Impact of Acute Exposure to High Altitude on Anterior Chamber Geometry

Gabriel Willmann,1 Andreas Schatz,1 Ahmad Zhour,1 Kai Schommer,2 Eberhart Zrenner,1 Karl U. Bartz-Schmidt,1 Florian Gekeler,1 and M. Dominik Fischer1

1Centre for Ophthalmology, University of Tübingen, Germany
2Department of Sports Medicine, Medical Clinic, University Hospital Heidelberg, Heidelberg, Germany

PURPOSE. This study aimed to quantify the impact of exposure to high altitude on individual layers of the cornea in regard to central corneal thickness (CCT) and the geometry of the anterior chamber angle (ACA). This work is related to the Tübingen High Altitude Ophthalmology study.

METHODS. Anterior segment spectral domain optical coherence tomography was used to quantify changes in individual corneal layers and to study ACA and angle opening distance (AOD). Peripheral oxygen saturation, heart rate, and scores of acute mountain sickness (AMS) were assessed in 14 healthy subjects at baseline (341 m) and altitude (4559 m) for respective correlations.

RESULTS. Longitudinal analysis revealed a significant ($P < 0.05$) increase of CCT during altitude exposure ($\text{CCT}_{\text{baseline}} = 539.27 \pm 32.30 \mu m$; $\text{CCT}_{\text{day1}} = 558.87 \pm 29.39 \mu m$; $\text{CCT}_{\text{day5}} = 567.17 \pm 33.40 \mu m$; mean $\pm$ SD) due to stromal edema. This change was completely reversible upon descent. Geometric measures of aqueous outflow structures remained consistent with no significant changes in AOD or ACA. Incidence of AMS on day 1 was 64% followed by a decrease in AMS scores over time spent at high altitude; while AMS correlated significantly with stromal edema formation just after arrival ($r = 0.71$; $P = 0.01$), no correlation was found on day 3 ($r = 0.05$; $P = 0.87$); no correlations were found for vital parameters.

CONCLUSIONS. Significant stromal edema was found during exposure to high altitude in healthy subjects. This seems to occur due to decreased atmospheric pressure under hypoxia but independent of systemic acclimatization. Other measures of anterior chamber geometry remained stable during the challenge to hypoxic conditions at high altitude.

Keywords: anterior segment, cornea, high altitude, hypoxia, eye

Exposure to altitude-related hypoxia is an increasingly relevant scenario due to rising popularity of high altitude trekking and mountaineering, where alterations of optical system parameters can potentially have deleterious effects. Indeed, visual orientation, reading instruments, and maps can become a life-saving necessity in mountaineering. Additionally, increasing numbers of people have undergone forms of corneal surgery before climbing, which might constitute an additional risk factor. At the same time, there is a growing body of literature suggesting significant alterations, which may affect proper visual function to critical components of the optical pathway such as the cornea due to high altitude exposure.2–5

Despite this obvious importance, high altitude ophthalmology studies face logistic challenges typical of fieldwork, where it may be necessary to use instruments more appropriate to the respective conditions, rather than gold standard techniques. Hence, most high altitude ophthalmology studies, for example, have used handheld devices to measure intraocular pressure6 or central corneal thickness (CCT),5 often under challenging conditions. Others have tried to circumvent this problem by recording changes several days after the exposure to altitude or simulating altitude hypoxia in hypobaric hypoxia chambers.7–10 However, measurements acquired any time after descent or in chambers may not necessarily reflect the changes during exposure to high altitude–related hypoxia.7,11 These difficulties may account for some of the variability in results and conflicting conclusions drawn from those studies.

