

ORIGINAL ARTICLE

Acute mountain sickness and retinal evaluation by optical coherence tomography

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PURPOSE. Acute mountain sickness (AMS), the commonest form of altitude illness, might represent early-stage high altitude cerebral edema (HACE). Optical coherence tomography (OCT) was used to evaluate optic nerve head (ONH) consequences following a sojourn to extreme altitude.

METHODS. This prospective study included 4 high-altitude expeditions in Himalayas. Twenty-four eyes of 12 healthy male climbers underwent baseline and postexpedition complete ophthalmic evaluation, including OCT to measure the peripapillary retinal nerve fiber layer (RNFL) thickness, ONH parameters, and macular thickness and volume. Lake Louise Scoring (LLS) self-report questionnaire was used to estimate AMS severity.

RESULTS. All mountaineers experienced symptoms of AMS (LLS: 5.1 ± 1.1 , range 4.0-7.0). Average peripapillary RNFL thickness showed a significant increase in postexpedition examination ($94 \pm 23 \mu\text{m}$, 47-115), compared with baseline values ($89 \pm 19 \mu\text{m}$, range 45-114) ($p=0.034$). Superior ($p=0.036$) and temporal ($p=0.010$) quadrants also showed an increased RNFL thickness following exposure to high altitude. Vertical integrated rim area (VIRA) was significantly higher in postexpedition examination ($0.71 \pm 0.43 \text{ mm}^3$, 0.14-1.50) than in baseline examination ($0.51 \pm 0.26 \text{ mm}^3$, 0.11-1.00) ($p=0.002$). Horizontal integrated rim width was significantly higher in postexpedition examination ($1.90 \pm 0.32 \text{ mm}^2$, range 1.37-2.34) than in baseline examination ($1.77 \pm 0.27 \text{ mm}^2$, 1.27-2.08) ($p=0.004$). There was no correlation between LLS and OCT parameters ($p>0.05$).

CONCLUSIONS. In climbers with AMS, OCT was able to detect subtle increases in the peripapillary RNFL thickness and in some ONH measurements, even in absence of HACE and papilledema. These changes might be a sensitive parameter in physiologic acclimatization and in the pathogenesis of AMS.

KEY WORDS. Cerebral edema, High altitude adverse effects, Optical coherence tomography papilledema, Retinal nerve fiber layer

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INTRODUCTION

Exposure to high altitude of unacclimated people of all ages and clinical conditions has made acute mountain sickness (AMS) a frequent disorder with a significant medical and socioeconomic impact (1). The most frequent initial

symptom of AMS consists of headache. Anorexia, vomiting, insomnia, dizziness, and fatigue are also common and usually self-limiting (2). Mild AMS may progress to severe altitude illness manifested by high altitude pulmonary edema (HAPE) or high altitude cerebral edema (HACE). There are few reports about the ophthalmologic effects of high

altitude, and most of them have focused on high-altitude retinal hemorrhages (HARH) (3-8). The signs of high altitude retinopathy (HAR) include not only HARH but also dilated retinal vessels and peripapillary hyperemia. The pathogenesis of HAR and its relationship with the pathophysiology of HACE and HAPE are not yet known. Increased intracranial pressure (ICP) seems to be the root cause of all high-altitude problems, including HACE, HAPE, and HAR (9, 10). There is evidence that an increase in cerebral blood flow resulting from altered autoregulation constitutes a risk factor for AMS and HACE by leading to capillary overperfusion and vasogenic cerebral edema (11). The retina represents the only part of the central nervous system (CNS) where nerve fibers are visible and can be measured by noninvasive means. Thus, several studies have demonstrated, by optical coherence tomography (OCT), alterations in the peripapillary retinal nerve fiber layer (RNFL) thickness in various neurologic disorders, such as multiple sclerosis, Alzheimer disease, Parkinson disease, and schizophrenia, suggesting that this technology might also prove useful in other neurodegenerative conditions (12-15). This is the first time that peripapillary RNFL thickness has been measured by OCT to determine if a subclinical papilledema can be detected several weeks following a sojourn to high altitude.

