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Sea-Level Assessment of Dynamic Cerebral Autoregulation Predicts Susceptibility to Acute Mountain Sickness at High Altitude

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Background and Purpose—Dynamic cerebral autoregulation is impaired in subjects who develop acute mountain sickness (AMS), a neurological disorder characterized by headache. The present study examined if the normoxic sea-level measurement of dynamic cerebral autoregulation would predict subsequent susceptibility to AMS during rapid ascent to terrestrial high altitude.

Methods—A dynamic cerebral autoregulation index was determined in 18 subjects at sea level from continuous recordings of middle cerebral artery blood flow velocity (Doppler ultrasonography) and arterial blood pressure (finger photoplethysmography) after recovery from transiently induced hypotension. Six hours after passive ascent to 3800 m (Mt Elbrus, Russia), the Lake Louise and Environmental Symptoms Cerebral Symptoms questionnaires were used to assess AMS.

Results—AMS scores increased markedly at high-altitude (Lake Louise: $+3\pm 2$ points, $P=0.001$ and Environmental Symptoms Cerebral Symptoms: $+0.6\pm 0.9$ points, $P=0.0003$ versus sea level). Inverse relationships were observed between the sea-level autoregulation index score and the high-altitude-induced increases in the Lake Louise ($r=-0.62$, $P=0.007$) and Environmental Symptoms Cerebral Symptoms ($r=-0.78$, $P=0.01$) scores. One subject with a history of high-altitude pulmonary and cerebral edema presented with the lowest sea-level autoregulation index score (3.7 versus group: 6.2 ± 1.0 points) and later developed high-altitude cerebral edema at 4800 m during the summit bid.

Conclusions—These findings suggest that a lower baseline autoregulation index may be considered a potential risk factor for AMS. This laboratory measurement may prove a useful screening tool for the expedition doctor when considering targeted pharmacological prophylaxis in individuals deemed “AMS-susceptible.” (*Stroke*. 2011;42:3628-3630.)

Key Words: acute mountain sickness ■ dynamic cerebral autoregulation ■ high-altitude ■ individual susceptibility ■ vasogenic edema

Acute mountain sickness (AMS) is a neurological disorder characterized by headache that is typically encountered by mountaineers after rapid ascent to high altitude. Current opinion, albeit controversial,¹ suggests that AMS is a mild form of high-altitude cerebral edema and that both syndromes share a common pathophysiology linked by vasogenic edematous brain swelling and intracranial hypertension.²

Recently, dynamic cerebral autoregulation was shown to be impaired during acute hypoxia³ and in direct proportion to AMS symptom scores⁴ suggesting it may represent a potential risk factor. However, the link between impaired dynamic cerebral autoregulation and symptomatology is not a universal finding³ and warrants further clarification. Thus, in the present study, we have adopted an alternative approach by examining if the biological variation in dynamic cerebral

autoregulation observed in the “healthy brain” at sea level would predict subsequent susceptibility to AMS during a rapid ascent to terrestrial high altitude.

Materials and Methods

Subjects and Design

After ethics approval, 18 subjects (13 male/5 female) aged 29 (mean) ± 9 (SD) years were recruited as part of a medical research expedition to Mt Elbrus (5740 m) in Russia. Five (male) had a history of severe AMS (AMS+) and of these, 1 had documented high-altitude pulmonary edema confirmed by chest radiography and 1 had 2 separate incidences of combined high-altitude pulmonary edema and high-altitude cerebral edema. All remaining subjects were altitude-naïve (AMS-). Measurements were performed at sea level 7 ± 2 days before departure for Russia and 6 hours after passive

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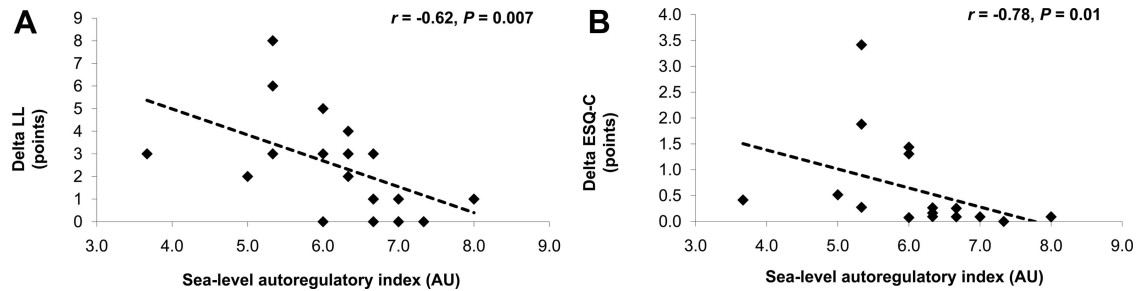


Figure. Inverse relationships observed between the baseline autoregulatory index (in arbitrary units [AU]) taken as the mean value obtained from 3 trials recorded at sea level and increase in the Lake Louise (LL: **A**) and Environmental Symptoms Questionnaires Cerebral Symptoms (ESQ-C: **B**) scores at 3800 m (Mt Elbrus, Russia).

ascent to 3800 m by cable car. Oral prophylaxis against AMS was avoided.

Dynamic Cerebral Autoregulation

Mean Arterial Pressure

Beat-to-beat arterial pressure waveforms were recorded continuously by finger photoplethysmography (Finometer PRO; Finapres Medical Systems, Amsterdam, The Netherlands).

Middle Cerebral Artery Velocity

The right middle cerebral artery was insonated with a 2-MHz pulsed transcranial Doppler ultrasound (Multi-Dop X4; DWL Elektronische Systeme GmbH, Germany) and secured with an adjustable headset.

