Reversible Increase of Central Choroidal Thickness During High-Altitude Exposure

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Purpose. This study aimed to quantify the impact of high altitude on choroidal thickness and relate changes of altered choroidal blood flow to clinical parameters and acute mountain sickness (AMS). This work is related to the Tübingen High Altitude Ophthalmology (THAO) study.

Methods. Enhanced depth imaging spectral-domain optical coherence tomography was used to quantify macular choroidal layer thickness. Peripheral oxygen saturation, heart rate, and AMS scores were assessed in eight healthy subjects at baseline (altitude, 341 m) and at altitude (4559 m) for respective correlations.

Results. Longitudinal analysis revealed a significant ($P = 0.011$, ANOVA) increase in central choroidal thickness (CCT) during altitude exposure ($CCT_{baseline} = 271 \pm 9$ µm; $CCT_{altitude} = 288 \pm 9$ µm) due to an increased choroidal blood flow. Incidence of AMS at altitude was 50%, peripheral oxygen saturation decreased by 25%, and heart rate increased by 39%. All changes were completely reversible after descent to low altitudes.

Conclusions. A small but significant increase in choroidal thickness was observed upon acute altitude exposure to 4559 m. This increase in choroidal blood flow was not related to AMS and was fully reversible after return to low altitude.

Keywords: acute mountain sickness, AMS, choroidal thickness, high altitude, hypoxia, ocular blood flow, optical coherence tomography

The retina is the most metabolically active tissue by weight in the human body, and its utilization of oxygen far exceeds even that of the brain.[1] However, it is important to keep in mind that retinal oxygenation, and therefore function, depends not only on the supply of retinal circulation but also on choroidal circulation. The total volume of choroidal blood flow exceeds that of retinal blood flow significantly and therefore has the capacity to supply most of the retina's oxygen. Both of the circulations have the ability to autoregulate and maintain a constant blood flow for stable oxygen delivery and levels under normal conditions.[2,3] However, under severe stress conditions such as high-altitude exposure, this hypoxic state may lead to a decrease in vascular resistance resulting in vasodilation to meet the very high metabolic demand for oxygen, which in turn may cause morphological changes to the choroid.[4]

The fact that blood flow of the brain is altered during the course of prolonged hypoxia is well documented.[5–7] It has been shown that cerebral blood flow increases primarily during high-altitude exposure in order to acclimatize.[8] Furthermore, it has been postulated that an increase in cerebral blood flow on a capillary level resulting from altered autoregulation leads to capillary overperfusion and vasogenic cerebral edema in the form of acute mountain sickness (AMS) and/or high-altitude cerebral edema (HACE).[9,10] According to this hypothesis, it is of great interest to further study the autoregulation of the choroidal circulation unit, also in regard to high-altitude illnesses.[11]

Conventionally, clinical evaluation of the choroid has been performed using indocyanine green angiography or B-scan ultrasonography. With the invention of spectral-domain optical coherence tomography (SD-OCT) with enhanced depth imaging (EDI), accurate quantitative measurements of choroidal morphology are now feasible.[12] Recent studies emphasize the interest and relevance of the choroidal vasculature for studying hypoxia-related diseases.[12–14]

The aim of our study was to compare choroidal thicknesses in healthy subjects before and during acute exposure to high altitude at 4559 m, using state-of-the-art equipment to investigate the choroid's response to severe hypoxia and to assess potential correlation with AMS and related clinical parameters.

Methods

Study Design

A total of 14 healthy subjects ascended to the Capanna Margherita (CM; Valais Alps, Italy) according to the following previously published ascent profile[15] (Fig. 1): day 0 from Gressoney (Italy), 1635 m, to Punta Indren, 3260 m, by cable car, followed by 2 hours of hiking to Capanna Gnifetti, 3647 m;