MATERIALS AND METHODS

Participants

This prospective, observational, and analytical cohort study was performed within the scope of 4 high-altitude expeditions in the Himalayas region, where several medical research projects were carried out. The study was approved by the Ethical Committee of the "Lozano Blesa" University Clinic Hospital, Zaragoza, Spain, and adheres to the tenets of the Declaration of Helsinki. Informed, written consent was obtained from all subjects before the examinations. Twelve healthy mountaineers with ages ranging from 31 to 48 years (43.0 ± 5.6 years) were enrolled and monitored. Their medical history included tobacco use in 2 climbers (10 and 20 cigarettes a day, respectively), and was otherwise unremarkable.

They were all male and members of 4 expedition teams to climb major peaks in the Himalayas, Nepal: Manaslu—2009 (8163 m), Anapurna—2010 (8091 m), Manas-

lu—2010 (8163 m), and Cho Oyu—2010 (8201 m). Maximum altitude reached ranged from 6500 m to 8163 m (7245 ± 681 m). Atmospheric conditions were not very different in all expeditions, with atmospheric pressure ranging from 505 to 590 bars at base camp and from 335 to 355 bars at summit. Maximum temperature ranged from 8°C to 12°C and minimum temperature (summit day) ranged from -10°C to -25°C. Wind speed (summit day) ranged from 20 to 60 km/h. None of the climbers used supplemental oxygen. Dexamethasone and acetazolamide were administered to one mountaineer (J.V.) who had severe headaches, and enoxaparin and acetylsalicylic acid were administered to 2 climbers (J.P. and A.P.) who complained of frostbite injuries. The average time between the moment of reaching the maximum height and the exploration time at return to the hospital in Zaragoza ranged from 13 to 24 days (17.8 ± 4.8 days).

Procedures

Twelve healthy climbers underwent baseline examination 2 weeks before the expedition and 2 weeks after returning from the expedition at the University Clinic Hospital of Zaragoza (247 meters above sea level). Pre-expedition and postexpedition examinations were performed by the same investigator (L.V.) obtaining information on demographics, clinic, and ascent-related history. To measure the severity of AMS, the Lake Louise Scoring (LLS) system for acclimatization grading was used (9). This scale is used as an indicative parameter of acclimatization level. From a self-report questionnaire, Lake Louise points were assigned on a 0 to 3 scale for headache, gastrointestinal symptoms, fatigue, dizziness, difficulty sleeping, and mental status, and 0 to 2 for peripheral edema and ataxia. All subjects with a headache and LLS >3 were considered to have AMS. Total score of 4 to 6 means mild AMS; 7 or more means severe AMS. All patients underwent magnetic resonance imaging (MRI) to exclude a diagnosis of cerebral edema, tumor, or vascular disease.

Climbers then underwent a complete ophthalmic evaluation, including assessment of best-corrected visual acuity (BCVA) with logMAR charts (Early Treatment Diabetic Retinopathy Study letters), Goldmann applanation intraocular pressure (IOP) measurement (mmHg), slit-lamp biomicroscopy, and dilated fundus examination. All participants had a corrected visual acuity of 20/20 or better with a refractive error between ± 2 spheric diopters, IOP less than 18

