AltitudeOmics: cerebral autoregulation during ascent, acclimatization, and re-exposure to high altitude and its relation with acute mountain sickness

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1University of Colorado Altitude Research Center, Department of Emergency Medicine, Anschutz Medical Campus, Aurora, Colorado; 2University of Colorado Colorado Springs, Department of Biology, Colorado Springs, Colorado; 3University of Lausanne, Institute of Sports Sciences, Lausanne, Switzerland; 4University of Geneva, Lemanic Doctoral School of Neuroscience, Geneva, Switzerland; 5University of Oregon, Department of Human Physiology, Eugene, Oregon; and 6University of Leicester, Leicester Royal Infirmary, Department of Cardiovascular Sciences, Leicester, United Kingdom

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Subudhi AW, Fan JL, Evero O, Bourdillon N, Kayser B, Julian CG, Lovering AT, Panerai RB, Roach RC. AltitudeOmics: cerebral autoregulation during ascent, acclimatization, and re-exposure to high altitude and its relation with acute mountain sickness. J Appl Physiol 116: 724–729, 2014. First published December 26, 2013; doi:10.1152/japplphysiol.00880.2013.—Cerebral autoregulation (CA) acts to maintain brain blood flow despite fluctuations in perfusion pressure. Acute hypoxia is thought to impair CA, but it is unclear if CA is affected by acclimatization or related to the development of acute mountain sickness (AMS). We assessed changes in CA using transfer function analysis of spontaneous fluctuations in radial artery blood pressure (indwelling catheter) and resulting changes in middle cerebral artery blood flow velocity (transcranial Doppler) in 21 active individuals at sea level upon arrival at 5,260 m (ALT1), after 16 days of acclimatization (ALT16), and upon re-exposure to 5,260 m after 7 days at 1,525 m (POST7). The Lake Louise Questionnaire was used to evaluate AMS symptom severity. CA was impaired upon arrival at ALT1 (P < 0.001) and did not change with acclimatization at ALT16 or upon re-exposure at POST7. CA was not associated with AMS symptoms (all R < 0.50, P > 0.05). These findings suggest that alterations in CA are an intrinsic consequence of hypoxia and are not directly related to the occurrence or severity of AMS.

transcranial Doppler; cerebral blood flow; cerebral oxygenation; transfer function analysis; hypoxia

Cerebral autoregulation (CA) is a general term used to describe dynamic myogenic, neurologic, and metabolic responses that adjust cerebrovascular resistance to maintain relatively constant cerebral blood flow across a wide range of perfusion pressures (25). Dynamic CA is said to be impaired if fluctuations in mean arterial blood pressure (ABP) lead to concurrent fluctuations in mean cerebral blood flow. Impairments in CA are associated with cerebrovascular disorders (3, 24, 31), yet the relative importance of CA in the development and course of certain pathologies is unclear.

Our initial interest in CA stemmed from the hypothesis that impaired CA may be involved in the development of acute mountain sickness (AMS), high-altitude headache, and cerebral edema (5, 7, 9, 16, 37). Conversely, we showed that impairments in CA upon acute exposure to hypobaric hypoxia preceded, but were not associated with, the development of AMS (2, 33, 35). Furthermore, since several cross-sectional studies demonstrated that impairments in CA persist from 1 to 30 days of high-altitude exposure (1, 2, 11, 12, 17)—when AMS is not present—and are evident in healthy, permanent high-altitude residents (12, 13), it seems reasonable to suggest that a shift in CA may be an inherent and relatively benign consequence of hypoxemia.

To date, no longitudinal studies have characterized CA and tested its relation with AMS during acute and chronic high-altitude exposures. Previous studies have either omitted CA measurements upon arrival at high altitude (7, 11, 17) or followed slow ascent profiles that allow for partial acclimatization before initial measurements (1, 12, 39). In this study, we present novel data from sea-level (SL) residents who rapidly ascended to high altitude (5,260 m; ALT1), acclimatized for 16 days (ALT16), and were subsequently re-exposed to high altitude after spending 7 days at low altitude (1,525 m; POST7). Specifically, we tested the hypotheses that CA would be: 1) impaired upon rapid ascent to high altitude, 2) unaffected by 16 days of acclimatization, 3) unaffected upon re-exposure to the same altitude, and 4) unrelated to the occurrence or severity of AMS.

