New Insights Into Changes in Corneal Thickness in Healthy Mountaineers During a Very-High-Altitude Climb to Mount Muztagh Ata

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Objective: To investigate the effect of very high altitude and different ascent profiles on central corneal thickness (CCT).

Methods: Twenty-eight healthy mountaineers were randomly assigned to 2 different ascent profiles during a medical research expedition to Mount Muztagh Ata (7546 m) in western China. Group 1 was allotted a shorter acclimatization time prior to ascent to 6265 m. The main outcome measure was CCT. Secondary outcome measures were oxygen saturation (SpO2) and symptom assessments of acute mountain sickness (cerebral acute mountain sickness score). Examinations were performed at 490, 4497, 5333, and 6265 m.

Results: Central corneal thickness increased in both groups with increasing altitude and decreased after descent. In group 1 (with the shorter acclimatization), mean CCT increased from 537 to 572 µm. Mean CCT in group 2 increased from 534 to 563 µm (P = .048). The amount of decrease in SpO2 paralleled the increase in CCT. There was no significant decrease in visual acuity. There was a significant correlation between CCT and cerebral acute mountain sickness score when controlled for SpO2 and age.

Conclusions: Corneal swelling during high-altitude climbs is promoted by low SpO2. Systemic delivery of oxygen to the anterior chamber seems to play a greater role in corneal oxygenation than previously thought. Adhering to a slower ascent profile results in less corneal edema. Visual acuity in healthy corneas is not adversely affected by edema at altitudes of up to 6300 m. Individuals with more acute mountain sickness–related symptoms had thicker corneas, possibly due to their higher overall susceptibility to hypoxia.

Prior to the expedition, all participants were randomly assigned to 1 of 2 ascent protocols on Mount Muztagh Ata (Figure 2), located in the western Xinjiang province in China. The ascent started at 3750 m above sea level and progressed to base camp (4497 m; barometric pressure, 447 torr), camp 1 (5333 m; barometric pressure, 392 torr), camp 2 (6265 m; barometric pressure, 335 torr), camp 3 (6865 m; barometric pressure, 333 torr), and then to the summit (7546 m; barometric pressure 301 torr) within 20 days in group 1 and 19 days in group 2. Group 1 was allotted a shorter acclimatization time prior to ascent to camp 2 than group 2 (7 vs 11 days from base camp to camp 2). All subjects underwent general and ophthalmic baseline examinations at the University Hospital Zurich before the expedition (490 m).

PRIMARY OUTCOME MEASURE

Ultrasound pachymetry was performed at the University Hospital Zurich and on the day after arrival at base camp (base camp 1), camp 1, and camp 2, and again at base camp (base camp 2) using a Pocket II Precision pachymeter (Quantel Medical Clermont-Ferrand, France). After benoxinate hydrochloride, 0.4%, single-dose units were administered (Novartis Pharma AG, Bern, Switzerland). CCT was determined by averaging 5 successive readings in each eye. A maximum standard deviation (SD) of 15 µm was defined a priori, and if this was exceeded, the complete measurement was repeated. According to the protocol, climbers were assessed in the same group at each examination starting at 9 AM, about 2 hours after awakening. Participants were asked to remove their contact lenses in the evening prior to the ophthalmic examinations.

SECONDARY OUTCOME MEASURES

Best-corrected visual acuity was measured using an Early Treatment Diabetic Retinopathy Study chart.6 Daily pulse oximetry was performed in the evening during quiet rest in a standing position with a finger pulse oximeter (Onyx 9500 SportStat; Nomin Medical Inc, Plymouth, Minnesota). Stable values after at least 3 minutes were recorded.

Cerebral AMS (AMS-c) scores on the Environmental Symptoms Questionnaire III were assessed daily during the expedition.6,9 The AMS-c score represents symptoms that seem to reflect altered cerebral function in conjunction with being ill.

Any drug intake was assessed by analyzing daily personal diaries. Medication other than nonsteroidal anti-inflammatory drugs could only be taken by prescription from the expedition physician. Temperature in the examination tents was measured with a digital thermometer.

