when subjects with and without increased MCAv were compared at 6 h HA and 48 h HA. Furthermore, there was no correlation between changes in neither absolute nor relative MCAv and AMS-C scores. Severity of AMS symp-

toms coincided well with reduction in SaO_2 ($r = -0.55$, $P < 0.05$). **Conclusion:** Our results suggest that there is a lack of relationship between changes in CBF velocity with symptoms of AMS, and that a substantial inter-subject variance exists in the CBF response to high altitude exposure.

Keywords

High-Altitude Sickness, Cerebral Blood Flow, Hypobaric Hypoxia, Transcranial Doppler Sonography

1. Introduction

Acute mountain sickness (AMS), characterized by headache, dizziness, nausea, breathlessness, fatigue and insomnia, may occur during rapid ascent to altitudes above 2500 m, in humans poorly acclimatized to such extreme conditions. Symptoms of AMS begin to show for 6 - 24 hours after high altitude exposure due to a delayed physiological response to reduced air pressure and lower oxygen concentration (West, Schoene, Luks, & Milledge, 2012).

The precise pathophysiology of AMS is not known, however, on the basis of early findings increased cerebral blood flow (CBF) in the first few hours of high altitude exposure may play an important role in the pathogenesis of AMS (Huang et al., 1987; Lassen, 1992; Baumgartner et al., 1994). Although early findings indicate that increased CBF is higher in those with AMS than those without AMS symptoms (Baumgartner et al., 1994), this has not been confirmed in later studies (Baumgartner et al., 1999; Dyer et al., 2008; Lucas et al., 2011). Recent field altitude studies demonstrated that the changes in CBF (velocity) show no clear relationship to symptoms of AMS, at least in the first hours at high altitude (Subudhi et al. 2014; Bian et al., 2014; Imray et al., 2014). Therefore, some authors concluded that CBF is not a relevant factor in the pathogenesis of AMS (Baumgartner et al., 1999).

The current study was carried out to study the relationship between changes in CBF velocity with symptoms of AMS in a group of healthy lowland young males during a 48 h decompression to a simulated altitude of 4572 m. (This study of CBF originated as self-employed part of a more comprehensive study investigating high altitude physiology of acute mountain sickness in US Army Research Institute for Environmental Medicine).

2. Material and Methods

2.1. Subjects

All of the original 10 volunteers were US male soldiers between the ages 20 - 24 years with a mean body weight 73 ± 10 kg and without any known medical or mental illness. Specific inclusion criteria included a lifelong low altitude residence and no exposure to altitude higher than 1000 m for at least 6 months immediately before this study. The subjects were not taking any medication at time

of the study, all were normotensive and had no history of cardiovascular, cerebrovascular or respiratory disease. All signed an informed consent with the US Army Research Institute for Environmental Medicine for participation in the high altitude sickness study. Volunteers could desert the study at any time. Constant medical attention and care by physicians was provided for the entire duration of the study.

2.2. Study Design

For each exposure, baseline examination of CBF velocity by means of transcranial Doppler (TCD) assessment was performed in a hypobaric chamber at an altitude of 50 m (barometric pressure, 755 mmHg; temperature, 20˚C) in the Army Research Institute of Environmental Medicine (Natick, MA, USA). The next morning, the chamber was decompressed to 429 mmHg over 15 min, simulating an altitude of 4572 m (hypobaric hypoxia). Two further TCD studies of CBF velocity were carried out at 6 h and 48 h after high altitude exposure. Volunteers remained in the decompressed chamber for 72 h, except for an approximate 2 h period (normobaric hypoxia; non-rebreathing face mask with O_2 partial pressure at the altitude of 4572 m) after 32 h when they were transferred to the MR imaging scanner site (Brigham & Women Hospital, Boston, MA, USA) to quantify possible brain swelling (Mórocz et al., 2001). Three weeks after the first altitude exposure (exposure I) the second altitude exposure (exposure II) was performed at the same laboratory conditions.

