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Intraocular Pressure During a Very High Altitude Climb

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More than 6 authors are listed because this complex high altitude research expedition required a great amount of work, the successful accomplishment of which could not have been achieved by fewer researchers. All authors contributed substantially to the study.

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Key words: intraocular pressure, high altitude, hypoxia, mountaineering, tonometry
Abstract

Introduction:
Reports on intraocular pressure (IOP) changes at high altitudes have revealed inconsistent and even conflicting results. The aim of this study was to investigate the effect of very high altitude and different ascent profiles on IOP in relation to simultaneously occurring ophthalmic and systemic changes in a prospective study.

Methods:
Prospective study in 25 healthy mountaineers who were randomly assigned to two different ascent profiles during a medical research expedition to Mt Muztagh Ata (7546m/24751ft). Group 1 was allotted a shorter acclimatization time prior to ascent than Group 2. Besides IOP, oxygen saturation (SaO₂), acute mountain sickness symptoms (AMS-c score) and optic disc appearance were also assessed. Examinations were performed at 490m/1607ft, 4497m/14750ft, 5533m/18148ft and 6265m/20549ft above sea level.

Results:
Intraocular pressure in both groups showed small but statistically significant changes: an increase during ascent from 490m/1607ft to 5533m/18148ft and then a continuous decrease during further ascent to 6265m/20549ft and upon descent to 4497m/14750ft and to 490m. Differences between groups were not significant. Multiple regression analysis (IOP dependent variable) revealed significant partial correlation coefficient of Beta= -0.25 (p=0.01) for SaO₂, and Beta = -0.23 (p=0.02) for acclimatization time.

Discussion:
Hypobaric hypoxia at very high altitude leads to small but statistically significant changes in IOP that are modulated by systemic oxygen saturation and correlate with optic disc swelling. Climbs to very high altitudes seem to be safe with regard to intraocular pressure changes.
Introduction

Traveling to high altitudes for recreational reasons is becoming increasingly popular and has been a subject of scientific interest ever since. Technical progress enables researchers to gain new insights into changes that occur within the human body upon exposure to natural hypobaric atmospheric conditions.

Intraocular pressure (IOP) changes at high altitudes have been the subject of several publications\(^1\,\,^4,\,6,\,8,\,9\). Yet results have been inconsistent. Findings range from a decrease\(^1,\,4,\,6,\,8,\,9\) through unchanged\(^5\), to an increase\(^1\) in IOP at moderate to high altitudes. Changes in intraocular pressure during an expedition to very high altitudes, i.e. more than 5500m/18045ft, have not been documented yet.

Depending on the degree of hypoxia\(^10\), ascent rate\(^11\) and individual susceptibility\(^12\), acute mountain sickness or even the less common high altitude cerebral edema (HACE) may occur. HACE results in increased intracerebral pressure (ICP) and hence in cerebral hypoperfusion with possible severe and fatal dysfunction\(^13\). Several studies suggest that a rise in ICP leads to an increase in IOP, and thus that IOP measurement could be a minimally invasive method to detect a rise in ICP\(^14\,\,16\). Therefore, a correlation of IOP with parameters indicating cerebral affection due to hypoxia would be of great interest.

The Muztagh Ata medical research expedition study included researchers from various medical specialties, such as pneumology, neurology, hematology and ophthalmology, in a holistic approach to prospectively assess hypoxia induced changes of the body. A list of the discipline specific studies along with references can be found in Table 1. We set out to investigate changes in IOP at very high altitudes (>6000m/19685ft) with two different ascent profiles and place these results into perspective with simultaneously occurring ophthalmic and systemic changes (e.g. optic disc status, cerebral acute mountain sickness scores including possible HACE, pulse oximetry).
Methods

Our working hypothesis was that IOP would decrease with altitude due to lower systemic oxygen saturation and decreased aqueous production.

Volunteers

This randomized, prospective, multidisciplinary, observational cohort study \textsuperscript{17-20} was performed within the scope of a high altitude medical research expedition on Mt. Muztagh Ata (7546m/24751 ft), Fig. 1. Mountaineers in good physical shape were included. Exclusion criteria were any type of ocular, cardiac or respiratory disease or history of high altitude pulmonary edema or high-altitude cerebral edema, history of ophthalmic disease or ophthalmic surgery (including cataract), contact lens wearers and intake of drugs other than non-steroidal antirheumatic agents during the expedition. The study was approved by the Ethical Committee of the University Hospital, Zurich, and adheres to the tenets of the Declaration of Helsinki (1983 revision). Informed, written consent was obtained from all subjects prior to the examinations.