METHODS

Study overview. This study was conducted as part of the AltitudeOmics project. Briefly, institutional ethics approval was obtained from the Universities of Colorado and Oregon and the U.S. Department of Defense Human Research Protection Office. Young, healthy SL residents were recruited from the greater Eugene, Oregon, area (elevation 128 m) and screened to exclude anyone who was born or had lived at altitudes >1,500 m for more than 1 yr or had traveled to altitudes >1,000 m in the past 3 mo. After obtaining written consent, physical exams and the Army Physical Fitness Test (push-ups, sit-ups, and a 3.2-km run) were performed to verify health and fitness status. Approximately 4 wk following SL measurements in Eugene, Oregon, subjects were flown to La Paz, Bolivia. They spent two nights at low altitude (1,525 m in Coroico, Bolivia) before being driven to the Chacaltaya Research Station at 5,260 m, while breathing supplemental oxygen. Acute responses to high altitude were assessed ~4 h after arrival and cessation of supplemental oxygen (ALT1). Subjects acclimatized to altitudes ranging from 3,800 to 5,260 m over the next 15 days, with most of the time (75%) spent at 5,250 m. On the 16th day (ALT16), measurements were repeated at 5,260 m before subjects were driven down to Coroico for either 7 or 21 days. Subjects were driven back to the laboratory at 5,260 m for POST7 or POST21 re-exposure measurements.

This report focuses on novel data regarding resting CA, evaluated immediately before a series of cerebrovascular, respiratory, and exercise interventions, as outlined elsewhere (32). We have carefully
avoided replication of data among reports, except where common variables were necessary to describe subjects’ basic physiologic status at the time points of interest [e.g., heart rate (HR), blood pressure, arterial blood gases].

**Subjects.** We studied 21 subjects at SL (12 men and nine women; 21 ± 1 yr old). Because of logistical problems upon arrival in Bolivia, complete data sets were not obtained on the first seven subjects upon arrival at ALT1. Since the first seven subjects comprised the cohort studied at POST21, longitudinal assessments of CA were limited to the remaining 14 subjects who completed the study at POST7.

**Physiology protocol.** All subjects were familiarized with study procedures during a practice session at least 48 h before experimental testing at SL. Subjects followed standardized exercise and dietary regimens for 24 h before each measurement period. At each time point, a 22-gauge catheter was inserted into a radial artery at least 1 h before instrumentation. Subjects were seated in an upright position for 15 min, while sensors were placed to measure physiologic variables of interest. Limb lead electrodes were used to measure ECG (BioAmp; ADInstruments, Colorado Springs, CO). ABP was monitored via a fluid-filled pressure transducer (Deltran II; Utah Medical Products, Midvale, UT) attached to the radial artery catheter. Core temperature was recorded telemetrically from an ingested pill (CorTemp; HQInc, Palmetto, FL). Cerebral blood flow velocity (CBFv) in the left middle cerebral artery (MCA) was measured by transcranial Doppler (2 MHz; Spencer Technologies, Seattle, WA) at depths ranging from 43 to 54 mm. Signal quality was optimized, and an M-mode screen shot was recorded to facilitate subsequent probe placements and insonation angles.

After verification of signal quality, resting data were recorded for 6 min, while subjects breathed room air to assess CA at each altitude. Continuous analog data [ABP, CBFv, ECG, oxygen (O2), and carbon dioxide (CO2)] were recorded at 200 Hz (PowerLab 16/30; ADInstruments) for offline analysis. Core temperature and arterial blood samples (2 ml) were taken during the last 30 s of measurement periods. Blood samples were taken from the radial artery catheter, and blood gases were analyzed for partial pressure of arterial CO2 (PaCO2) and partial pressure of arterial O2 (PaO2) in triplicate (RAPIDLab 248; Siemens, Erlangen, Germany) and corrected for body temperature (15, 29).

Acute mountain sickness. Self-reported sections of the Lake Louise Questionnaire (LLQ) were used to assess AMS on ALT1 and POST7 (~12 h after arrival). Moderate and severe AMS was defined as LLQ ≥ 3, and LLQ ≥ 6, including headache, respectively (27).