2.3. Transcranial Doppler Ultrasound Examination

CBF velocity was estimated by the measurement of middle cerebral artery blood flow velocity (MCAv) at a depth of 50 to 55 mm using a 2-MHz pulsed Multi-Dop T device (DWL Elektronische Systeme GmbH, Sipplingen, Germany). The monitoring 2-MHz probe was fixed with a specially designed glasses type holder, allowing continuous recording without modification of the insonation angle. The mean MCAv in left middle cerebral artery was averaged from the nine minutes of continuous recording of arterial TCD signal. Mean MCAv obtained in each individual was used for further statistical analysis. All TCD examinations were performed by the same examiner (P. Ondruš).

2.4. Arterial Oxygen Saturation and End-Tidal CO_2

Resting arterial oxygen saturation (SaO_2) was measured by pulse oximetry, and the end-tidal CO_2 ($ETCO_2$) tension by rapidly responding analyzers (LB-2; Beckman Coulter, Anaheim, CA, USA and S3-A; Applied Electrochemistry Inc., Sunnyvale, CA, USA, respectively).

2.5. Assessment of Acute Mountain Sickness

The diagnosis and severity of AMS was assessed utilizing the Environmental Symptoms Questionnaire (ESQ), which was administered at 06.00 h, 12.00 h, and 20.00 h during hypoxic exposure. In order to determine the presence of

AMS, a weighted average of cerebral symptoms (AMS-C) was calculated from the ESQ scores. AMS-C score of >0.7 indicates the presence of AMS (Sampson et al., 1983).

2.6. Statistical Analysis

Intra- and inter-subject comparisons were analyzed using a paired *t*-test, and one-way ANOVA with Bonferroni multiple analysis. The relationship between-SaO_2, $ETCO_2$ or AMS-C score and the changes in %MCAv from that at sea-level were determined by Pearson correlation analysis. Significance was accepted at $P < 0.05$, two-tailed. The PASW statistics 19.0 (SPSS Inc. Chicago, IL, USA) was used for statistical analysis.

3. Results

Eight of the ten volunteers fulfilled the criteria for at least one high altitude exposure and underwent the TCD and blood gas examinations. One of the 10 original volunteers had to leave the study due to clinical symptoms of AMS (AMS-C score 3.4) after a few hours of hypobaric exposure, and data obtained from another subject were excluded for missing a TCD examination. Three weeks later, six volunteers (2 of remaining 8 subjects voluntarily quit the study) repeated the hypobaric hypoxia exposure II. During exposure I, 3 of the 8 subjects developed AMS while during exposure II, 2 of 6 subjects sustained AMS.

Changes in mean MCA velocity, AMS-C score, SaO_2 and $ETCO_2$ summarized across exposures I and II are shown in Table 1.

Mean MCAv increased ($P = 0.02$) during high altitude (HA) from baseline values 53.8 to 56.1 (+4.2%) and 66.8 (+24.2%) $cm \cdot s^{-1}$ at 6 h HA and 48 h HA, respectively. During a period of 6h HA, the MCAv increased in 7 subjects, but remained unchanged or decreased in 5. Thus there was a substantial inter-subject variance in CBF velocity, especially in the early state of altitude exposure. However, our data suggest that the increase in MCAv during the exposure I was also observed in the exposure II (6 h HA 56.4 ± 12.3 *vs* 55.0 ± 13.6 and 48 h HA 68.1 ± 13.5 *vs* 66.4 ± 14.0 $cm \cdot s^{-1}$, $P = 0.83$ - 0.85), irrespective of AMS-C score. Individual measurements of CBF before and during the first and second altitude exposure are shown in Figure 1.

Table 1. Mean MCA flow velocity, acute mountain sickness-cerebral score, arterial O_2 saturation, and end-tidal CO_2 during decompression to 4557 m.