Autoregulatory Index

This was determined using the thigh cuff inflation–deflation technique.⁵ Briefly, bilateral thigh cuffs were connected to a Hokanson E20 (Bellevue, WA) and inflated to 30 mm Hg above the recorded systolic blood pressure for 3 minutes. Lower-limb ischemia was confirmed using Doppler by a lack of blood flow in the dorsalis pedis artery. Cuffs were subsequently deflated (<0.1 second) and the process repeated 3 times with a 8-minute intertrial recovery period. An autoregulatory index was assigned to each of the trials after computation of a second-order linear differential equation⁶ and ranged between 0 arbitrary units (entirely passive autoregulation) and 9 (most brisk autoregulation). The mean (autoregulatory index) value of the 3 trials was determined and used in subsequent analyzes as the index of dynamic cerebral autoregulation.

Acute Mountain Sickness

The Lake Louise and Environmental Symptoms Questionnaire Cerebral scoring systems were used to assess AMS as previously described.⁷

Statistical Analysis

Given the small sample size, data were analyzed using nonparametric statistics. Changes from sea level to high altitude and differences between AMS+ versus AMS– were analyzed using Wilcoxon matched pairs signed ranks and Mann Whitney *U* tests, respectively. The relationship between sea-level autoregulatory index scores and AMS scores were examined using a Spearman rank correlation coefficient. Significance was established at $P < 0.05$.

Results

Thigh-cuff deflation during the assessment of dynamic cerebral autoregulation resulted in an average (of 3 separate trials) dynamic reduction (taken as the nadir) in mean arterial pressure of 22 ± 5 mm Hg (range, 19–26 mm Hg) relative to the baseline observed during the period of cuff inflation ($P = 0.0002$). AMS scores increased from 0 ± 0 (Lake Louise) and 0.0 ± 0.0 points (Environmental Symptoms Questionnaires Cerebral Symptoms) points at sea level to 3 ± 2 and 0.6 ± 0.9 points at high altitude ($P = 0.001$ and $P = 0.0003$,

respectively). The autoregulatory index scores were comparable ($P = 0.12$) between AMS+ (5.5 ± 1.1 arbitrary units) and AMS– (6.4 ± 0.9 arbitrary units). In contrast, the Figure illustrates the inverse relationships observed between the sea-level autoregulatory index score and the respective increases in Lake Louise (Figure A) and Environmental Symptoms Questionnaires Cerebral Symptoms (Figure B) scores. The subject with the combined history of high-altitude pulmonary edema and high-altitude cerebral edema presented with the lowest sea-level autoregulatory index score (3.7 arbitrary units versus group: 6.2 ± 1.0 arbitrary units) and subsequently developed high-altitude cerebral edema (truncal ataxia and clouded consciousness) at 4800 m during the summit bid.

Discussion

The major novel finding in the present study is that a lower baseline (sea-level) autoregulatory index score may prove a potential risk factor for AMS during subsequent ascent to high altitude, accounting for up to 60% of the observed variance. These subtle imperfections in dynamic cerebral autoregulation, detectable in the healthy brain as part of normal biological variation, indicate that the “AMS-susceptible” individual may be less capable of buffering rapid surges in mean arterial pressure and, consistent with the traditional paradigm,² inherently more vulnerable to vasogenic edematous brain swelling and intracranial hypertension at high altitude.

The observation that dynamic cerebral autoregulation becomes impaired during hypoxia corroborates diffusion-weighted MRI evidence for mild vasogenic brain swelling of the corpus callosum.⁸ Thus, disordered cerebral autoregulation has the capacity to disrupt the blood–brain barrier and cause mild hyperperfusion.⁹ However, the link to symptomatology remains more tenuous given the failed attempts to detect any “additional” vasogenic brain swelling or intracranial hypertension in AMS. Furthermore, why such a minor shift of water into the corpus callosum should trigger the cephalalgia of AMS remains an added complication.

However, the inverse relationships observed in the present study between sea-level autoregulatory index and AMS symptom scores did not occur by “chance alone,” thus forcing a reappraisal of the previous interpretation that impaired dynamic cerebral autoregulation is simply an incidental finding.^{4,10} However, we recognize that the small sample size used in the present study and corresponding constraints

imposed on statistical power may limit generalization to the wider community of mountain climbers who are at risk of developing AMS. Furthermore, the assessment of dynamic cerebral autoregulation using the thigh cuff inflation–deflation technique has, like other methods,¹¹ inherent limitations, the most notable being assessment of the brain’s cerebral autoregulation response to a hypotensive as opposed to a hypertensive challenge, the latter being more appropriate given the proposed link to intracranial hypertension. Future studies need to consider transfer function analysis of sinusoidal mean arterial pressure oscillations “forced” through repeated squat–stand or lower body negative pressure maneuvers to more reliably engage cerebral autoregulation given that there is evidence to suggest that cerebral autoregulation is more effective at dealing with an increase (as opposed to a decrease) in mean arterial pressure.¹² These improved methods that have yet to be applied in the setting of AMS combined with serial diffusion-weighted MRI measurements will provide clearer insight into the underlying mechanisms.

Given the insidious nature of AMS and its prevalence during commercial expeditions,² early recognition of “susceptible individuals” through the measurement of dynamic cerebral autoregulation at sea level may provide a useful screening tool for the expedition doctor who may want to consider targeted pharmacological prophylaxis and thus prevent further neurological complications at high altitude.

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Disclosures

None.

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