**Data analysis.** Transfer function analyses were used to assess dynamic CA, based on spontaneous fluctuations in the raw ABP and CBFv signals, as described previously (33, 34). Briefly, 6-min recordings of instantaneous ABP and CBFv were reduced to beat-by-beat averages, resampled at 5 Hz, and transformed from the time-to-frequency domain using fast Fourier transformations (512 points/segment with 40% overlap). The transfer function from mean ABP to CBFv was expressed in terms of coherence, gain, and phase shift in the very low frequency range (0.02–0.07 Hz), where dynamic CA is most active (21, 22), as well as in low (0.07–0.20 Hz) and high (0.20–0.35 Hz) frequency ranges. All data were used in subsequent statistical analyses. Reduction in phase shift was considered the primary criterion for impaired CA, because it signifies shorter delay in transmission of pressure (ABP) into flow (CBFv) or a reduction in the ability of the cerebrovascular system to buffer changes in ABP and maintain consistent blood flow. Yet, since increases in gain (increase in CBFv relative to a change in ABP) and coherence (linear correlation between ABP and CBFv) may also suggest CA impairment (8, 24, 41), all three transfer function metrics are reported. To address difficulties in interpreting possible permutations of these three variables, the inverse transfer function of the resulting gain and phase shift was used to express results in the time domain as a step function that could be fitted to one of 10 curves representing a single autoregulation index (ARI) score (36). An ARI score of zero indicates complete lack of autoregulation, and nine indicates perfect autoregulation.

**Statistics.** For calculating descriptive statistics (mean ± SD) and verifying normality (D’Agostino and Pearson tests), variables were analyzed by repeated-measures ANOVA to evaluate the effect of time on CA metrics with Fisher’s least significant difference post hoc tests and the Holm procedure to correct for multiple comparisons (α = 0.05).

Spearman ρ correlations were run to evaluate relations between CA metrics and the severity of LLQ symptom scores. Specifically, we tested the ability of CA assessments, measured at SL and upon arrival at ALT1, to predict ensuing symptoms of AMS (7). Also, because AMS classification is dichotomous (i.e., positive vs. negative), we used receiver-operating characteristic (ROC) analyses (14, 18) to evaluate the sensitivity (true positive rate) and specificity (true negative rate) of the ability of ARI scores to detect mild and severe AMS. The ROC area under the curve (AUC) statistic was used as an indicator of test accuracy. An AUC of 1.0 signifies a perfect test, with no chance of false-positive or false-negative results, whereas an AUC of 0.5 signifies a meaningless test, where the probability of identifying a true positive result is only 50%.

**RESULTS**

Effect of rapid ascent to high altitude. At SL, resting cardiovascular (HR, ABP, CBFv) and CA (coherence, gain, phase shift, and ARI scores) measurements were characteristic of young, healthy individuals with intact CA (Table 1 and Fig. 1). From SL to ALT1, PaO2 and PaCO2 decreased (65% and 26%, respectively; P < 0.001; Table 1). This degree of hypoxia increased HR (P < 0.001) but did not affect mean ABP or CBFv. Very low frequency power spectral density of ABP and

### Table 1. Resting data

<table>
<thead>
<tr>
<th>Variable</th>
<th>SL</th>
<th>ALT1</th>
<th>ALT6</th>
<th>POST7</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO2 mmHg</td>
<td>103 ± 5</td>
<td>36 ± 3*</td>
<td>45 ± 4*</td>
<td>42 ± 4††</td>
</tr>
<tr>
<td>PaCO2 mmHg</td>
<td>37 ± 4</td>
<td>28 ± 2*</td>
<td>21 ± 3*</td>
<td>24 ± 3††</td>
</tr>
<tr>
<td>HR beats/min</td>
<td>73 ± 9</td>
<td>90 ± 18*</td>
<td>95 ± 12*</td>
<td>85 ± 15‡‡</td>
</tr>
<tr>
<td>ABP mmHg</td>
<td>77 ± 6</td>
<td>76 ± 14</td>
<td>81 ± 10</td>
<td>76 ± 8</td>
</tr>
<tr>
<td>CBFv cm/s</td>
<td>62 ± 9</td>
<td>63 ± 14</td>
<td>59 ± 7</td>
<td>57 ± 9</td>
</tr>
<tr>
<td>PSD ABP mmHg²/Hz</td>
<td>11 ± 13</td>
<td>9 ± 4</td>
<td>10 ± 16</td>
<td>12 ± 16</td>
</tr>
<tr>
<td>PSD CBFv cm²/s²/Hz</td>
<td>13 ± 19</td>
<td>10 ± 16</td>
<td>11 ± 19</td>
<td>12 ± 16</td>
</tr>
<tr>
<td>Coherence</td>
<td>0.42 ± 0.12</td>
<td>0.64 ± 0.15*</td>
<td>0.70 ± 0.16*</td>
<td>0.55 ± 0.12‡‡</td>
</tr>
<tr>
<td>Gain</td>
<td>0.64 ± 0.24</td>
<td>0.88 ± 0.35*</td>
<td>0.85 ± 0.25*</td>
<td>0.97 ± 0.33††</td>
</tr>
<tr>
<td>Phase shift radians</td>
<td>0.48 ± 0.28</td>
<td>0.17 ± 0.21*</td>
<td>0.27 ± 0.09*</td>
<td>0.25 ± 0.19*</td>
</tr>
<tr>
<td>ARI</td>
<td>4.4 ± 1.0</td>
<td>2.8 ± 0.9*</td>
<td>2.8 ± 1.0*</td>
<td>3.3 ± 1.6*</td>
</tr>
</tbody>
</table>