The Tübingen High Altitude Ophthalmology (THAO) study tried to overcome these challenges by using the research facilities at Capanna Margherita (4559 m, Italy), where state-of-the-art instrumentation could be operated under standardized conditions.11,12 As such, the study design and location provided ideal logistical solutions to such an undertaking with the additional benefit of an established ascent profile already used in numerous previous studies on high altitude medicine especially in regard to acute mountain sickness (AMS) and high altitude pulmonary edema.13,14

This study aimed to quantify changes of individual layers in the central cornea and anterior chamber angle (ACA) and anterior opening distance (AOD) as measures of anterior chamber geometry during acute exposure of healthy volunteers to high altitude using high-resolution anterior segment optical coherence tomography (AS-OCT). In contrast to methods used in previous studies,7–5 which reported total thickness of the central cornea, AS-OCT allowed us for the first time to objectively quantify the impact of altitude exposure on distinct
anatomical corneal layers and to study these changes in regard to AMS by using a previously established exposure protocol in unacclimatized subjects. In addition, this method also allowed us to quantify changes in the anterior segment angle geometry, which often constitute determining clinical factors in pathological changes of intraocular pressure (IOP) due to their known effect on the aqueous outflow resistance and regulation of intraocular pressure. As such ACA and AOD may play a role in IOP changes during high altitude exposure and quantitative assessment of these additional geometric endpoints seemed relevant.

**Materials and Methods**

**Study Design**

Fourteen healthy subjects ascended to the research facility at Capanna Margherita (CM; Valais Alps, Italy) according to a previously published ascent profile (Fig. 1). Subjects started from Gressoney (Italy) at 1635 m to Punta Indren at 3260 m by cable car on day 0 followed by 2 hours of trekking to the Capanna Gnifetti at 3647 m and further ascent on day 1 to CM 4559 m within 4 to 6 hours. Ascent of all subjects was completed within 24 hours from Gressoney to CM and all subjects spent three nights (from day 1 to day 4) at the research facility at high altitude before descending back to Gressoney on day 4. Before and after high altitude exposure, subjects had to spend 14 days below 2000 m to exclude confounding effects due to previous altitude exposure and to AMS by using a previously established exposure protocol in unacclimatized subjects. In addition, this method also allowed us to quantify changes in the anterior segment angle geometry, which often constitute determining clinical factors in pathological changes of intraocular pressure (IOP) due to their known effect on the aqueous outflow resistance and regulation of intraocular pressure. As such ACA and AOD may play a role in IOP changes during high altitude exposure and quantitative assessment of these additional geometric endpoints seemed relevant.

**Anterior Segment Optical Coherence Tomography**

To quantitatively measure the thickness of individual layers of the cornea, CCT, ACA, and AOD at 500 μm two identical Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg, Germany) devices fitted with the same prototype anterior segment lens provided by the manufacturer were used for baseline recordings and for measurements at altitude as previously described. To minimize diurnal variation, all subjects (only right eyes) were assessed once a day at 9:00 AM, approximately 2 hours after awakening. All recordings were performed by the same investigator. Briefly, subjects were placed in a room with standard lighting conditions and instructed to fixate the projected visual target from the Spectralis HRA+OCT instrument with their right eye. First, high-resolution line scans of the central cornea were recorded to determine CCT and the thickness of individual layers of the cornea. Next, the gaze of subjects was directed to 30° adduction to expose the temporal limbus corneae directly to the lens of the Spectralis HRA+OCT. High-resolution line scans of the temporal part of the anterior chamber were recorded to determine ACA and AOD at 500 μm at the 9 o’clock position. For all line scans, nine recordings were averaged while correcting for eye movements using the proprietary TruTrack function in order to triple signal to noise ratio.

To ensure comparability of iterative measurements by correcting for errors such as tilt and orientation, we exported the data from the baseline recordings performed at the University Eye Hospital Tübingen in the proprietary format (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 helicopter transport (Air Zermatt AG Heliport, Zermatt, Switzerland) in airfreight containers and re-assembly at altitude to ensure comparability of measurements as previously described. On day 3, two of the subjects were not available for AS-OCT imaging due to discomfort and only data from 12 subjects were recorded.

