ORIGINAL RESEARCH

Optic Nerve Sheath Diameter and Acute Mountain Sickness

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Objective.—Increased intracranial pressure (ICP) may contribute to acute mountain sickness (AMS). Measuring optic nerve sheath diameter (ONSD) by ultrasound (US) is a noninvasive technique to detect elevated ICP, and increased ONSD has been associated with AMS. We hypothesized that ONSD would increase with acute, rapid ascent to 4300 m and that increased ONSD would be associated with symptoms of AMS. We further hypothesized that treatment with oxygen at 4300 m would reduce symptoms and ONSD.

Methods.—A cohort study was performed comparing US measurement of ONSD in healthy subjects at 1400 m and 18 hours after rapid ascent to 4300 m, both before and after oxygen treatment and between subjects with and without AMS (Lake Louise Score ≥ 3).

Results.—Among 57 subjects, 29 (51%) experienced AMS after rapid ascent to 4300 m. In subjects without AMS, mean ONSD did not increase at 4300 m. In subjects with AMS, mean ONSD increased at 4300 m and was higher than in those without AMS. Treatment with oxygen lowered mean ONSD in subjects with AMS but not in those without AMS. Individual responses to altitude and oxygen varied greatly within groups, and the relationship between ONSD and AMS symptoms was weak.

Conclusions.—In this controlled study, mean ONSD increased in subjects with AMS at high altitude. However, individual variation was high, and most ONSD values were below the clinical threshold for raised ICP. Observed differences were small, of questionable clinical importance, and within the range of precision of the US machine. Overall, our data do not support a role for increased ICP in mild to moderate AMS.

Key words: acute mountain sickness, optic nerve sheath diameter, intracranial pressure, cerebral edema, hypoxia, high altitude

Introduction

Rapid ascent to altitudes greater than 2500 m may cause acute mountain sickness (AMS), characterized by headache plus other symptoms such as gastrointestinal upset, fatigue, dizziness, and sleep disruption.¹ More rapid ascents, especially to higher altitudes, are associated with a higher risk of AMS and even cerebral edema.² Increased intracranial pressure (ICP) arguably plays a role in the development of moderate to severe AMS.^{3,4} The “tight-fit hypothesis” suggests that as brain volume increases

with hypobaric hypoxia within a nonconforming structure, so does ICP. When elevations in ICP are ineffectively compensated for or improperly buffered, then the defining symptoms of AMS may develop.⁵ This hypothesis to explain the development AMS has not yet been sufficiently tested.

The gold standard for measuring ICP is through direct access of the ventricular system with pressure monitoring systems that are placed during invasive neurosurgical procedures. It is neither generally practical nor ethical to use these methods to obtain ICP measurements at high altitude in human research subjects, although it has been done.⁵

Optic nerve sheath diameter (ONSD) has been used as a surrogate for estimating ICP because the optic nerve

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sheath is contiguous with the meninges and therefore subject to pressure changes in the intracranial space. Such pressure changes are transmitted equally throughout the cerebrospinal fluid, thereby leading to increases in ONSD. Numerous, high-quality studies in patients with head trauma, intracranial infection, or mass lesions demonstrate that ICP correlates directly with ONSD.⁶ Optic nerve sheath diameter can be measured noninvasively with portable ultrasound (US) machines with low interobserver and intraobserver variability.^{7,8} At present, ONSD is only a qualitative measurement of elevated ICP, and a recent meta-analysis suggests that ONSD measurements of 5.2 to 5.9 mm are indicative of raised ICP.⁶

This technique, owing to its inherent advantages, has been used to detect elevated ICP at high altitude.^{4,9} These studies demonstrated that ONSD increased in climbers ascending to high altitude, and greater ONSD measurements were associated with the presence and severity of AMS in high altitude trekkers.^{4,9,10} We therefore hypothesized that ICP, as measured by US ONSD, would increase with acute, rapid ascent to high altitude (4300 m) and that a greater change in ONSD would be associated with symptoms of AMS. We further hypothesized that treatment with oxygen at high altitude would reduce both symptoms and ONSD.