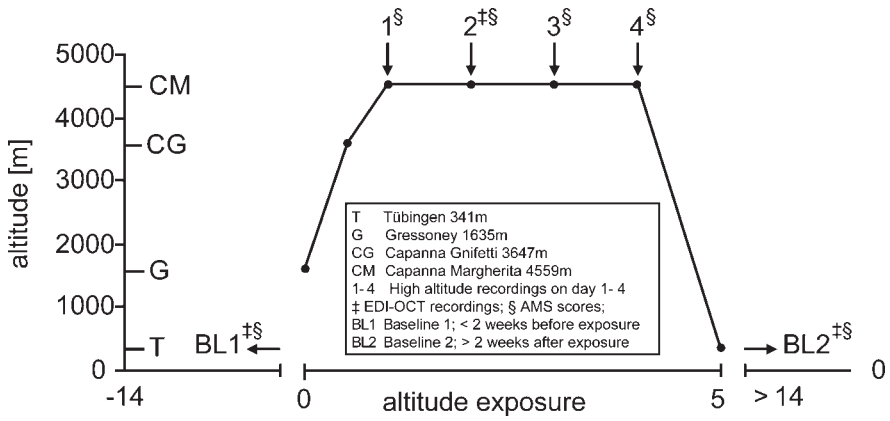

Figure 1. Ascent profile of the THAO study. *Abscissa* shows time course of measurements (*legend in box*), and the *ordinate* illustrates altitudes: T, Tübingen, 341 m; G, Gressoney, 1635 m; CG, Capanna Gnifetti, 3647 m; CM, Capanna Margherita, 4559 m. Enhanced depth imaging for quantification of choroidal thickness was performed at baseline 1, day 2, and baseline 2 (‡), whereas acute mountain sickness was assessed every day (§).

and day 1 ascent to CM, 4559 m, in 4 to 6 hours. All subjects ascended within 24 hours from Gressoney to CM and spent 3 nights (days 1–4) at CM before descending back to Gressoney on day 4. Before baseline (BL) recordings (BL1 = before, and BL2 = after the climb) and ascent, subjects had to spend >14 days below 2000 m to exclude confounding effects due to previous altitude exposure. All subjects were healthy and physically fit (seven females, seven males; 25–54 years of age). Clinical assessment of AMS and vital parameters was performed as previously published.[15] Briefly, Lake Louise (LL) and AMS cerebral score (AMS-C) of the Environmental Symptom Questionnaire (ESQ III) were used twice daily to assess prevalence of AMS, defined as LL $\geq$ 5 in the presence of headache and AMS-C $\geq$ 0.70.[16]

Ophthalmological exclusion criteria were presence of disorders affecting the macular region, best corrected visual acuity (BCVA) of >0.3 (logMAR) in either eye, and optical opacities limiting imaging quality. Enhanced depth imaging in the macula was performed at BL1, on day 2 at altitude, and at BL2 in all but one subject: unfortunately, one male subject had an incomplete data set at BL1 and was therefore excluded from further analysis. The study was performed in accordance with the tenets of the Declaration of Helsinki 1975 (1983 revision) and was approved by the local institutional review board (IRB Ethik-Kommission der Medizinischen Fakultät und am Universitätsklinikum Tübingen, IEC project number: 258/2010B01). All subjects gave written informed consent after having been informed of the nature of the research expedition. All equipment was transported by helicopter (Air Zermatt AG Heliport, Zermatt, Switzerland) in airfreight containers provided by the manufacturers.

Spectral-Domain Optical Coherence Tomography

To quantitatively measure changes in the central retinal tissue, two identical Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg, Germany) devices were used for BL measurements and for the measurements at altitude, as previously described.[17] Briefly, pupillary mydriasis was induced in subjects, using tropicamide eye drops, 5 mg/mL (Mydriaticum Stulln; Pharma Stulln, Stulln, Germany). High-resolution volume scans centered on the fovea were recorded with a scan pattern of 30 $\times$ 25° with 31 B-scans at 245-μm intervals. In order to triple signal-to-noise ratio, nine scans were averaged while correcting for eye movements using the proprietary TruTrack function. To ensure comparability of iterative measurements by correcting for errors such as tilt and orientation, we exported the data from the BL recordings performed at the University Eye Hospital Tübingen in the proprietary format (file extension .E2E) and imported it prior to follow-up measurements at altitude. Careful calibration of the laser light source of the Spectralis HRA+OCT device was performed after reassembly at altitude to ensure comparability of measurements as described in detail elsewhere.[17] Built-in software (Eye Explorer version 1.6.4.0; and Viewing Module version 5.3.2.0 [Spectralis]) was used to calculate subfoveal choroidal thickness values by using the line tool after manual segmentation of the choroid–sclera interface (Fig. 2).

Statistical Methods

Data were analyzed using Statistical Package for Social Sciences version 21 software (SPSS, Inc., Chicago, IL, USA) for Macintosh OSX (Apple, Inc., Cupertino, CA, USA). Statistical longitudinal analysis was performed using factorial analysis of variance (ANOVA) algorithm for repeated measures. Post hoc analysis was performed using Student's *t*-test with Bonferroni correction. Bivariate correlation analysis (Spearman's rank correlation) was performed to evaluate a possible correlation between choroidal thickness measurements and clinical data for AMS (AMS-C, heart rate, and peripheral capillary oxygen saturation [SpO_2]). Data are mean $\pm$ standard error unless indicated otherwise. A P value of <0.05 was set as the significance level.