Ascent profile

For security reasons and in order to study the effect of acclimatization, the participants were randomly distributed into two groups with different ascent profiles (Fig. 2). The average ascent rate was 190 and 200 m/d (623 and 656ft/d), for group 1 and group 2 respectively. The climb began at 3750m (12300ft) in a village called Subash and progressed to base camp (BC = 4497m/14750ft), camp 1 (C1 = 5533m/18148ft), camp 2 (C2 = 6265m/20549ft), camp 3 (C3 = 6865m/22517ft) and to the summit (7546m/24751ft) within 20 (group 1) and 19 (group 2) days.

Measurements

All participants underwent general and ophthalmic baseline examinations one month prior to the expedition (ZH) at the University Hospital of Zurich, Switzerland, (490m/1607ft). At the time of
the expedition, examinations were performed during the ascent on the subsequent day upon
arrival at each new high camp, i.e. from BC to C2, and at return to base camp (BC2). Each
mountaineer had to have reached at least C2 to be included in the evaluation.
Intraocular pressure (IOP) was measured with the Tono-Pen XL (Reichert, Inc., Depew, NY
USA) by placing the tip of the device onto the central cornea after local anesthe-
sia with oxybuprocaine 0.4% SDU Faure (Novartis Pharma AG, Basel, Switzerland). Three complete
measurements were taken; the average was calculated and recorded. All three readings used for
calculating the average were required to have a standard deviation of ≤ 5%, as shown on the
instrument’s digital display. The tonometer was calibrated prior to each examination session
according to the manufacture’s guidelines.
Central corneal thickness (CCT) measurements during the expedition\textsuperscript{20} were performed with the
Pocket II Precision pachymeter (QUANTEL MEDICAL, Clermont-Ferrand, France) after IOP
measurements. CCT was determined in micrometers (µm) by averaging 5 successive readings in
each eye. A maximum standard deviation of 15µm was defined a priori, and if this was
exceeded, the complete measurement was repeated.
Fundus photographs were acquired using a handheld digital fundus camera (Genesis-D, Kowa
Inc., Tokyo, Japan). Photographs were analyzed by three independent ophthalmologists. Optic
discs were graded being either not swollen, equivocal, or swollen\textsuperscript{17}.
Measurements were performed after one night of acclimatization\textsuperscript{19} at similar times of day in
order to minimize the effect of strenuous exercise\textsuperscript{21} and diurnal variation\textsuperscript{22}.
Cerebral acute mountain sickness (AMS-c) scores on the Environmental Symptoms
Questionnaire III\textsuperscript{23} were assessed daily during the expedition. The AMS-c score represents
symptoms that seem to reflect altered cerebral function. A score of 0.7 or greater reliably
identifies a person with AMS. It pertains to items including light-headedness, headache,
dizziness, dim vision, off-coordination, gastrointestinal tract upset, and weakness. The score is
calculated by the sum of all item scores (range, 0-5) multiplied by their respective factorial weight and then multiplied by 0.1927.

Daily pulse oximetry was performed in the evening during quiet rest in a standing position with a finger pulse oximeter (Onyx 9500 SportStat, Nonin Medical Inc., Plymouth, MN, U.S.A.). Stable values after at least 3 minutes were recorded. Temperature was measured using a digital thermometer in the examination tent.

**Statistical analysis**

Statistical analysis was performed with commercially available statistical software packages (SPSS 13, SPSS Inc., Chicago, IL, USA and Statistica 6, Statsoft INC, Tulsa, OK). Test for normal distribution was performed using the Kolmogorov-Smirnov test. Measurements at each altitude between the two groups were compared using the unpaired Student’s t-test (including Welch-correction). Repeated measures analysis of variance (ANOVA) was performed with combined data of groups 1 and 2 to assess changes in IOP over the different altitudes. Assumption of sphericity was assessed using Mauchly’s test. In case of a statistically significant result, post-hoc testing with Bonferroni’s correction was applied.