Methods

SUBJECTS

Healthy volunteers between the ages of 18 and 70 years were recruited from Colorado Mesa University. Exclusion criteria included 1) significant preexisting cardiovascular or pulmonary disease, diabetes, trying to conceive, or pregnancy; 2) bleeding disorder or anticoagulation medication use (including aspirin); 3) alcohol consumption 24 hours before ascent; 4) current viral infection or flulike symptoms; 5) use of acetaminophen or nonsteroidal anti-inflammatory drugs during the study; 6) allergies to sulfa drugs; or 7) sleeping at an altitude above 2133 m 30 days before the study. The Colorado Mesa University Institutional Review Board approved this study.

STUDY PROTOCOL

Baseline ONSD was obtained at 1400 m 2 weeks before ascent or 4 months after ascent. Subjects were driven to the summit of Pike's Peak at 4300 m from 1400 m in 4 hours. Optic nerve sheath diameter measurements were made within 4 hours of arrival and after 18 to 23 hours at 4300 m, or earlier if the subject became too ill before the 18-hour time point. Subjects filled out Lake Louise

Score (LLS) questionnaires at baseline, on arrival to 4300 m, and after 18 hours at high altitude or earlier if the subject became too ill before the 18-hour time point.

Effects of oxygen were evaluated at baseline and after 18 hours at 4300 m. Subjects were treated with 30 minutes of oxygen by nasal cannula after initial ONSD measurement, and then ONSD was measured again. Oxygen was titrated to raise peripheral oxygen saturation to greater than 90% at 4300 m. Heart rate and oxygen saturation were measured by Datex-Ohmeda TuffSat (GE Healthcare, Helsinki, Finland) contemporaneously with ONSD measurements.

Acute mountain sickness was defined as an LLS of 3 or greater with headache. Subjects who experienced severe symptoms and wished to receive treatment before the 18-hour time point had ONSD and LLS measured at that time and were then placed on oxygen to raise saturation above 90% for 30 minutes, and ONSD and headache scores were measured again. Subjects were then treated with further oxygen and dexamethasone as necessary to relieve symptoms of AMS.

OPTIC NERVE SHEATH DIAMETER MEASUREMENTS

Two operators measured ONSD noninvasively by US (Micromaxx, Sonosite, Bothell, WA) using a D2 13-6 MHz transducer (Sonosite, Bothell, WA). Every attempt was made to have the same operator scan the same subjects at all time points. Subjects lay supine, with eyes closed. A thick layer of US gel was applied to the high-frequency US transducer, and the handheld US probe was gently placed on the external surface of the upper eyelid without compressing the eye. A minimum of 3 axial images showing the optic nerve sheath posterior to the globe in line with the posterior aspect of the lens was obtained from each eye and digitally recorded. The cross-sectional diameter of the optic nerve sheath was measured 3 mm posterior to the globe in real time, and again by an independent, blinded observer from the recorded images. Measurements made by the blinded observer were used for our data analysis. The 3 best images, as defined by the inclusion of the posterior lens and clear margins of the optic nerve sheath, were selected by the blinded observer and measured using Image J64 software (National Institutes of Health, <http://rsbweb.nih.gov/>; Figure 1).

DATA ANALYSIS

Statistical analyses were done using Excel (Microsoft Corp, Redmond, WA) and VassarStats (<http://faculty.vassar.edu/lowry/VassarStats.html>). Mean ONSD mea-

Figure 1. Representative ultrasound image demonstrating the inclusion of the posterior lens and the point at which optic nerve sheath diameter (ONSD) was measured.

measurements were calculated from the 3 measurements made by the independent observer, and the mean of the right and left eyes was used for analyses. We compared ONSD as a function of time and altitude by a 2-way analysis of variance with repeated measures for between-subjects analysis to compare those with and without AMS. There was a significant interaction between ONSD and AMS. Therefore, we used paired Student's *t* tests for further comparisons within groups and independent Student's *t* tests for comparisons between those with and without AMS. We evaluated the relationship between ONSD and LLS using correlation coefficient. The effects of oxygen and dexamethasone on ONSD in subjects with headache were analyzed using a Student's *t* test for correlated samples.