**Measurements of Individual Corneal Layers, CCT, ACA, and AOD at 500 μm**

Built-in software (Eye Explorer v1.6.4.0 and Spectralis Viewing Module 5.3.2.0) automatically corrects for curvature of the anterior ocular surface. Proprietary analysis tools (calliper)
were used to calculate the thickness of individual corneal layers, CCT, ACA, and AOD independently by two masked, experienced investigators (AZ, MDF). For corneal thickness values, line scans across the apex of the cornea were analyzed for tear film, epithelium, stromal, and combined Descemet’s membrane and endothelial thickness (Fig. 2). The software’s calibrated callipers were used to quantify layers and values from both investigators were averaged after calculating inter-observer variability. For ACA and AOD values, the “500 Calliper tool” was placed on the scleral spur (SS) landmark structure (full arrowhead in Fig. 3a). After locating the endothelial surface 500 μm distant from the SS with the apex (Fig. 3b) of the triangular calliper tool, AOD was calculated as distance perpendicular from this point to the anterior iris surface. Lastly, the most peripheral recess of the ACA (empty arrowhead in Fig. 3a) was defined to calculate the angular degree between the adjacent sides (Fig. 3b).

Clinical Assessment of High Altitude Exposure

For assessment of clinical parameters of high altitude exposure, parameters of AMS were determined as previously described. Briefly, Lake-Louise (LL) and the AMS-cerebral scores (AMS-C) of the Environmental Symptom Questionnaire (ESQ III) were used once for baseline recording at BL1 and BL2, and twice daily during altitude exposure. In line with previous literature, AMS was assumed when both scores met the cut-off criteria set for LL ≥ 5 in the presence of a headache and AMS-C ≥ 0.70 as described previously. Measurements of oxygen saturation and heart rate (HR) were performed once at each baseline investigation and at high altitude in the morning.
before getting up and in the evening after >5 minutes rest with a finger pulse oximeter (oxy control 4c; Geratherm Medical AG, Geschwenda, Germany). Values were recorded after one minute of steady measurement.

Statistical Methods

Statistical analysis was performed using JMP (Version 8.0.2; SAS Institute, Cary, NC). Detailed longitudinal analysis was achieved by multivariate analysis of variance (MANOVA) for repeated measures. To evaluate a possible correlation between changes in thickness of individual corneal layers and AMS or basic physiologic parameters, Pearson’s correlation coefficient was calculated. Shapiro-Wilk test showed that all relevant data sets were normally distributed (AMS-C, P = 0.11; HR, P = 0.27; SpO2, P = 0.35; central stromal thickness, P = 0.22). Interobserver variability was assessed with the coefficient of repeatability (data presented for BL1 and day 1). In addition, intraclass correlation coefficients (ICC) were calculated for all time points and including all data sets (single layers, ACA and AOD) for every time point. Data are shown in terms of intra-individual variability with intraclass correlation coefficients for all time points and was assessed with the coefficient of repeatability (data distributed (AMS-C, P = 0.11; HR, P = 0.27; SpO2, P = 0.35; central stromal thickness, P = 0.22). Interobserver variability was assessed with the coefficient of repeatability (data presented for BL1 and day 1). In addition, intraclass correlation coefficients (ICC) were calculated for all time points and including all data sets (single layers, ACA and AOD) for every time point. Data are shown in terms of intra-individual variability with intraclass correlation coefficients for all recorded values ICCBL1 = 0.98, ICCday1 = 0.94, ICCday3 = 0.96, and ICCBL2 = 0.98. Likewise, repeatability coefficients (RC) indicated robust methodology and data sets both at baseline (RCACA = 26.38 μm, RCAOD = 5.75 μm, RCtearfilm = 4.05 μm, RCendothelium = 3.75 μm, RCstroma = 10.10 μm, RCtearfilm = 1.25 μm) and at altitude (RCACA = 41.53 μm, RCAOD = 5.81 μm, RCtearfilm = 5.48 μm, RCendothelium = 3.66 μm, RCstroma = 7.08 μm, RCtearfilm = 1.25 μm). Statistical analysis of all data sets showed no statistical difference between baseline recordings before and after acute exposure to high altitude (BL1 versus BL2), thus indicating the stability of our baseline recordings and the reversibility of any changes associated with high altitude exposure.

All 14 healthy subjects successfully climbed to the research facility at CM and showed a moderate, yet statistically highly significant (P < 0.05) thickening of the CCT on day 1 and day 3 (CCTbaseline = 539.27 ± 32.30 μm versus CCTday1 = 558.87 ± 29.39 μm versus CCTday3 = 567.17 ± 33.40 μm; mean ± SD) during their exposure to high altitude compared to baseline recordings (Figs. 2a, 2b). Specifically, the central cornea showed significant thickening of the stromal layer but no changes in any other component of the corneal tissue during high altitude exposure (Figs. 2c–f; Table 1). This change was completely reversible upon descent and no subject demonstrated persisting structural or functional sequel.