*Different from sea level (SL); †different from arrival at 5,260 m (ALT1); ‡different from after 16 days of acclimatization (ALT16). n = 14; mean ± SD. POST7, re-exposure to 5,260 m after 7 days at 1,525 m; PaO2, partial pressure of arterial oxygen; PaCO2, partial pressure of arterial carbon dioxide; HR, heart rate; ABP, arterial blood pressure; CBFv, cerebral blood flow velocity; PSD, power spectral density; ARI, autoregulation index.
CBFv was unaltered, but increases in transfer function coherence (P < 0.001) and decreases in phase shift (P < 0.05) and ARI score (P < 0.001) were consistent (in 13 of 14 subjects) with the definition of impaired CA at ALT1.

**Effect of acclimatization to high altitude.** Acclimatization increased resting PaO2 (27%) and decreased PaCO2 (22%) from ALT1 to ALT16 (both P < 0.001), without affecting HR, ABP, or CBFv. Measures of CA at ALT16 were unchanged from ALT1 and remained impaired relative to SL in the very low frequency range (all P < 0.010; Table 1 and Fig. 1).

**Effect of re-exposure to high altitude.** Resting PaO2 and PaCO2 at POST7 fell between ALT1 and ALT16 values (all P > 0.05 vs. ALT1 and vs. ALT16), indicating that the degree of acclimatization achieved at ALT16 was partially maintained at POST7. Assessments of CA at POST7 were similar to those at ALT1 and ALT16 and remained impaired relative to SL in the very low frequency range (P < 0.050; Table 1 and Fig. 1).

**Association between CA and AMS.** Of the 21 subjects, 17 reported symptoms of at least moderate AMS at ALT1 (LLQ = 6.4 ± 2.2), 10 of who met the criteria for severe AMS (LLQ = 7.8 ± 1.7). Correlations among CA metrics preceding the development of AMS symptom were weak (all r < 0.50, P > 0.050; Fig. 2). The ROC analysis revealed that ARI scores measured at SL were not sensitive or specific predictors of moderate (AUC = 0.54, P = 0.788) or severe (AUC = 0.69, P = 0.139) AMS. Additionally, the degree of impairment in CA (measured as the change in ARI from SL to ALT1) was not a sensitive or specific predictor of moderate (AUC = 0.53, P = 0.881) or severe (AUC = 0.72, P = 0.124) AMS. None of the 14 subjects studied at POST7 reported symptoms of AMS; thus associations with CA could not be tested.

**DISCUSSION**

The key findings of this study were that CA, as assessed by transfer function analysis, is 1) impaired upon rapid ascent to high altitude, 2) unaffected by acclimatization or 3) subsequent re-exposure to the same altitude, and 4) not a sensitive or specific predictor of AMS. Based on our results, we question whether the so-called impairment in CA that persists at high altitude is characteristic of pathological insufficiency in cerebrovascular regulation (16) or alternatively, reflects a relatively benign relaxation in autoregulation.

**Effect of high altitude on CA.** This is the first longitudinal study of CA at high altitude—from rapid ascent through acclimatization and upon re-exposure after a short period at low altitude. We show that impairment of CA was a consistent characteristic across this high-altitude exposure profile. Increased transfer function coherence and gain, along with reduced phase shift and ARI score upon rapid ascent, were all consistent with the definition of impaired CA at ALT1 (LLQ = 6.4 ± 2.2), 10 of who met the criteria for severe AMS (LLQ = 7.8 ± 1.7). Correlations among CA metrics preceding the development of AMS symptom were weak (all r < 0.50, P > 0.050; Fig. 2). The ROC analysis revealed that ARI scores measured at SL were not sensitive or specific predictors of moderate (AUC = 0.54, P = 0.788) or severe (AUC = 0.69, P = 0.139) AMS. Additionally, the degree of impairment in CA (measured as the change in ARI from SL to ALT1) was not a sensitive or specific predictor of moderate (AUC = 0.53, P = 0.881) or severe (AUC = 0.72, P = 0.124) AMS. None of the 14 subjects studied at POST7 reported symptoms of AMS; thus associations with CA could not be tested.
hypoxia was achieved in a matter of minutes (5, 10, 26, 34), and studies of trekkers, where several days of progressive ascent preceded initial high-altitude measurements (1, 2, 12, 37). Impaired CA at rest in acute hypoxia is a consistent finding among all but one study (26), suggesting that neither the mode nor rate of ascent appears to affect the general assessment.