Results

We enrolled 57 volunteers. Nine subjects had either a missing or a technically inadequate scan (eg, posterior lens not visible in image) at 1 time point. Thus, 48 subjects had data available for comparisons between baseline and high altitude. Data were available for evaluating the effects of oxygen on ONSD at high altitude in 56 subjects. The table shows summary statistics of measurements made at each time point.

Figure 2 shows individual ONSD measurements at baseline and after 18 hours at 4300 m. There was no difference in mean ONSD at baseline between those who experienced AMS and those who remained well (Table). Subjects with AMS had greater mean ONSD at high altitude compared with at low altitude, and greater ONSD at high altitude when compared to those without AMS (Table). In subjects without AMS, mean ONSD did not change at high altitude. We found no relationship between peripheral ONSD and oxygen saturation ($r^2 = .06$, data not shown) or between ONSD and LLS ($r^2 = .08$, data not shown).

Figure 3 shows ONSD after 18 hours at high altitude before and after oxygen treatment. Oxygen had no effect on mean ONSD in any subjects at low altitude (Table). At high altitude, we observed a small decrease in mean ONSD after oxygen treatment in those with AMS, but not in those who were well (Table). We were able to assess symptomatic response to oxygen and ONSD simultaneously in 17 subjects with AMS. Of those who had headache assessed before and after treatment with oxygen, 12 had relief of their headache with oxygen for 30 minutes and 5 had no or minimal relief. In the subgroup of 12 patients who had relief of their headache with oxygen, there was no change in mean ONSD before (0.44 cm; 95% confidence interval [CI], 0.38 to 0.50) and after oxygen treatment (0.42 cm; 95% CI, 0.37 to 0.47).

Nine subjects became sufficiently ill to require dexamethasone, and complete data were available on 7 of them. There was no difference in mean ONSD in symptomatic subjects measured before dexamethasone (0.49 cm; 95% CI, 0.42 to 0.56) and after, at the time when symptoms had resolved (0.42 cm; 95% CI, 0.34 to 0.50).

Discussion

We found an increase in mean ONSD in subjects who experienced AMS after rapid ascent to 4300 m and a greater mean ONSD at high altitude compared with those subjects without AMS. We also found that at 4300 m treatment with oxygen decreased mean ONSD in subjects with AMS, but had no effect on those without. Despite these observed mean differences, AMS symptoms, oxygen saturation, and clinical response to oxygen and dexamethasone were not clearly related to ONSD.

This finding of increased ONSD in AMS should be interpreted with caution for several reasons. Despite an overall mean increase in ONSD, there was large individual variability in the ONSD values with altitude, AMS, and oxygen and no correlation with LLS scores. Furthermore, the differences observed, while statistically significant, were small. Although ONSD corresponds to increased ICP at diameters greater than 0.52 to 0.55 cm,⁶

Figure 2. Change in optic nerve sheath diameter (ONSD) from baseline to 18 hours at 4300 m or too ill to continue study in individual subjects ($n = 48$). Well subjects are designated by gray, mean in red with circles; subjects with acute mountain sickness (AMS) are designated by black lines, mean in heavy black with circles.

few of our ONSD measurements reached this threshold. The small changes in ONSD we observed within the normal range are unlikely to be clinically important. Our ONSD measurements do not suggest pathologically elevated levels of ICP, but whether they reflect small changes in brain volume remains unclear.

Our results support those of previous studies that demonstrate increased ONSD at high altitude in those with AMS.^{4,9} Unlike our observations, however, previous reports documented surprisingly high ONSD measurements, even in asymptomatic patients.^{4,9} Such values are similar to those reported in obtunded patients with confirmed elevated ICP by invasive monitoring.⁶ Our results may differ from previous investigations because of the difference in ascent profile. Our subjects had a rapid,

acute exposure whereas previous studies were done in trekkers ascending more gradually.^{4,9}

The difference in ONSD values between our study and others might also be accounted for by scanning technique. Visualization of the posterior lens was one of our criteria for an adequate image because it confirms scanning in a perpendicular plane and minimizes falsely high ONSD measurements from scanning across the optic nerve sheath at an oblique angle. It is not clear whether other studies using ONSD at altitude used this standard.