AMS-C scores and HR reached highest levels on day 1 after arrival at CM, whereas oxygen saturation was expectably decreased (Table 2) with overall lower but non-significant changes in AMS positive subjects (data not shown). Incidence of AMS was 64% in the evening 6 hours after arrival at CM on day 1 and prevalence decreased in the following days as expected with acclimatization (morning of day 2 = 50%,
morning of day 3 = 21%, morning of day 4 = 14%; Table 2). This was in clear contrast to the stromal edema, which showed further increases from day 1 to day 3 despite systemic acclimatization of subjects (Figs. 2c–f; Table 1). Geometric measures of the ACA remained consistent with no significant changes in AOD or ACA during exposure to high altitude as illustrated in Figure 3 and Table 1.

As previous studies have provided equivocal results regarding a correlation between AMS and ocular changes under hypoxia and/or at high altitude, we calculated the association between AMS-C, HR, and SpO2 and changes of stromal thickness in the central cornea on day 1 and again on day 3 when respective measurements were performed. As shown in Figure 4, there was a significant correlation between stromal thickness and AMS-C on day 1 (r = 0.71; P = 0.01), but not on day 3 (r = 0.05; P = 0.87; Figs. 4a, 4b). None of the other correlation analyses (HR, SpO2) suggested a dependency between systemic measures and stromal edema formation (Figs. 4c–f). Subgroup analysis showed that subjects with more pronounced stromal edema did not have significant different AMS-C, LL, or SpO2 values from subjects with less pronounced stromal edema formation (data not shown).

**DISCUSSION**

**Corneal Edema Formation**

Hypoxia is a common pathogenic mechanism in corneal edema formation. Even contact lens wear and lid closure overnight can cause a measurable increase in corneal thickness in healthy eyes. While other ocular tissues such as retina and choroid are directly perfused and as such able to adapt to different levels of oxygenation, the cornea as an avascular tissue solely relies on oxygen tension of tear film and, to a lesser extent, aqueous fluid. Without the ability to regulate local oxygen provision, corneal endothelial pump function is diminished under hypoxic conditions and corneal edema forms below a certain threshold level needed to maintain corneal transparency. Experiments under local anoxic/hypoxic conditions in human subjects and rabbits have shown that epithelium remains largely unchanged, indicating that the increased total corneal thickness is most likely due to stromal edema formation. This observation was supported by further experimental evidence, which showed that oxidative metabolism is reduced in hypoxic epithelial cells, which adapt to anaerobic glycolysis for energy production. This leads to increased lactate production, which diffuses posteriorly across the stroma and endothelium to be eliminated via the aqueous humor. Increased lactate concentration within the corneal stroma leads to an osmosis-driven influx of water and a further reduced activity of the endothelial pump function, which is already challenged by hypoxia itself. Excess hydration of the corneal stroma disrupts the normally uniform periodic spacing of Type I collagen fibrils, creating light scatter. In addition, excessive corneal hydration can result in edema of the corneal epithelial layer, which creates irregularity at the optically critical tear film–air interface. Both stromal light scatter and surface epithelial irregularity contribute to degradation of optical performance of the cornea and can compromise visual acuity, which is of great importance during high altitude endeavors.

Our data show that exposure to high altitude-related hypobaric hypoxia challenges the avascular corneal tissue and leads to a moderate, selective swelling of the corneal stroma without evidence for epithelial or endothelial edema formation. The moderate nature of these changes is in accordance with previously published results of the THAO study and other studies, in which no significant changes on best-corrected visual acuity measurements could be observed during altitude exposure.