Altitude		MCAv		AMS-C score	SaO_2 (%)	$ETCO_2$ (mm Hg)
Height (m)	Time (hours)	$cm \cdot s^{-1}$	% sea level			
<50	0	53.8 ± 6.3*	100	-	-	-
4572	6	56.1 ± 12.9	104.2 ± 23.8	0.91 ± 1.09	77.1 ± 8.8	32.9 ± 4.0
4572	48	66.8 ± 14.2	124.2 ± 26.2	0.39 ± 0.40	77.9 ± 5.6	31.0 ± 2.8
P ANOVA		0.02	0.00	0.08	0.54	0.01

*Data are expressed as mean ± SD (calculated across altitude exposures I and II).

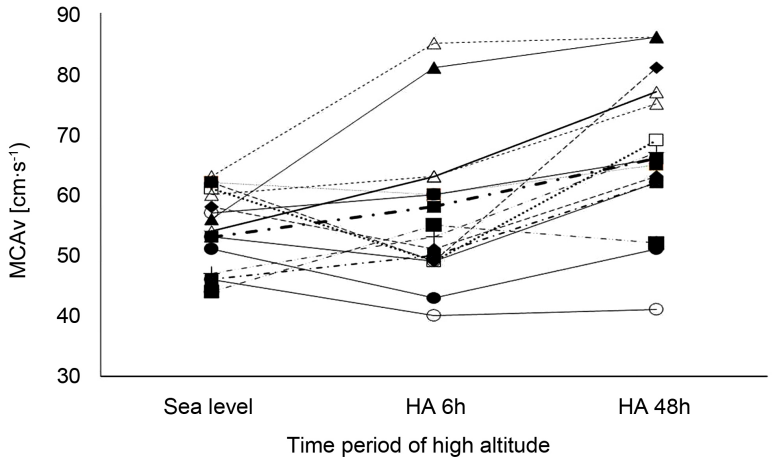

Figure 1. Individual measurements in MCAv before and during the first (•) and second altitude exposure (◦).

The AMS-C scores decreased ($P = 0.08$) with increased duration of exposure (mean ± SD 0.91 ± 1.09 at 6 h HA *vs* 0.39 ± 0.40 at 48 h HA). No difference in AMS-C scores was observed when subjects with and without increased MCAv were compared at 6 h HA *versus* 48 h HA. In this context, the changes in %MCAv did not correlate with AMS-C score (r = −0.10, $P = 0.69$) during the first 48 h of altitude exposure (**Figure 2**). In contrast, severity of AMS symptoms coincided well with reduction in SaO_2 at 48 h HA (r = −0.55, $P < 0.05$).

Both SaO_2 and $ETCO_2$ were decreased over time during altitude exposure (77% ± 8% and 32 ± 4 mmHg, respectively); the lower concentrations remained unchanged for the entire length of the study. SaO_2 as well as $ETCO_2$ showed difference ($P < 0.05$) when subjects with and without increased MCAv were compared at 6 h HA, but not at 48 h HA. During altitude exposure, the changes in %MCAv correlated positively with probably decreased $ETCO_2$ (32 ± 4 mm Hg; r = 0.47, $P < 0.05$) and negatively with a similar low SaO_2 (77% ± 8%; r = −0.43, $P < 0.05$) (**Figure 3** and **Figure 4**).

4. Discussion

In this study we examined the relationship between changes in CBF velocity with symptoms of AMS in a group of lowland male subjects at a simulated altitude of 4572 m. The major findings of the current study showed that mean MCAv significantly increased within the first 2 days of altitude exposure, and suggested a lack of a (linear) relationship between MCAv and symptoms of AMS. However, immediately upon altitude exposure, the mean MCAv remained essentially unchanged or even decreased in the most of study subjects.