Multiple regression analysis was used to analyze correlations between IOP as the dependent variable and independent variables (ascent group and different times of acclimatization, SaO2, cerebral acute mountain sickness (AMS-c) score, central corneal thickness (CCT), altitude, optic disc appearance) and age. The time of acclimatization was defined as the amount of days during the expedition starting from Subash. Correlation between environmental temperature and IOP as well as pachymetry and IOP was analyzed using bivariate regression analysis. Normally distributed data are presented as mean ± standard deviation (SD), not-normally distributed data are expressed as median and range (minimum and maximum). A two sided α-error (p-value) of less than 0.05 was considered statistically significant.


Results

Seven out of a total of 32 climbers included in the ophthalmic branch of the study were excluded because of either incomplete data collection during the expedition (n=4), a history of refractive surgery on both eyes (LASIK, n=1) or due to drug intake during the examination period (n=2). Of the 25 climbers included, 5 were female and 20 male. Mean age in groups 1 and 2 were 42±12 years and 45±9 years, respectively, without a significant difference between groups (p=0.54). 17 mountaineers (9 in group 1 (Gr1), 8 in group 2 (Gr2)) reached the summit.

Intraocular pressures in both ascent groups increased from ZH to C1 and then continuously decreased while further ascending to C2, re-descending to BC2 as shown in Table 2. Maximum IOP measurements never exceeded 21mmHg in both groups. Due to logistic reasons, group 1 could not be examined at BC2. No significant differences between ascent groups were found at any altitude (ZH p=0.78, BC1 p=0.77, C1 p=0.65, C2 p=0.82). Thus for further analyses, measurements of both groups were combined. Mean IOP changes for both groups are shown in Fig. 3. ANOVA revealed a significant IOP-altitude interaction (p=0.01). The significant differences between IOP values at each altitude found in post-hoc testing are illustrated in Fig. 3.

Central corneal thickness increased from 537 to 572 µm in group 1 and from 534 to 563 µm in group 2 with increasing altitude and decreased after decent20. Oxygen saturation (SaO₂) measurements, and AMS-c scores are shown in Table 3. IOP measurements were undertaken in the same windless tent with temperatures varying from 9° (minimum temperature at C2) to 37° (maximum temperature at BC) Celsius during the day with a mean of 21°C±7.

Multiple regression analysis with IOP as the dependent variable revealed a partial correlation coefficient of Beta= -0.25 (p=0.01) for SaO₂, -0.23 (p=0.02) for acclimatization time, -0.11 (p=0.18) for ascent group, 0.02 (p=0.85) for AMS-c score, -0.09 (p=0.32) for optic disc swelling, and 0.13 (p=0.13) for age. No multicollinearity was detected. No statistically significant
correlation between environmental temperature and IOP values were found (ZH \( r = 0.16 \ p = 0.26 \), BC1 \( r = -0.18 \ p = 0.20 \), C1 \( r = 0.17 \ p = 0.24 \), C2 \( r = -0.10 \ p = 0.49 \), BC2 \( r = -0.21 \ p = 0.32 \)). Analysis testing for a correlation between pachymetry and IOP at each altitude did not reveal significant results (ZH \( r = 0.05 \ p = 0.95 \), BC1 \( r = 0.19 \ p = 0.19 \), C1 \( r = 0.23 \ p = 0.11 \), C2 \( r = -0.93 \ p = 0.52 \), BC2 \( r = 0.25 \ p = 0.24 \)).
Discussion

This study reveals two main findings: Firstly, only small but statistically significant changes in intraocular pressure (IOP) over time were found during an expedition to very high altitudes. Secondly, IOP correlated with oxygen saturation at various altitudes.

Our findings for the initial but statistically insignificant increase in IOP at 4497m/14750ft parallel the results of Somner et al. Thereafter, the decline in IOP at further ascent to higher altitudes (at 6265m/20549ft), at which severe systemic hypoxia occurs, may be due to depleted oxygen supply to the non-pigmented ciliary epithelium and hence to decreased aqueous humor production. Aqueous production seems to become impaired after a certain systemic hypoxia threshold has been reached, which is supported by the statistically significant negative correlation between oxygen saturation in the participants at various heights and their IOP. The pathophysiology behind this phenomenon may be comparable to that reported in other conditions with impaired oxygen supply to the ciliary body such as in ocular ischemic syndrome or in severe cases of giant cell arteritis.