Results

Clinical Parameters and AMS Scores at High Altitude

Clinical parameters of peripheral oxygen saturation decreased to 73.75 $\pm$ 4.81% in all subjects in the morning after arrival at high altitude compared to BL measurement of 98.63 $\pm$ 1.58% before exposure; mean SpO_2 for subjects suffering from AMS (AMS+) = 71.75 $\pm$ 5.40% and 75.75 $\pm$ 3.03% for healthy subjects (AMS–) at high altitude ($P > 0.05$); overall heart rate (HR) increased to 80.50 $\pm$ 9.43 min^{-1} compared to BL rate of 58.00 $\pm$ 7.22 min^{-1}; mean HR for AMS+ = 86.25 $\pm$ 6.57 min^{-1} and 74.75 $\pm$ 8.29 min^{-1} for AMS– subjects in the morning after arrival at high altitude ($P > 0.05$). All changes in clinical parameters were completely reversed after descent to low altitudes.

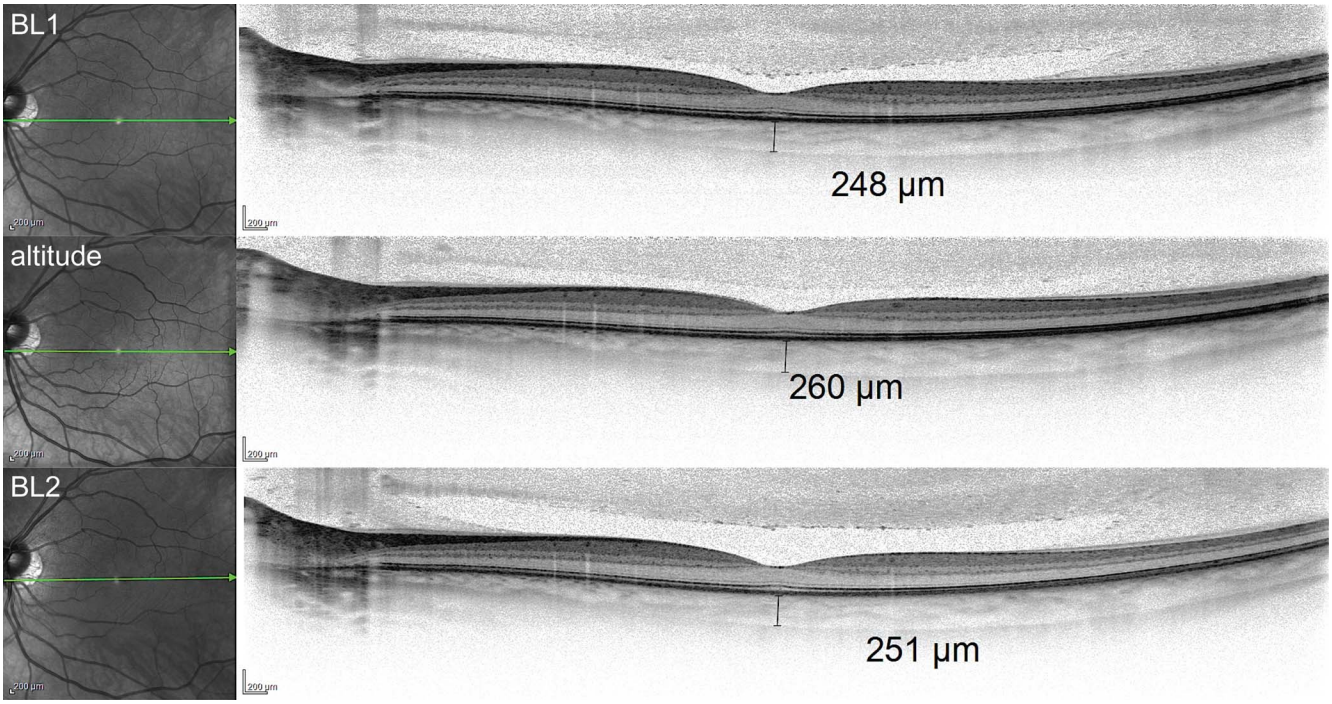

FIGURE 2. Representative recordings were made with enhanced depth imaging spectral-domain optical coherence tomography in the same healthy subject. Central choroidal thickness increases from baseline (BL1 [*top*]) to altitude (day 2 [*middle*]) and recovers after descent (BL2 [*bottom*]).