STATISTICAL ANALYSIS

Statistical analyses were computed with commercially available software packages (SPSS, version 13; SPP Inc, Chicago, Illinois; Statistica 6, StatSoft Inc, Tulsa, Oklahoma; and Instat 3.06; Graphpad Inc, La Jolla, California). Differences between groups for normally distributed variables (Kolmogorov-Smirnov test) were assessed by analysis of variance for repeated measurements using 1 dependent variable (CCT), 1 grouping factor (group), and 1 within-subject factor (altitude). Assumption of sphericity was tested using the Mauchly sphericity test. When significant time × group interactions occurred, a separate analysis of variance for repeated measurements was performed in each group. If within-group analysis of variance was significant, differences between groups were tested at each time using unpaired t test and Bonferroni correction for multiple testing. Data are expressed as mean (SD) unless otherwise noted. Bivariate linear regression analysis was applied to investigate a possible correlation between SpO2 and CCT measurements. Multiple regression analysis was used to analyze associations between CCT and independent variables (SpO2, AMS-c scores, and age). Two-sided P < .05 was considered statistically significant.

RESULTS

Six participants of the initially 34 enrolled were excluded because of ocular disease prior to the expedition (n = 2) or incomplete data collection during the expedition (n = 4). Three contact lens wearers, 1 mountaineer with a history of laser-assisted in situ keratomileusis surgery on both eyes, and 2 mountaineers with drug intake (one of these a contact lens wearer) were analyzed separately (total, n = 5).

MAIN OUTCOME MEASURE

Central corneal thickness readings were normally distributed in each group at each altitude, and no significant differences of variances were detected. There was a significant altitude × group (ie, 2 different ascent profiles) interaction regarding the mean CCT (P = .048) (Figure 3A and Table).
Mean CCT in group 1 (short acclimatization) was increased at base camp 1 (547 µm [55 µm]) compared with that at University Hospital Zurich (537 µm [44 µm]) and remained stable at camp 1 (544 µm [56 µm]). Thereafter, a significant increase (*P*<.001, compared with University Hospital Zurich) was noted at camp 2 (572 µm [51 µm]).

Mean CCT in group 2 (longer acclimatization) steadily increased from the measurement at University Hospital Zurich (534 µm [28 µm]) to camp 2, where the thickest CCT readings (573 µm [29 µm]) were documented (they were significantly higher compared with measurements at all other altitudes) (Table and Figure 3A). On descent to base camp 2, CCT decreased to values that were significantly different from the ones at the same altitude before ascent (563 µm [28 µm] at base camp 2 vs 554 µm [31 µm] at base camp 1, *P*<.05). For logistical reasons, base camp 2 measurements were only performed in group 2.

**SECONDARY OUTCOME MEASURES**

Best-corrected visual acuity did not decrease significantly during the course of the expedition. Mean temperature during examinations on Mount Muztagh Ata was 21°C (SD, 7°C; range, 9°C-37°C).

Mean age (42 years in group 1, 43 years in group 2) and mean AMS-c scores did not differ significantly between groups (*P*=.68 and *P*=.35, respectively). The AMS-c scores and SpO₂ measurements were unavailable for group 2 at base camp 2 because of logistical reasons (bad weather conditions).

Oxygen saturation measurements during the expedition for both groups were significantly lower than values recorded at baseline at University Hospital Zurich. During ascent, SpO₂ decreased significantly at each altitude in both groups, except for the climb from camp 1 to camp 2 in group 2. On descent in group 1, measurements at base camp 2 compared with base camp 1 did
not differ significantly (Figure 3C). As seen in Figure 3, the decrease in SpO2 during ascent from base camp 1 to camp 1 was more marked in group 2 than group 1.

Multiple regression analysis with CCT as the dependent variable and ascent group, SpO2, AMS-c score, and age as independent variables revealed a partial correlation coefficient of β = .12 (P = .20) for ascent group, β = -.11 (P = .22) for SpO2, β = .24 (P = .01) for AMS-c score, and β = .05 (P = .57) for age. Multicolinearity was not observed.

Bivariate linear regression analysis for each group with SpO2 as an independent variable and CCT as a dependent variable showed a Pearson correlation coefficient of r = −0.19 at a significance level of P = .08 in group 1 and a correlation coefficient of r = −0.37 (P < .001) in group 2 (Figure 3D).