Our findings are consistent with reports of several field or chamber studies focusing on acclimatization to hypoxia at high altitudes over a period of hours to days. Baumgartner et al. (1999) reported, in similarly aged men, an unchanged mean MCAv with a small relative rise (~9%) compared with baseline values after 6 hours of exposure at altitude of 4559 m. In this same chamber study, the

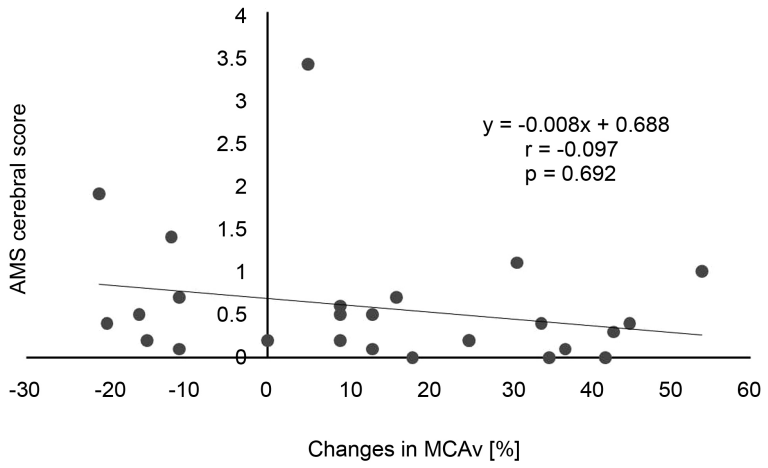

Figure 2. Relation between changes in MCAv and AMS-C score.

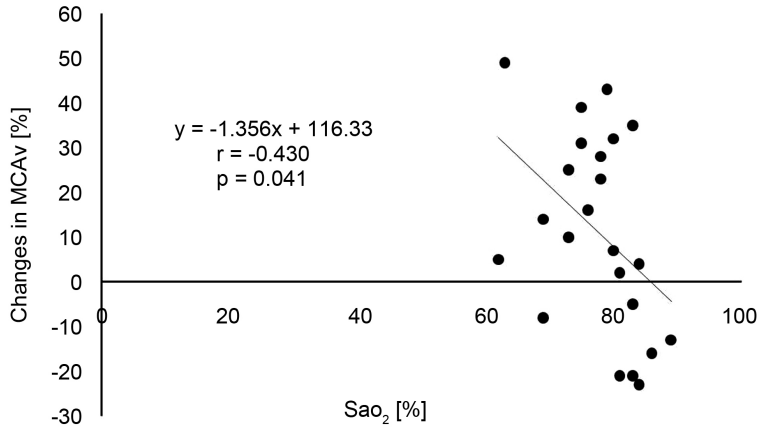

Figure 3. Relation between changes in MCAv and arterial oxygen saturation.

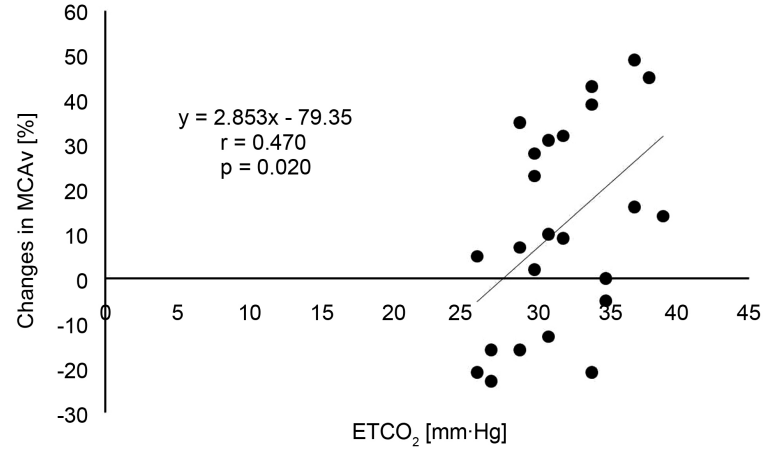

Figure 4. Relation between changes in MCAv and end-tidal carbon dioxide.