Table 2. Overview of AMS-Related Parameters

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Baseline (BL1)</th>
<th>Day 1</th>
<th>Day 3</th>
<th>Baseline (BL2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMS-C</td>
<td>0.00 ± 0.00</td>
<td>1.05 ± 0.67</td>
<td>0.65 ± 0.72</td>
<td>0.00 ± 0.00</td>
</tr>
<tr>
<td>LL</td>
<td>0.00 ± 0.00</td>
<td>5.72 ± 3.08</td>
<td>4.06 ± 3.04</td>
<td>0.00 ± 0.00</td>
</tr>
<tr>
<td>HR</td>
<td>60.33 ± 7.22</td>
<td>89.44 ± 5.92</td>
<td>76.78 ± 11.39</td>
<td>58.67 ± 6.33</td>
</tr>
<tr>
<td>SpO2</td>
<td>98.50 ± 1.29</td>
<td>70.56 ± 5.18</td>
<td>74.22 ± 5.62</td>
<td>98.28 ± 1.32</td>
</tr>
</tbody>
</table>

Data are presented as mean of absolute values ± SD.
exposure to high altitude according to our ascent profile seems to be safe for healthy subjects because it does not alter visual acuity and is completely reversible after descent to lower altitudes.4,5 Indeed, it is comparable to diurnal fluctuations due to lid closure, which can cause corneal thickening of up to 3.9% overnight.25 However, exposure to more extreme altitudes, at which hypoxia is more severe, may result in a greater corneal edema, which may even lead to visual problems.1,2

**Correlation Between Corneal Edema and AMS**

There is conflicting evidence on the correlation of AMS and related parameters versus ocular changes due to exposure to

---

**FIGURE 4.** Pearson correlation analyses between changes in stromal thickness on day 1 (left) and day 3 (right) versus respective measures of AMS-related endpoints in AMS positive (square data points) and AMS negative (circles) subjects. Stromal edema formation is only significantly correlated with AMS-C on (a) day 1 ($r = 0.71, P < 0.01$) but not on (b) day 3 ($r = 0.05, P = 0.87$). (c-f) Vital parameters such as heart rate (HRday1, $r = 0.15, P = 0.60$; HRday3, $r = 0.22, P = 0.45$) or blood oxygenation levels ($SpO_2$day1, $r = -0.45, P = 0.11$; $SpO_2$day3, $r = 0.21, P = 0.46$) do not correlate with changes in stromal thickness.
high altitude, such as optic disc swelling, changes in central retinal thickness, intraocular pressure changes, and ocular circulation.\textsuperscript{11,22–23} Regarding corneal edema formation at altitude, Bosch et al.\textsuperscript{3} found an increase in CCT using ultrasound pachymetry and reported a correlation between CCT values and both SpO\textsubscript{2} measurements and AMS-C scores. Comparison of two cohorts with different ascent profiles led the authors to conclude that a slower acclimatization profile resulted in less corneal edema.

This is in contrast to our findings, in which a significant increase in CCT is met with increased AMS-C scores (from 0 at BL1) only on day 1. It is well known that successful acclimatization reduces AMS-C scores and thus the incidence of AMS, and improves related physiological measures such as SpO\textsubscript{2} and HR over consecutive days. In our study, CCT showed a continuous rise from day 1 until day 3 while at the same time the incidence of AMS rapidly decreased and HR and SpO\textsubscript{2} increased (Table 1). This finding is supported by another study by Morris et al.,\textsuperscript{4} which also found a continuous increase of CCT during 7 days of altitude exposure (5200 m). This may indicate that the effects of acclimatization directed towards increasing systemic SpO\textsubscript{2} are effective to reduce AMS-related parameters but do not play a major role in resolving stromal edema formation caused by hypoxic stress. Indeed, since only a small proportion of the corneal oxygen demand is met by diffusion from the aqueous humor, and oxygen is mainly supplied transcorneally via tear fluid to the aqueous humor, the atmospheric oxygen pressure might well be one dominant factor.\textsuperscript{5} This in turn would explain why an increase in systemic SpO\textsubscript{2} through acclimatization is not effective in resolving the edema.

However, it is important to keep in mind that the these studies feature different study designs. Thus, respective confounding factors such as exercise would be expected to have variable influence, which makes a direct comparison difficult.