By evaluating CA upon initial exposure and after 16 days at high altitude, we were able to determine if changes in CA occur with acclimatization, as might be expected with increased PaO₂ (2, 35), decreased PaCO₂ (19, 23, 26), and further sympatoexcitation (1). On the contrary, we found no change in CA over the course of acclimatization (Table 1). Our longitudinal findings are consistent with other cross-sectional studies, demonstrating impaired CA at various time points after arrival at high altitude (1, 2, 7, 11, 12, 37) and in permanent high-altitude residents (12, 13). These results may indicate that assessment of CA are less sensitive to changes in PaO₂ and PaCO₂ near their respective extremes. Alternatively, a slight improvement in CA, due to increased PaO₂ (2, 35), may have been masked if the opposing effects of PaCO₂ (19, 23, 26) and/or sympatoexcitation (1) on CA were heightened over time at altitude. Further testing with manipulation of arterial gases and sympathetic activity is necessary to determine the relative influence of arterial gases and neural stimulation on CA at high altitude, yet impaired CA remains a consistent, functional consequence across time at high altitude.

As an additional test of the hypothesis that impaired CA is a consistent response to hypoxemia, we sent subjects down to low altitude for 7 days and re-evaluated their CA response after a second rapid ascent back to high altitude. Upon re-exposure, the measured impairment in CA was similar to that observed upon the first ascent (ALT1) and after acclimatization (ALT16). Together, these results demonstrate that impaired autoregulation was a consistent characteristic of hypoxemia across our study and imply that slow fluctuations in arterial pressure were dampened less effectively by the cerebral vasculature, regardless of the state of acclimatization. What remains to be determined is if such a tenuous pressure-flow relation may be potentially harmful.

Relation of CA to AMS. Impairment of CA has been suggested to play a role in the development of AMS by either permitting cerebral overperfusion and mechanical disruption of the blood brain barrier (i.e., vasogenic cerebral edema) when mean ABP is elevated or by cerebral underperfusion and exacerbation of cerebral hypoxia/ischemia when mean ABP is lowered (9, 16). In the present study, we found no correlation between measures of CA and subsequent AMS symptom scores (Fig. 2), which opposes the notion that lower CA predisposes people to AMS or conversely, that higher CA confers protection from AMS. Our additional ROC analyses of AMS status confirmed that ARI scores were neither sensitive nor specific indicators for the development of moderate or severe AMS upon arrival at high altitude. These findings are congruent with our previous report following the time course of changes in CA and AMS symptoms over the first 10 h of exposure to hypobaric hypoxia (35), where we found similar levels of CA impairments in subjects who eventually developed AMS or stayed healthy, but are at odds with other studies showing some association between CA and AMS symptoms (5, 37). Our data also counter a recent finding that SL assessments of CA predict ensuing severity of AMS (7).

Discrepancies among studies may be explained by the various methods used to assess CA (transfer function vs. leg cuff; see Limitations below), the questionnaires used to assess AMS (LLQ vs. Environmental Symptoms Questionnaire), and the statistical approach used to evaluate the relation between CA and AMS (correlation vs. ROC). We acknowledge that caution should be exercised when interpreting correlations with an ordinal-level variable, such as the LLQ score, because by definition, the scale has limited mathematical meaning. For example, a LLQ score of six does not imply that symptom severity is exactly twice that of a score of three. Due to the intrinsic level of measurement, we believe that LLQ scores are best restricted to dichotomous classification of positive or negative AMS status and thus place more emphasis on the negative results of our ROC analysis. We encourage others to consider this method of analysis for future AMS studies.