changes in MCAv did not correlate with AMS-C scores. Subudhi et al. (2014) examined acute response of CBF in 21 healthy volunteers rapidly ascended to 5260 m (Chacaltaya, Bolivia). Although CBF increased globally by ~70% within 2 - 4 h of altitude, the mean MCAv remained unchanged in comparison with

baseline values. Furthermore, changes in CBF were not associated with the incidence or severity of AMS. In another field study, Lucas et al. (2011) found in healthy young 11 males and 6 females that upon initial arrival at an altitude of 5050 m (Khumbu Valley, Nepal) mean MCAv was elevated (up 30% *vs* sea-level), but returned to sea-level values within 7 - 9 days. The balance of arterial blood gases oxygen/carbon dioxide accounted for a large part (~40%) of the observed variability leading to changes in CBF at high altitude. Poulin et al. (2002) described in nine healthy subjects (6 males, 3 females) a decline in CBF to values below the initial control value after 24 h of simulated altitude exposure for arterial P_{O2} of 60 Torr (equivalent to altitude of ~2800 m and ~3400 m for non-responders and responders, respectively), followed by a subsequent rise within 48 h. The changes in CBF velocity were very closely related to changes in end-tidal CO_2 tension.

The general consensus is that upon acute exposure to altitude CBF initially rises and returns to near baseline values within the first few days or 1 - 2 weeks of acclimatization (Huang et al., 1987; Jensen et al., 1990; Baumgartner et al., 1994; Lucas et al., 2011; Subudhi et al., 2014). The magnitude in the changes in CBF after altitude exposure depend upon two stimuli with opposing influences on the cerebral circulation: arterial hypoxia and arterial hypocapnia. Arterial hypoxia arises as a ventilatory response to reduced air pressure and lower oxygen concentration in high altitude and tends to cause vasodilatation (Wilson et al., 2011; Imray et al., 2014), whereas arterial hypocapnia occurs as a consequence of the reflex hyperventilation and may cause vasoconstriction (Atkinson, Anderson & Sundt Jr., 1990). Moreover, these stimuli are not constant over time if one remains at a constant altitude because in prolonged hypoxic conditions, arterial hypoxia is reduced and CBF undergone some degree of adaptation to hypocapnia (Poulin et al., 2002). In this context, it is clear that differences in the magnitude of these mechanisms may cause the well-known intra- and inter-individual variance in changes in CBF after initial altitude exposure (Baumgartner et al., 1999).

In our study, the mean MCAv remained unchanged at 6 h after acute exposure to altitude. One possible explanation of the failure of increased flow velocity upon simulated altitude may be small or delayed influence of the respiratory gases on the cerebral blood circulation in the early period of altitude. However, it seems highly unlikely because in our subjects, MCAv was permanently and significantly related to variations in $ETCO_2$ tension. It seems that an initial hypocapnia probably has the predominant effect and inhibits the possible initial hypoxic cerebral vasodilation. Therefore, CBF velocity remains essentially unchanged or may diminish below starting sea-level values in the early stage of altitude exposure. Of course, as time progresses, the rise in CBF observed in our and aforementioned studies may be the result of increased sensitivity of CBF to acute variations in both hypoxia and increased CO_2 during the 48 h of hypoxia (Poulin et al., 2002).

Our study of CBF was performed in conjunction with a study that used a nov-

el MR imaging technique to examine cerebral tissue volume before and after high altitude exposure in the same subjects within the same study. Specifically, alterations in CBF, brain volume and intracranial pressure may play critical roles in the development of AMS, particularly the neurological symptoms, headache and dizziness (Imray, Wright, Subudhi, & Roach, 2010). The chamber values for cerebral tissue swelling due to hypobaric hypoxia have been reported previously (Mórocz et al., 2001). In brief, a significant ($P < 0.001$) brain swelling of 36.2 ± 19.6 ml (2.8% ± 1.5%) develops after 32 h of hypobaric hypoxia. The brain edema in our subjects was diffuse in nature, having a predominantly gray mater origin, and without significant relation to AMS-C score. Yet the combination of these brain tissue volume data with the additional CBF values from our study indicate a weak association between changes in brain tissue volume and CBF variations (**Figure 5**).