**Aqueous Outflow Configuration and IOP**

Previous ophthalmological studies at high altitude have produced equivocal results regarding the effect of high altitude on IOP. None of these studies used the gold standard technique (Goldman tonometry) to measure IOP for logistical reasons, but relied on portable devices. While some studies reported an increase, others documented a decrease or no change.\textsuperscript{6,30–41} Bosch et al.\textsuperscript{3} described an increase in IOP from baseline recordings (490 m) to an altitude of 5550 m, with a subsequent decrease of IOP during the ascent to 6265 m and descent back to baseline altitude. A positive correlation of IOP values with SpO\textsubscript{2} data in their subjects led the authors to hypothesize that oxygen deprivation causes a decrease in aqueous humor production in the nonpigmented ciliary epithelium with a consequent decrease in IOP.

Clinically, the most common form of increased IOP is observed in patients with primary open-angle glaucoma and other less common forms of glaucoma. One common denominator of these conditions is an increased outflow resistance of aqueous humor rather then changes of aqueous humor production. The geometry of aqueous outflow facilities in the ACA constitutes an important determinant of outflow resistance. Therefore, it was of interest to investigate, whether ACA and AOD would change during exposure to high altitude. Our data clearly show, that these parameters remained constant throughout the study, which makes it unlikely that anterior chamber geometry plays a major role in the dynamics of IOP fluctuations due to high altitude exposure.

**Limitations of the Study**

Our data show considerable interindividual differences in CCT change, which was expected from the existing literature demonstrating individual susceptibility profiles to corneal hypoxia.\textsuperscript{5,12–15} Unfortunately, we were not able to perform measurements on day 2 at altitude, which would have been helpful in order to draw a more in-depth conclusion about the correlation of AMS in regard to CCT. However, respective correlations of AMS of day 2 with CCT values of day 1 and day 3 revealed no correlation (data not shown). Thus, the positive correlation of AMS versus CCT on day 1 remains puzzling, and it can only be speculated that this stromal edema may initially overlap with the incidence of AMS, but that the systemic effects of acclimatization do not play a major role in resolving stromal edema formation caused by hypoxia.

ACA and AOD do not describe the aqueous outflow pathway in total. Specifically, current AS-OCT devices do not sufficiently resolve distal outflow structures such as collector channels and intrascleral vasculature. This limits the complete assessment of outflow mechanics by quantitative or qualitative analysis of relevant anatomical landmarks. However, successful application of customized OCT devices in this regard shows the potential of future developments.\textsuperscript{18} Additionally, the current study investigated the anterior chamber geometry only through line scans at the 9 o’clock position, while aqueous outflow structures may vary across the full 360°. However, since we investigated intrasubject longitudinal changes, the chosen location might be regarded as being less important than the relative variations over time. Finally, it would be interesting in future studies to investigate subjects with history of refractive surgery and/or glaucoma to explore their response to high altitude-related hypoxia.

**Conclusion**

This is the first study showing the response of all corneal layers to exposure to high altitude–related hypobaric hypoxia. In addition, the use of high resolution AS-OCT provided quantifiable imaging data of the aqueous outflow configuration. Both data sets provide new insight into adaptation of the ocular system to high altitude and into the discussion of biomarkers and the unknown pathophysiologicy of AMS. The lack of a significant correlation on day 3 between corneal edema formation versus measures of mountain sickness or related physiological measures indicates that the underlying mechanisms of corneal edema formation and AMS differ to a considerable extent but may initially overlap. While AMS is most probably regulated by systemic acclimatization responses, corneal edema formation seems to be more directly dependent on atmospheric oxygen pressure and does not resolve with higher blood oxygenation.

**Acknowledgments**

The Tübingen High Altitude Ophthalmology (THAO) study group thanks the Wilderness Medical Society (WMS) for their financial and Heidelberg Engineering for their technical support and for providing their instruments under extreme research conditions.

Disclosure: G. Willmann, Heidelberg Engineering (F); Novartis (F); Alcon (F); Bausch & Lomb (F); Allergan (F); Ursapharm (F); Optima Pharma (F); Wilderness Medical Society (R); A. Schatz, None; A. Zhour, None; K. Schommer, None; E. Zrenner, None; K.U. Bartz-Schmidt, None; F. Gekeler, None; M.D. Fischer, None
References