Overall, given the similarity in CA responses among individuals with a wide range of AMS scores, we do not believe that changes in CA cause AMS. This assertion is supported further by the complete lack of association between impaired CA at POST7 when no symptoms of AMS were reported and previous reports documenting impaired CA in healthy, high-altitude natives (12, 13). Nonetheless, we must acknowledge that the alteration in CA upon acute altitude exposure may set up a tenuous pressure-flow relation that could permit AMS to develop if other, yet-unidentified factors are present at the same time.
Since impairment of CA appears to be a consistent physiological response in hypoxic environments and unrelated to AMS status, it is tempting to speculate that the underlying change in the cerebral pressure-flow relation may actually promote successful acclimatization or adaptation to chronic states of hypoxemia (4). It is possible that impairment of CA could promote cerebral oxygen delivery in a time of need, since it allows greater cerebral perfusion for a given increase in ABP. This potentially beneficial consequence of impaired CA during hypoxic stress might outweigh the relative risk of reduced cerebral perfusion if ABP were to drop. We therefore raise the possibility that the term “impaired CA” may be a misnomer, because it implies an association with pathology that has yet to be substantiated in acute or chronic hypoxemia. We suggest that “relaxation of CA” might be a more accurate term to describe changes in the cerebral pressure-flow relation from normoxia to hypoxia in the absence of pathology.

Limitations. One major limitation affecting the field is the lack of a gold-standard method to assess CA. We have chosen to evaluate rhytmical fluctuations in CA via transfer function analysis, primarily because we believe it captures the natural cerebral pressure-flow relation over time and thus has greater practical relevance over methods that induce larger, more abrupt changes in ABP, as with leg-cuff inflation/deflation, rapid tilting, or more sustained changes in ABP, such as with pharmaceutical interventions. Still, we acknowledge that transfer function analysis of resting data monitors relatively subtle fluctuations in ABP and CBFv, which if amplified, may not show impairment in CA (39). These factors may limit the generalizability of resting CA assessments and lead to an overstatement of the clinical relevance of the findings. Additionally, there are no universal standards for the parameter settings used in transfer function analysis or interpretation of subsequent results, which makes comparisons among studies problematic. Future work is needed to clarify differences in methods used to assess CA in hypoxemic states and evaluate if these changes are generalizable to clinical settings.

Most CA studies rely on transcranial Doppler measurements of flow velocity and assume that vessel diameter is unchanged; yet, there is evidence to suggest that this assumption may be invalid at extreme altitudes (39, 40). Dilation of the MCA at ALT1 may explain why MCA velocity did not follow the expected increase in CBF upon acute exposure to high altitude (30). We do not believe potential MCA dilation affected our interpretation, because the phase shift—our primary criterion for assessing changes in CA—measures the relative timing of oscillations in ABP and CBFv and thus is largely independent of absolute flow. However, since small changes in diameter can have profound effects on flow (flow ~ radius$^4$), future studies must consider the use of continuous flow measurements, instead of velocity measurements, to assess CA accurately in hypoxia.

Finally, our measurements of CA were limited to the MCA and relied on pressure measurements taken in the radial artery. Since regional differences in cerebrovascular regulation have been reported recently (20, 28, 38), more specific measurements of regional pressure and flow are needed to characterize CA fully.

Conclusions. Our data demonstrate that the initial impairment of CA upon acute exposure to high altitude is invariant with acclimatization and re-exposure, suggesting that relaxation in the regulation of the cerebral pressure-flow relation is a characteristic response to hypoxia that is unaffected by the degree of acclimatization. Since changes in CA do not follow the progression and resolution of AMS, we question the clinical relevance of impaired CA at high altitude.

ACKNOWLEDGMENTS

This paper is part of a series, titled “AltitudeOmics,” which together, represents a group of studies that explored the basic mechanisms controlling human acclimatization to hypoxia and its subsequent retention. Many people and organizations invested enormous amounts of time and resources to make AltitudeOmics a success. Foremost, the study was made possible by the tireless support, generosity, and tenacity of our research subjects. AltitudeOmics principal investigators were Colleen G. Julian, Andrew T. Lovering, Andrew W. Subudhi, and Robert C. Roach. A complete list of other investigators on this multinational-collaborative effort, involved in development, subject management, and data collection, supporting industry partners and people and organizations in Bolivia that made AltitudeOmics possible, is available elsewhere (32).

GRANTS

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DISCLOSURES

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS


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REFERENCES

1. Ainslie PN, Lucas SJ, Fan JL, Thomas KN, Cotter JD, Tzeng YC, Burgess KR. Influence of sympathoexcitatio...