Figure 3 shows the variations in CCT at different altitudes. During ascent from base camp 1 to camp 1, there was a greater increase in mean CCT in group 2 (6 µm) than in group 1 (3 µm). From camp 1 to camp 2, differences in CCT of 28 µm and 13 µm were noted in groups 1 and 2, respectively. Central corneal thickness at camp 2 in group 1 was measured after a shorter time following arrival at base camp (7 days) compared with those of group 2 between base camp 1 and camp 2 (11 days). Considering the decrease in CCT from camp 2 to base camp 2, we found no correlation between decrease and age (β = .05, P = .76). The changes of CCT measurements during the expedition in contact lens wearers and in the one climber with prior laser-assisted in situ keratomileusis paralleled those of the normal climbers (Figure 3B).

Two climbers, whose violent headaches had been nonresponsive to nonsteroidal anti-inflammatory drugs, were treated with 250 mg of acetazolamide, 8 mg of dexamethasone, and 20 mg of nifedipine on the second to last day of the observation period. Intake of these drugs took place more than 24 hours before examination. Central corneal thickness readings in the mountaineers after drug intake were similar to those of all the other mountaineers.

### CONCLUSIONS

Four main findings of interest concerning CCT changes in healthy mountaineers were revealed by our study. (1) For the first time, in a very-high-altitude setting, a substantial increase in CCT (up to 13%) was documented during the ascent to 7564 m, followed by a subsequent rapid decrease on descent. (2) Changes in systemic SpO2 paralleled those of CCT, showing that a slower acclimatization profile resulted in less corneal edema. (3) Edema did not affect Early Treatment Diabetic Retinopathy Study visual acuity. (4) A significant and strong correlation between CCT and symptoms of AMS (AMS-c score) was observed.

The exact cause of corneal swelling due to hypoxic conditions is still the subject of controversy in numerous publications. Davson16 was the first to describe changes in different corneal hydration states in excised eyes. A comprehensive review by Bonanno11 highlights multiple factors that induce hypoxic corneal edema, which is caused almost entirely by swelling of the stroma.12-19 Oxidative metabolism is reduced in hypoxic epithelial cells, which convert to anaerobic glycolysis for energy production, leading to increased lactate production. The latter diffuses posteriorly across the stroma and the endothelium and is then washed out by the aqueous humor. The higher lactate concentration within the corneal stroma may lead to an osmosis-driven influx of water15-17 and a reduced activity of the endothelial pump function.18 Moreover, anterior surface hypoxia due to reduced atmospheric oxygen pressure leads to endothelial hypoxia, further reducing the pump function and resulting in a swelling of the cornea.19 Environmental oxygen partial pressure plays a prominent role in corneal oxygen supply. Only a small proportion of the corneal oxygen demand is met by diffusion from the aqueous humor,20 and oxygen is mainly supplied transcorneally via tear fluid to the aqueous humor.21 However, under conditions of low environmental oxygen supply and hence grossly impaired transcorneal oxygen transport, endothelial supply of physically bound oxygen in the anterior chamber may become increasingly important.

We did find a difference in the measured SpO2 and CCT values in the 2 groups with different ascent protocols. Climbers in group 1 were allotted less time for acclimatization than those in group 2. As seen in Figure 3, the decrease in SpO2 during ascent from base camp 1 to camp 1 was more marked in group 2 than in group 1. This was paralleled by a greater CCT increase in group 2, though CCT in all climbers was measured at the same altitude with the same environmental oxygen pressure. Thereafter a more marked increase in thickness from camp 1 to camp 2 was noted in group 1, which also presented a more extensive drop in SpO2 than group 2. These findings further support our hypothesis that blood SpO2 becomes more important for the endothelial pump function when environmental oxygen pressure and thus tear film SpO2 is reduced to a critical level. Our results thus highlight the importance of aqueous humor oxygen delivery. Systemic delivery of oxygen to the anterior chamber seems to play a greater role in corneal oxygenation than previously thought.

Central corneal thickness measurements at base camp 2, eg, at base camp after having reached the summit and descended, were slightly, albeit significantly, higher than at base camp 1, after 16 days on the mountain. Impaired endothelial pump function seems to recuperate quickly but not fully during prolonged hypoxia to clear stromal
hydrate the corneal endothelium. The time of recovery with repeated measurements of CCT during a short time postexposition to high altitudes should be a topic for future studies.

