A Review of Cerebral Edema, Cerebral Perfusion, and Intracranial Pressure Elevations in Acute Sickness

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Abstract
We hypothesized that cerebral alterations in edema, perfusion, and/or intracranial pressure (ICP) are related to the development of acute mountain sickness (AMS).

Introduction

The underlying pathophysiology of acute mountain sickness (AMS) remains poorly understood. It has long been hypothesized that AMS is related to cerebral edema and/or elevations in intracranial pressure (ICP) (Sutton and Lassen 1979). Some evidence further suggests that AMS may be caused by mild cerebral edema of vasogenic origin (Hackett et al. 1998; Bailey et al. 2004; Wilson and Milledge 2008). Alternatively, it has been suggested that vasogenic edema is an adaptive response to hypoxic exposure and that AMS instead represents a maladaptive cytotoxic edema state (Fischer et al. 2004; Kallenberg et al. 2007; Lawley et al. 2013). More limited evidence suggests that not only hypoxia, but the hypobaria of high altitude may contribute to the development of AMS (Roach et al. 1996; Schommer et al. 2010; Fulco et al. 2011; DiPasquale et al. 2015), possibly through alterations in body fluid regulation (Roach et al. 1996), although this remains controversial (Girard et al. 2012; Millet et al. 2012a,b; Mounier and Brugniaux 2012). In addition, an association between exercise and increased AMS has been described (Roach et al. 2000; Mairer et al. 2012), but this has not been reliably found (Rupp et al. 2013). The relationship between AMS, exercise duration, and cerebral edema has been difficult to investigate due to logistical challenges of conducting brain imaging in hypoxic environments along with exercise.

The few studies using conventional MRI and CT scans to investigate cerebral changes with AMS have found inconsistent evidence of increased cerebral edema or swelling (Levine et al. 1989; Morocz et al. 2001; Mairer et al. 2012). Subjects in these prior studies could not be continuously exposed to altitude, however, requiring either descent from hypobaric hypoxia for scanning, or switching to normobaric hypoxia. Symptom reduction or the lack of sustained hypobaria may have contributed to the inconsistencies. It is thus preferred that cerebral monitoring be conducted before, during, and after ascent to high altitude while the key environmental conditions are sustained and the AMS pathophysiologic process is active.

In this study, we investigated the hypothesis that AMS is related to alterations in cerebral edema, perfusion, and ICP. We simultaneously investigated the role of hypobaria and exercise in the evolution of cerebral physiology in relation to AMS. To achieve this, we utilized radio- frequency near- infrared spectroscopy (RF- NIRS) and ONSD ultrasonography techniques to measure cerebral parameters before, during, and after exposure to reduced barometric pressure, hypoxia, and exercise.

Environmental exposures

Subjects were naïve to the assigned conditions. They were not provided any information on which room was for NN, NH, or HH, and all research personnel used supplemental oxygen regardless of the condition.

NN was performed in the hypobaric chamber at $P_B = 752$ mmHg, which enabled secure sealing of the chamber door, further ensuring subject naivety ($PIO_2 = 147.3$ mmHg; 300 m equivalent altitude). HH was performed in the hypobaric chamber ($P_B = 439$ mmHg; $PIO_2 = 81.9$ mmHg; 4400 m equivalent altitude). NH was performed at ambient pressure in a hard vinyl- sided hypoxia room (Colorado Altitude Training, Boulder, CO) with ambient oxygen partial pressure matched to the HH condition at 91.7 mmHg ($P_B = 760$ mmHg; $PIO_2 = 86.1$ mmHg; 4400 m equivalent altitude). Following all testing, subjects were asked if they knew which conditions they participated in, and >90% could not or incorrectly guessed their experimental condition.

Exercise

After ascent was complete, subjects assigned to 60 min of exercise began cycling immediately while subjects assigned to 10 min began 50 min later , so that all exercise sessions ended at the same time of exposure. Cycling was performed at $52.1 \pm 4.4\%$ of heart rate reserve (HR_{rsv}) (Excalibur Lode, Groningen, The Netherlands). HR_{rsv} was calculated using age- predicted HR_{max} and HR_{rest} measured on a day prior to the environmental exposures to minimize anticipatory effects. Target HR was stabilized within 5–8 min. Absolute exercising workload was adjusted to maintain target HR. Exercising HR was measured via 3- lead ECG (Physioflow, Poissy, France).