Several studies considered increased CBF after high altitude exposure as an important co-factor in the etiology of AMS (Jensen et al., 1990; Van Osta et al., 2005). In our study, five of the original 10 subjects had clinical symptoms of AMS in at least one of the high altitude exposure studies. One subject had to quit the study within a few hours of exposure, suffering from headache, nausea and general discomfort. According to our medical records, the symptoms of AMS occurred in the same three subjects in both altitude exposures. Most volunteers reported mild symptoms of AMS within 6 - 24 h of hypobaric hypoxia; however, only 4 out of 12 subjects met clinical definition of AMS. Adaptation to hypoxia/hypocapnia during prolonged hypobaric conditions most likely explains the observed decrease of AMS-C score with increasing duration of high altitude exposure. Severity of AMS symptoms in our subjects coincided well with reduction in arterial oxygen saturation as described previously Hussain et al. (2001).

In recent studies, the pathogenic role of CBF in the etiology of AMS has been doubted. In support of this conclusion, Ainslie & Subudhi (2014) provided convincing data from four different field studies looking at individual measurements of CBF and AMS symptoms, showing no direct association. Additionally,

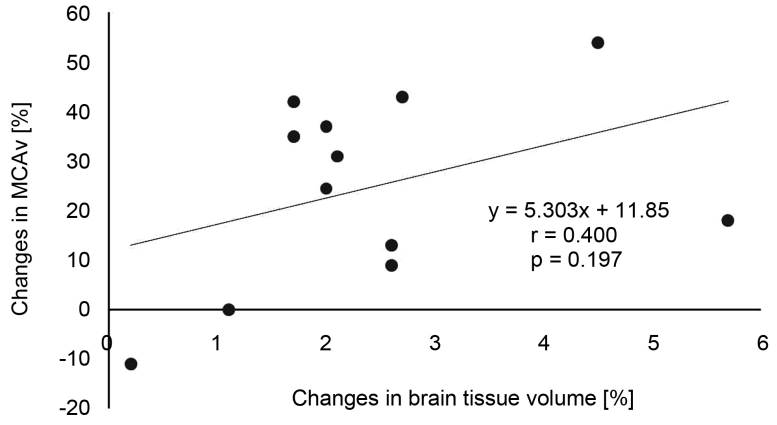

Figure 5. Relation between changes in MCAv and brain tissue volume. Data combined from altitude chamber study (Mórocz et al., 2001).

altitude chamber studies revealed that the CBF velocity measured in the middle cerebral artery is substantially unchanged compared to sea-level value, and, moreover, with no clear relationship to symptoms of AMS, at least in the first few hours of simulated altitude (Baumgartner et al., 1999; Subudhi et al., 2014). Our findings solidly confirmed the lack of relationship between changes in CBF with symptoms of AMS, at least in the first two days of high altitude exposure.

However, these results should be interpreted with caution because it is possible that: 1) changes in a global CBF may not reflect the changes in the small cerebral vessels that likely have greater contribution to the symptomatology of AMS, 2) other risk factors associated with increased CBF that may cause AMS, especially metabolic, genetic and endocrine factors, and 3) our measurements were carried out in highly controlled laboratory conditions i.e. in an altitude chamber with the absence of cold, stress, exercise, exhaustion, dehydratation and other influences associated with mountaineering.

One major limitation of this study is the small sample size due to the possible health hazards in unpleasant hypoxic conditions. However, we are confident about the observed trends and relative changes in CBF velocity in our altitude chamber experiment.

5. Conclusion

The current study suggests that changes in CBF alone are not a causative factor for the development of AMS (or brain swelling). In overall, the CBF values remain unchanged within the first few hours after altitude exposure, followed by subsequent progressive increase at 48 h. CBF is more sensitive to the variations in the end-tidal CO_2 than in the SaO_2 concentration. Furthermore, we demonstrate a substantial inter-individual variance in CBF response to high altitude exposure. Further studies are needed to investigate the tiny regulators (nitric oxide, adenosine, calcitonin gene-related peptide, etc.) with great potential for CBF regulation and brain function at high altitude.

Conflict of Interest

There is no conflict of interest.

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