Previously, Morris et al. found an average increase in CCT of 3.3% at an altitude of 5200 m. This is comparable with our results at 5533 m (camp 1), where an average increase of 3.2% was documented. Continuing with ascent and subjecting the body to more marked hypoxia leads to further increase of CCT, as seen in our climbers. Despite the marked increase in CCT, Early Treatment Diabetic Retinopathy Study visual acuity never deteriorated during our expedition. It seems that visual acuity in healthy corneas is not adversely affected despite the presence of edema at altitudes up to 6300 m. It is most likely that an even higher ascent to extreme altitudes above 8000 m induces more extensive endothelial pump function failure and may result in profuse edema leading to dangerous visual loss.

As previously shown, individuals who are more affected by AMS symptoms demonstrate more marked ocular changes with respect to optic disc swelling and ocular circulation. Accordingly, we expected individuals with more AMS-related symptoms to have thicker corneas owing to their evidently higher overall susceptibility to hypoxia. Our results of a significant correlation of CCT with AMS-c scores support this hypothesis.

We found no correlation between age and CCT. This may be surprising since it has been shown that corneal hydration control under hypoxic conditions is impaired in older subjects. Our older climbers appeared to be more robust and less affected by the significant decrease in SpO2 than some of their younger colleagues during the expedition; fewer AMS-related symptoms and less optic disc swelling were detected in this subgroup. This may explain the lack of difference in endothelial pump function compared with the younger climbers.

Acetazolamide is used as a mainstay for the prevention and treatment of AMS and high-altitude cerebral edema. Carbonic anhydrase activity can be found in several ocular tissues, including the cornea, where it plays a central role in endothelial cell function. There are several reports of negative effects of systemically and locally applied acetazolamide on the endothelium. Although we did not observe any adverse effects in our 2 climbers who took acetazolamide during the expedition, we did find increasing endothelial impairment during ascent. Thus, we suggest that acetazolamide be used with caution in climbers who have reduced endothelial cell function as found in diseases such as Fuchs endothelial dystrophy, as this might worsen the corneal edema.

Ultrasound pachymetry is considered the gold standard for measuring corneal thickness and has an excellent repeatability. Although newer measurement techniques with even higher repeatability are available, we chose handheld ultrasound pachymetry owing to transportation reasons. Limitations of our study include lack of daily CCT measurements. Not all measurements could be performed at every altitude owing to difficult weather conditions.

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In Memoriam: Steven M. Podos, MD (1937-2009)

Steve Podos died on October 10, 2009, of complications related to an autoimmune vasculitis. Born and raised in New York City, Steve graduated Summa Cum Laude from Princeton University. He received his MD degree from Harvard Medical School and interned at the University of Utah Affiliated Hospitals. He took his ophthalmology residency at Barnes Hospital, Washington University School of Medicine, in St Louis, Missouri. He was Chief Resident at Barnes, and then spent 2 years at the National Institutes of Health. He returned to Washington University for 6 years, rising to the rank of Professor of Ophthalmology. In 1975 he was appointed Chair of the Department of Ophthalmology at The Mount Sinai School of Medicine in New York. He served as Chair for 30 years and retired in 2005. He directed the training of nearly 150 ophthalmology residents and more than 50 glaucoma fellows. Steve served on the editorial boards of several leading ophthalmology journals and for 5 years was the Editor in Chief of Investigative Ophthalmology and Visual Science. He received numerous honors during his lifetime and delivered 20 named lectures.

Steve was the consummate academic ophthalmologist. He authored or coauthored nearly 300 articles, chapters, and textbooks. Reading his curriculum vitae, one is impressed by the breadth of topics covered: ocular manifestations of homocystinuria, pars plana cysts in multiple myeloma, lyphema, inborn errors of metabolism, congenital diseases, and, of course, glaucoma. He was a respected world authority on the understanding and management of glaucoma. He wrote or cowrote more than 200 articles on all facets of glaucoma. I was privileged to coauthor an article with him titled “Transient Open-Angle Glaucoma Associated With Sickle Cell Trait.”

Steve was a lifelong student of ophthalmology. His professional accomplishments were in the top tier of international ophthalmology. He was a true polymath in the best sense of the word, and there was no subject that he could not carry out a lucid and penetrating discussion on. His legacy lives on in the countless people he taught, worked with, and treated.

I am grateful to Dr Morton Goldberg for sharing his eulogy, delivered on October 13, 2009, at Steve’s funeral.

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