Incidence of AMS (LL $\geq$ 5 and AMS-C $\geq$ 0.7) was 50% ($n = 4$ of four subjects) in the morning after arrival at high altitude. The overall scores for AMS in all subjects were LL = 6.50 $\pm$ 0.87 for AMS+ subjects and 3.25 $\pm$ 2.38 for AMS– subjects; and the average AMS-C score for AMS+ subjects = 1.43 $\pm$ 0.47 and 0.35 $\pm$ 0.17 for AMS– subjects.

Choroidal Thickness Increases During Acute Exposure to High Altitude

Delineation of the interface between choroid and sclera can be difficult even with EDI and depends on attenuation of the laser light by structures in the optical pathway (e.g., retinal pigment epithelium) by means of scatter and reflection and, to a lesser degree, by absorption.[18] When segmenting the choroidal layer in the SD-OCT recordings, we had to exclude five subjects from quantification due to poor delineation between the choroid and underlying sclera. This might, in part, have been caused by signal attenuation due to edema formation of layers anterior of the choroid, which has been reported by this group elsewhere.[17,19]

In the remaining 8 subjects, mean $\pm$ standard error choroidal thickness on average increased from 274 $\pm$ 9 µm at BL to 288 $\pm$ 9 µm at altitude (Fig. 3). This change was fully reversed, and choroidal thickness was 271 $\pm$ 9 µm at the second BL measurement ($\geq$14 days post exposure). Even though the mean change of choroidal thickness was only 5% to 6% in total, the intraindividual changes reached robust levels of statistical significance ($P = 0.011$, ANOVA). Post hoc pairwise comparison with Bonferroni adjustment reported $P = 0.175$ between initial BL1 measurements and altitude and $P = 0.006$ between altitude and measurement after high-altitude exposure (BL2).

Choroidal Changes Do Not Correlate With Markers of Altitude Sickness

As previous studies have provided equivocal results regarding a correlation between systemic markers of altitude sickness and choroidal thickness under hypoxia and/or at high altitude, we calculated the associations among AMS-C, heart rate or SpO_2, and changes of choroidal thickness in these eight subjects.[11,20] There was no significant correlation between choroidal thickness values and AMS-C ($P = 0.51$) as an established indicator of altitude-related sickness. Likewise, no significant correlation was found for the clinical parameter heart rate ($P = 0.63$) or SpO_2 ($P = 0.08$). Scatterplots show no clear pattern indicative of a linear or nonlinear relationship (Fig. 4).

DISCUSSION

Choroidal Thickness at High Altitude

In our study, we clearly show that acute exposure to high-altitude–related hypoxia leads to an increase in choroidal

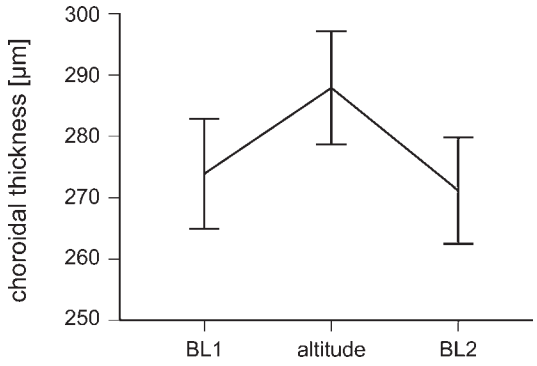

FIGURE 3. Changes in central choroidal thickness are shown during acute exposure to high altitude in healthy subjects. Mean values of central choroidal thickness are shown with mean error *whiskers* in a longitudinal follow-up of eight subjects at baseline before ascent (BL1), at altitude (4559 m), and again after descent to baseline altitude (341 m). Factorial ANOVA for repeated measures indicates statistically significant ($P = 0.011$) increases in central choroidal thickness at altitude.