Near-infrared spectroscopy measurements

Near- infrared spectroscopy measurements were made with a customized 4- wavelength RF- NIRS system (ISS, Champaign, IL), incorporating 690, 780, 830, and 850 nm light sources and two source- detector separations (1.25 and 3.5 cm) in each of two sensor pads. For localization, structural (MEMPRAGE) and BOLD- contrast functional MRI maps were imported into a Brainsight- 2 stereotactic system (Rogue Research, Montreal, Canada) and used to localize the two NIRS probes over regions of multitask response- related activation in the anterior prefrontal cortex on a subject- by- subject basis. All locations were over the anterior middle frontal gyrus, typically within 1 cm of F3 and F4 in the International 10/20 system (Homan et al. 1987). Measurements were made at 12.5 Hz during quiet, seated rest to obtain stable baseline tissue perfusion and scattering measurements. Near- infrared spectroscopy data was analyzed using custom software, portions of which are included in the HomER NIRS processing package. Additionally, the slope method (Hueber et al. 2001), which determines scattering (μ_s'), oxy- hemoglobin (HbO_2), deoxyhemoglobin (HHb), and total hemoglobin (HbT) concentrations while simultaneously eliminating effects from overlying tissue layers such as scalp, was used. Since scattering affects all four wavelengths similarly, we computed a mean μ_s' across wavelengths to reduce variability. Immediately after the resting baseline period, subjects conducted three 5 sec Valsalva maneuvers (at 40 sec intervals) followed by three 5 sec Mueller maneuvers (also at 40 sec intervals).

Maneuvers were made by continuously exhaling (Valsalva) or inhaling (Mueller) against a fixed gradient to maintain a manometer pressure of 40 mmHg. Trials were dropped when this pressure could not be maintained (<1% of all trials). We then measured the initial hemodynamic response (baseline- to- peak/- trough) associated with each maneuver. If ICP was substantially elevated, we hypothesized that the response to Valsalva (Mueller) maneuvers would be reduced (enhanced) due to cerebral counter pressure. For baseline measures, NIRS data was averaged over a 100 sec period during each recording session that was deemed free of motion artifacts (rare but occasionally occurred). For Valsalva (Mueller) maneuvers, we computed the change in HHb and HbO_2 concentrations between the mean of the 5 sec prior to Valsalva (Mueller) and the response at the peak (trough).

Given the nature of the RF- NIRS technology, it is possible for "crosstalk" to occur between measurements, wherein a change in scattering is interpreted as a change in absorption (μ_a) or vice versa. Since the identified changes in both scattering and absorption were small, we conducted two follow- up titration experiments with our ISS instrument. In the first, a solution of India ink was diluted while maintaining fixed 1% Intralipid concentration ($\mu_s' = 10$), measuring μ_a and μ_s' at six dilution steps. Regression analysis revealed a mean $\Delta\mu_s' = 16.9 \pm 2.7$ cm^{-1} per unit change in μ_a. Thus, the observed Δ[HbT] $= +3.3$ μmolL^{-1}, equivalent to $\Delta\mu_a = 0.005$, would be expected to generate a crosstalk $\Delta\mu_s' = 0.08 \pm 0.01$ cm^{-1}. This is less than a quarter of the observed scattering change and hence not a substantial contributor to our scattering results. In the second titration, a 1% concentration of Intralipid was diluted with an India ink and water solution to maintain a constant absorption ($\mu_a = 0.0133$) while decreasing scattering. We again measured μ_a and μ_s' at six dilution steps (up to a 30% reduction in μ_s'). Regression analysis of μ_a versus μ_s' gave a mean (across wavelengths) change of 0.08 ± 0.002 in μ_a per unit change in μ_s'. The observed $\Delta\mu_s' = 0.35$ cm^{-1} would be expected to generate crosstalk of $\Delta\mu_a = 0.0028 \pm 0.0007$, or Δ[HbT] $= 1.8 \pm 0.4$ μmolL^{-1}. Thus, the potential crosstalk from the observed μ_s' change of 0.35 cm^{-1} to [HbT] was approximately half of the observed Δ[HbT] $= 3.3$ μmolL^{-1}. The crosstalk error bounds cannot explain the entire observed increase in [HbT], but it is possible that crosstalk from our observed scattering change influenced our [HbT] concentration estimates.

In this study, we investigated three cerebral measures previously hypothesized to be related to the development of AMS, normobaric hypoxia, and hypobaric hypoxia during environmental exposures. The findings included: (1) a significant increase in light scattering through brain tissue, μ_s', previously associated with cerebral edema; (2) a significant but small increase in [HbT] associated with AMS+, suggesting mildly increased cerebral perfusion; and (3) a significant but small increase in ONSD associated with AMS illness, suggesting mildly elevated ICP.

Our first finding was the significant increase in scattering. Changes in light scattering in tissue can arise from various causes, specifically including alterations in refractive index, particle size distributions, or tissue density. Hemorrhage and edema are the most common cerebral changes that would alter these properties. However, hemorrhage would also be associated with a strong increase in light absorption and [HbT] (due to pooling of highly absorbing hemoglobin), whereas edema involves buildup of water and should cause very small or no change in absorption.

Conclusion

Our NIRS results support the hypothesis that even in asymptomatic individuals, exposure to either NH or HH results in measurable cerebral edema, and that AMS contributes additional cerebral edema. As compared with asymptomatic subjects, those with AMS also had evidence of increased cerebral perfusion and mildly elevated ICP, suggesting a cerebral response to AMS development. The nature, cause, time course, and interindividual variability of the additional edema associated with AMS, and associated perfusion or ICP changes remains to be understood.

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