Previous work using magnetic resonance imaging,¹¹ direct ICP measurement,^{3,5} slit-lamp biomicroscopy,¹² and optical photography¹⁰ has documented that brain swelling and optic nerve swelling occur at high altitude, after both rapid and gradual ascent. These studies have

Table. Summary statistics of measurements reported as mean with 95% confidence interval unless otherwise noted

Variable	Baseline	Arrival 4300 m	18 hours at 4300 m or too ill to continue
Total n	57		
Male n (%)	29 (51)		
Age (years)	24 (range 18–70)		
Peripheral O ₂ saturation (%)		81 (80.5–81.5)	85 (84.6–85.4)
LLS	0.4 (0.35–0.45)	1.7 (1.6–1.8)	2.2 (2.0–2.4)
LLS (median [IQR])	0 (0–1)	2 (1–2)	2 (0–3)
AMS n (%)			29 (51)
ONSD all subjects (cm)	0.40 (0.38–0.42)		0.42 (0.40–0.44)
ONSD well (cm)	0.41 (0.38–0.44)		0.40 (0.37–0.43)
ONSD well after 30 min of O ₂ (cm)	0.41 (0.35–0.46)		0.40 (0.38–0.42)
ONSD AMS+ (cm)	0.40 (0.38–0.42)		0.43 (0.41–0.45)*
ONSD AMS+ after 30 min of O ₂ (cm)	0.37 (0.34–0.40)		0.41 (0.39–0.43)†

AMS, acute mountain sickness; IQR, interquartile range; LLS, Lake Louise Score; ONSD, optic nerve sheath diameter.

* $P < .05$ compared with well subjects at high altitude.

† $P < .05$ compared with AMS subjects before oxygen treatment at high altitude.

not confirmed, however, a clear relationship between brain swelling and AMS.^{5,12} Furthermore, not all studies have found evidence of brain swelling after acute high altitude exposure.¹³ Although severe brain swelling is well documented in cases of high altitude cerebral edema (HACE),¹⁴ the relationship between AMS, HACE, and ICP is still undetermined, and the mechanisms of brain swelling at high altitude remain controversial.^{15,16}

LIMITATIONS

Our investigation has several strengths. We used a high-risk ascent profile,² and half the subjects experienced AMS. We had a relatively large number of subjects for a field study, and within-subject measurements, under all conditions, were available for analysis. Nonetheless, our study also has several limitations. Despite a mean increase in ONSD, almost one third of the subjects with AMS had a decrease in ONSD at high altitude. The response to oxygen at high altitude was similarly variable. The individual factors that lead to this variation remain to be identified.

We found no effect of dexamethasone on ONSD, but we cannot exclude the possibility that this subgroup was too small to detect a difference. This limitation is also true of the subgroup in whom we measured effects of oxygen on both ONSD and headache symptoms. However, given the dramatic clinical response to dexamethasone and oxygen, any difference in ONSD that we might have missed is likely to be of little clinical significance.

Finally, one must also consider the technical limits of US when interpreting our ONSD measurements as a

surrogate for ICP. We used 2 operators for the scans, and some subjects were not scanned by the same operator at all time points. Prior work has shown excellent intraobserver reliability for ONSD measurement by US.^{9,17,18} The resolution of the 13-6 MHz probe is only to within a tenth of a millimeter (0.01 cm). Prior studies have cited a difference of 0.02 cm¹⁷ to 0.04 cm⁹ as acceptable interobserver and intraobserver reliability, meaning it is possible that the magnitude of difference seen in our own and others' work could be attributed simply to variation in measurement.

Conclusions

Mean ONSD increased in subjects with AMS at high altitude. However, we found significant individual variation, and most of our subjects had ONSD values below the clinical threshold for raised ICP. Observed differences were small and within the range of precision of the US machine. Overall, our data do not support a role for increased ICP in mild to moderate AMS. Attractive as it seems for investigating raised ICP at high altitude non-invasively, optic nerve sheath US may not be an adequate tool for addressing this issue.

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Figure 3. Change in optic nerve sheath diameter (ONSD) after 18 hours at 4300 m or too ill to continue study before and after 30 minutes of oxygen treatment ($n = 56$). Well subjects are designated by gray, mean in red with circles; subjects with acute mountain sickness (AMS) are designated by black lines, mean in heavy black with circles.

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