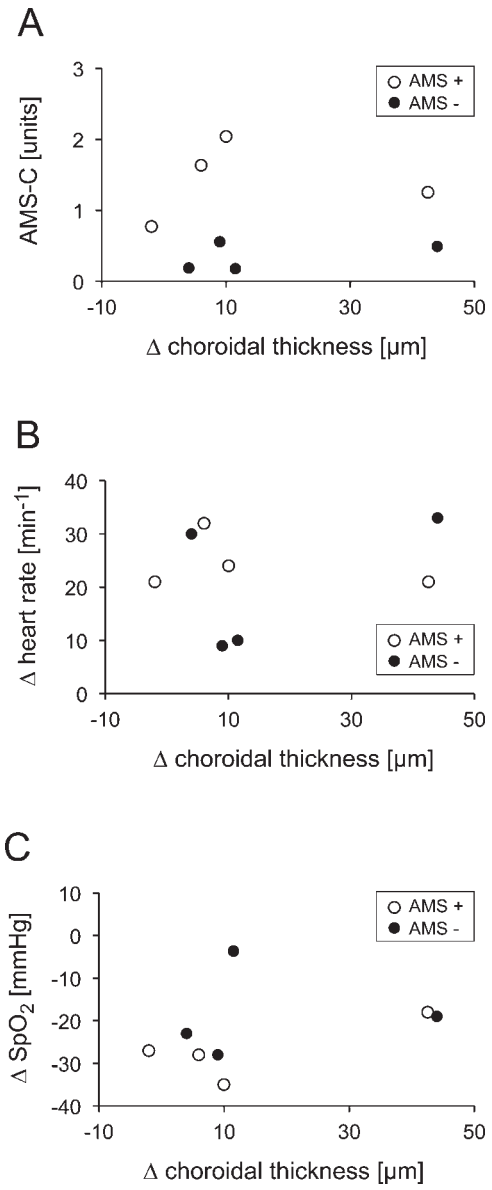

Figure 4. Bivariate correlation analysis of changes in central choroidal thickness (CCT) and indicators of acute mountain sickness. Neither AMS-C scores ($P = 0.51$) (**A**), heart rate ($P = 0.63$) (**B**), nor SpO_2 ($P = 0.08$) (**C**) correlated significantly with CCT. There is no clear relationship between systemic measurements of altitude sickness and CCT. This is also indicated by the distribution of data from individuals who were affected (AMS+ [*white circles*]) and unaffected (AMS– [*black circles*]) in the scatterplots.

thickness, presumably to counterbalance hypoxia by reactive hyperperfusion with the ultimate goal of maintaining a steady state of oxygen supply to the photoreceptors in the retina. This change would be predicted to reverse with mid- to long-term physiological adaptations on a systemic level such as increased hematocrit and others. A study investigating choroidal thickness in patients suffering from a chronic hypoxic insult support this hypothesis.[13] In concordance, choroidal thickness decreased again to levels very close to the initial readings at ≥2 weeks after descent at the second BL recording.

Correlation Among Choroidal Thickness, Clinical Parameters, and AMS

A number of previous studies have linked changes in ocular physiology and anatomy to systemic parameters affected by high-altitude exposure and the severity of high-altitude illnesses of potential cerebral origin such as AMS. These studies followed the thought that the eye presents a window to the brain and that the anatomical relationship, with communicating fluid spaces and axonal continuities between both entities, might lead to useful biomarkers for these high-altitude–related diseases affecting humans exposed to high altitude.[21] Furthermore, ocular findings may contribute to the fundamental understanding of the pathophysiology of AMS, which is still not entirely understood.[22] However, very few studies have succeeded in meeting the logistical challenges provided by high-altitude research and have used gold-standard techniques to systematically produce reproducible results in a prospective manner. In this study, we applied state-of-the-art imaging with test-retest variability in the single micrometer range to study even small changes in ocular anatomy before, during, and after exposure to high altitude.[23,24] Nevertheless, we did not find any evidence for correlating systemic vital markers or for symptoms of AMS such as AMS-C scores, heart rate, or SpO_2 with subtle but statistically significant changes in choroidal thickness. This is in line with previous reports from this group, showing that ocular changes are not associated with AMS.[15,25,26]

Limitations of the Study

The nature of the study resulted in different recording environments such as differences in air composition between BL measurements and measurements at high altitude. As SD-OCT measurements in such an environment have never been performed before, systemic errors cannot entirely be ruled out. However, great care was taken, for example, to calibrate light sources and other factors, according to the strict guidance by the manufacturers. Another potentially confounding factor was time of examination as the choroidal thickness underlies diurnal variation.[27] We therefore tried to record all EDI scans at the same time of the day (±10 min) for each subject, but this was not possible in all cases for logistical reasons. Refractive error due to axial length measurements in the eye was another source of variation of choroidal thickness but is more relevant to interindividual analysis.[28–30] Here we performed an intraindividual, longitudinal analysis, and refractive error as a factor related to axial length did not change significantly over the time of the study (data not shown). Finally, the nature of the study precluded the inclusion of a greater number of subjects, which makes the detection of significant changes more difficult.

Conclusions

We have shown that even a small number of subjects demonstrate a statistically significant increase of choroidal thickness due to acute exposure to high altitude. This change is completely reversible upon descent and is not correlated to systemic parameters or AMS.

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