The rationale behind randomizing the climbers into two groups with different ascent profiles was to assess differences in the measured parameters which may have been due to distinct acclimatization times. Safety reasons also played a role in keeping the ascent groups limited. Duration between examinations at BC1 and C2 was seven days in group 1 and eleven days in group 2 (see Fig. 2). As no significant differences in the IOP values in the ascent groups were found, the differences in acclimatization time might have been too little to detect IOP behavior changes between the two groups. IOP reduction over time did occur, however, and a significant negative correlation between acclimatization time and IOP measurements was found in our analysis. Pressures at BC2 (4497m), 13 days after having climbed to substantially higher altitudes following the initial measurements, were significantly lower than the ones at the same altitude (BC1). Thus, hypoxia during a prolonged stay at high altitudes may also lead to reduced
aqueous production and therefore to the decline in intraocular pressure measured at 6250m (C2)\textsuperscript{1,26}. But overall, the duration of systemic hypoxia seems to play a greater role in IOP reduction compared to the extent of hypoxia. Yet, from the current data, no estimation can be made upon the amount of contribution of acclimatization towards IOP reduction.

No statistically significant correlation was found between IOP and optic disc swelling or AMS-c scores. As reported earlier\textsuperscript{27}, a high incidence of optic disc swelling has been observed in more than half of our volunteers with increasing altitude, representing increasingly severe hypoxia. All evidence pointed towards hypoxia-induced increase in brain volume as the most probable etiology of the optic disc swelling, with a potential consecutive increase in intracranial pressure (ICP). Several studies support the hypothesis that a rise in ICP leads to an increase in IOP. Thus IOP measurement could be used as a minimally invasive method to detect a raise in ICP\textsuperscript{14-16}.

Other investigators\textsuperscript{28,29}, found no correlation between IOP and optic disc swelling, i.e. a rise in ICP. Nevertheless, due to the small changes in IOP noted at different altitudes, which were clinically insignificant, we suggest that measuring the IOP in climbers at high altitudes is not an appropriate method to detect an increase in ICP.

In addition, acute strenuous exercise is known to lower the IOP\textsuperscript{21}. However, 10 minutes after stopping the exercise, Price et al. detected no significant IOP difference to baseline data\textsuperscript{21}. Our participants were examined on the day following ascent to a new high camp, thus allowing for at least 15 hours of rest. Based on the study design with moderate ascent rate, the influence of physical exercise should have been minimal on all our measured parameters.

IOP readings are largely influenced by mechanical properties of the eye. These properties may be altered by the development of corneal edema and are neither linear nor measurable to date\textsuperscript{30,31}. Previous reports indicate a greater accuracy in IOP measurements by the TonopenXL on edematous corneas\textsuperscript{32-34}. In normal corneas, the TonoPenXL has been shown to be least affected by CCT when comparing it to other transportable handheld tonometers\textsuperscript{35}. Due to its portability
and ease of use, we chose the lightweight TonopenXL for our expedition. Concerning temperature variations during the expedition, especially low temperatures that may decrease battery voltage output, the manual of the Tonopen XL explicitly states, that in the event of low battery output, the display shows the letters “LoB”. In the situation of low temperature, that may affect the transducer, the device may be inactivated or the calibration process may be slowed down. During our expedition, no such events occurred.

Measuring IOP in such conditions as in a low temperature environment, can alter the measurement results by causing a decrease in episcleral venous pressure. There was no correlation between temperature and IOP measurements at any altitude in this study. As shown in our study, changes in IOP during very high altitude mountaineering are small and insignificant from a clinical point of view, which is in conjunction with previous studies. In essence, exposure to very high altitudes results in a slight decrease in IOP. Considering our data from the highest IOP examinations to date, in addition to already existing data, we conclude that measuring the IOP is not a useful screening method for incipient and potentially harmful altitude-dependent diseases. In summary, in healthy persons climbs to very high altitudes seem to be safe with regard to intraocular pressure changes.
References


Table 1: Overview of the discipline specific studies. The first column denotes the discipline, the second column the title of the studies performed and the third column lists the respective reference.

<table>
<thead>
<tr>
<th>Discipline</th>
<th>Discipline-specific studies</th>
<th>References (partially to be found in the manuscript text)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ophthalmology</td>
<td>Incidence of optic disc swelling at very high altitudes</td>
<td>Arch Ophthalmol 2008, Ref. 13</td>
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<tr>
<td></td>
<td>Effect of high altitude on ocular blood flow</td>
<td>J Appl Physiol 2009, Ref 14</td>
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<td></td>
<td>Effect of high altitude on corneal thickness in healthy mountaineers</td>
<td>Arch Ophthalmol, in press, Ref 16</td>
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<td></td>
<td>Incidence of retinal hemorrhages and their implications during a high altitude climb</td>
<td>Manuscript submitted</td>
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<td>Effect of high altitude on corneal topography</td>
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<td>Manuscript submitted</td>
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<td>Hematology</td>
<td>Effect of high altitude on glomerular filtration rate</td>
<td>Acta Physiol (Oxf). 2008 Mar;192(3):443-50</td>
</tr>
<tr>
<td></td>
<td>Changes in coagulation parameters during a high altitude climb</td>
<td>Manuscript submitted</td>
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Table 2: Summary of Intraocular Pressure Measurements in Groups 1 and 2 at each examination height. All values are represented in mmHg. N - number of mountaineers, SD – one standard deviation.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Minimum</th>
<th>Maximum</th>
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<tbody>
<tr>
<td>Group 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZH</td>
<td>13</td>
<td>13.4</td>
<td>2.5</td>
<td>8.0</td>
<td>17.3</td>
</tr>
<tr>
<td>BC1</td>
<td>13</td>
<td>13.9</td>
<td>2.6</td>
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<td>13</td>
<td>14.7</td>
<td>2.4</td>
<td>10.6</td>
<td>19.6</td>
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<tr>
<td>C2</td>
<td>13</td>
<td>13.5</td>
<td>2.2</td>
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<table>
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<th>SD</th>
<th>Minimum</th>
<th>Maximum</th>
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<td>Group 2</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>ZH</td>
<td>12</td>
<td>12.8</td>
<td>3.4</td>
<td>6.3</td>
<td>21.0</td>
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<tr>
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<td>3.2</td>
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<tr>
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<td>13.9</td>
<td>3.4</td>
<td>8.3</td>
<td>19.3</td>
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<tr>
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<td>18.3</td>
</tr>
<tr>
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<td>12.3</td>
<td>3.0</td>
<td>7.6</td>
<td>19.3</td>
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Table 3: Oxygen saturation measurements (SaO$_2$ in %) (mean ± standard deviation) and AMS-c scores [median and range (minimum-maximum)] in both groups at different altitudes.

<table>
<thead>
<tr>
<th></th>
<th>ZH</th>
<th>BC1</th>
<th>C1</th>
<th>C2</th>
<th>BC2</th>
</tr>
</thead>
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<td><strong>Group 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SaO$_2$</td>
<td>98 ± 0.89</td>
<td>91 ± 8.31</td>
<td>79 ± 6.13</td>
<td>74 ± 7.79</td>
<td>87 ± 5.34</td>
</tr>
<tr>
<td>AMS-c</td>
<td>0 (0-0)</td>
<td>0.08 (0-0.88)</td>
<td>0.13 (0-1.15)</td>
<td>0.17 (0-2.42)</td>
<td>0 (0-0.18)</td>
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<td><strong>Group 2</strong></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>SaO$_2$</td>
<td>98 ± 0.79</td>
<td>83 ± 2.69</td>
<td>74 ± 3.92</td>
<td>73 ± 4.52</td>
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<tr>
<td>AMS-c</td>
<td>0 (0-0)</td>
<td>0.04 (0-0.74)</td>
<td>0.09 (0-0.57)</td>
<td>0.08 (0-0.76)</td>
<td>N/A</td>
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</tbody>
</table>
Figure legends

Figure 1: Photograph of Mt. Muztagh Ata (7546m/24751ft) in Western Xinjiang Province, China. Inset: a climber having his fundus photographed in a high camp examination tent.

Figure 2: Ascent profiles of both climbing groups on Mt Muztagh Ata. Examinations are marked by a « X ». Altitudes are shown in meters (m) and feet(ft) above sea level.

Figure 3: Development of intraocular pressure in both groups. The combined values of both groups are normally distributed. Circles denote the mean, whiskers show the standard deviation of intraocular pressure at different altitudes. Brackets with asterisks (*) denote statistically significant differences.
Figure 2

Ascent Profiles

altitude [m]  altitude [ft]

1  3  5  7  9  11  13  15  17  19  21  23

# of days of expedition

- group 1
- group 2
- stay same
- x = acclimation
Figure 3

![Graph showing IOP (mean ± SD) at different altitudes (490m, 4497m, 5533m, 6265m, 4497m) with asterisk indicating significant difference.](image)