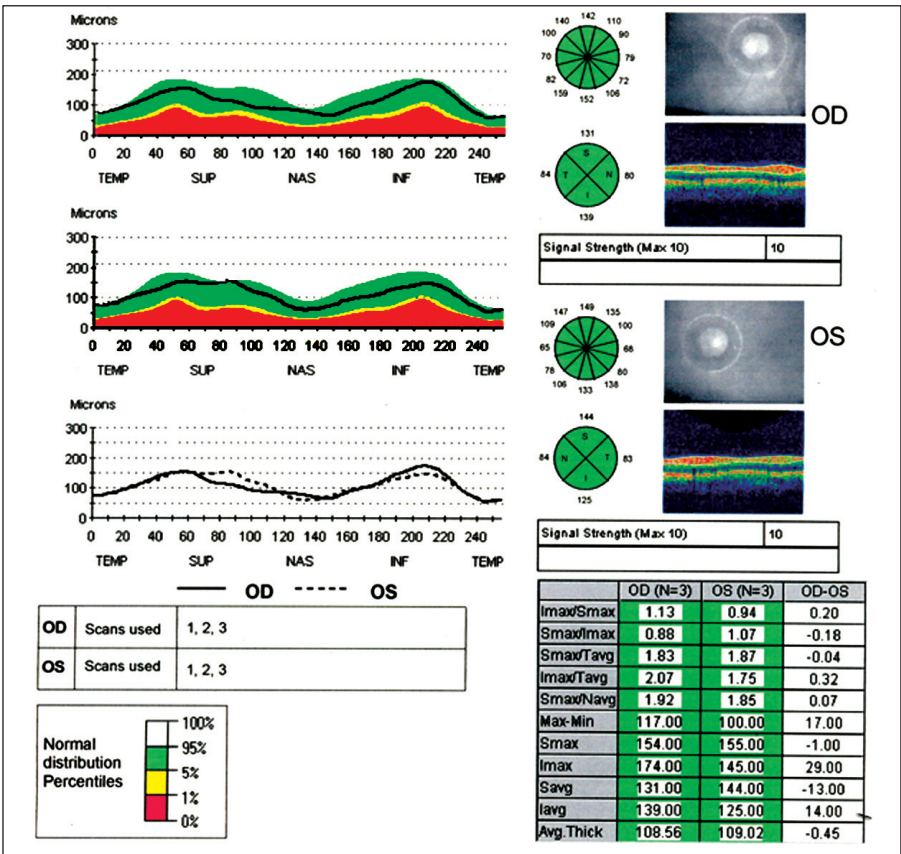


Fig. 1 - Retinal nerve fiber layer (RNFL) thickness was automatically calculated by the fast RNFL thickness (3.4) strategy of Stratus optical coherence tomography.

mmHg, and showed an absence of findings of HAR (retinal vascular dilation, retinal hemorrhages, or papilledema). Optical coherence tomography was performed with the Stratus OCT (Carl Zeiss Meditec Inc., Dublin, California, USA) after pharmacologic mydriasis with 1% tropicamide. Only high-quality images (signal strength ≥ 7) were included. Each patient underwent scans to measure RNFL thickness, optic nerve head (ONH) parameters, and macular thickness at the same visit. RNFL thickness was automatically calculated by the fast RNFL thickness (3.4) strategy (Fig. 1). Three 360° circular scans with a diameter of 3.4 mm centered on the optic disc were performed. The software allows the mapping of the thickness data according to both quadrant-by-quadrant and clock-hour analyses. We considered the average values of 3 different measurements per quadrant (superior, inferior, nasal, and temporal): the overall data obtained in all quadrants were identified as overall RNFL thickness. Optic nerve head measurements were obtained by the fast optical disk scanning protocol (Fig. 2), which consists of 6 radial scans in a spoke-like pattern centered on the ONH. The ONH parameters were

automatically calculated, including cup/disc area ratio, horizontal cup/disc ratio, and vertical cup/disc ratio. Macular thickness measurements were obtained by the fast macular thickness protocol (Fig. 3), which consists of 6 radial scans (each 6 mm) in a spoke-like pattern centered on the fovea, with each radial scan spaced 30° apart. To fill the gaps between scans, the OCT uses interpolation. Stratus OCT software calculates retinal thickness as the distance between the first signal from the vitreoretinal interface and the signal from the anterior boundary of the retinal pigment epithelium. The map is composed of 9 sectorial thickness measurements in 3 concentric circles with diameters of 1 mm, 3 mm, and 6 mm. The area bounded by the outer (6-mm) and middle (3-mm) circles forms the outer ring, and the area bounded by the middle (3-mm) and inner circles (1-mm) forms the inner ring. The central 1-mm circular region represents the foveal area. Total average macular thickness, average macular thicknesses in the inner (1-3 mm) and outer (3-6 mm) rings, and the central 1-mm fovea thickness were analyzed in the study. Total macular volume was calculated automatically by the OCT software.

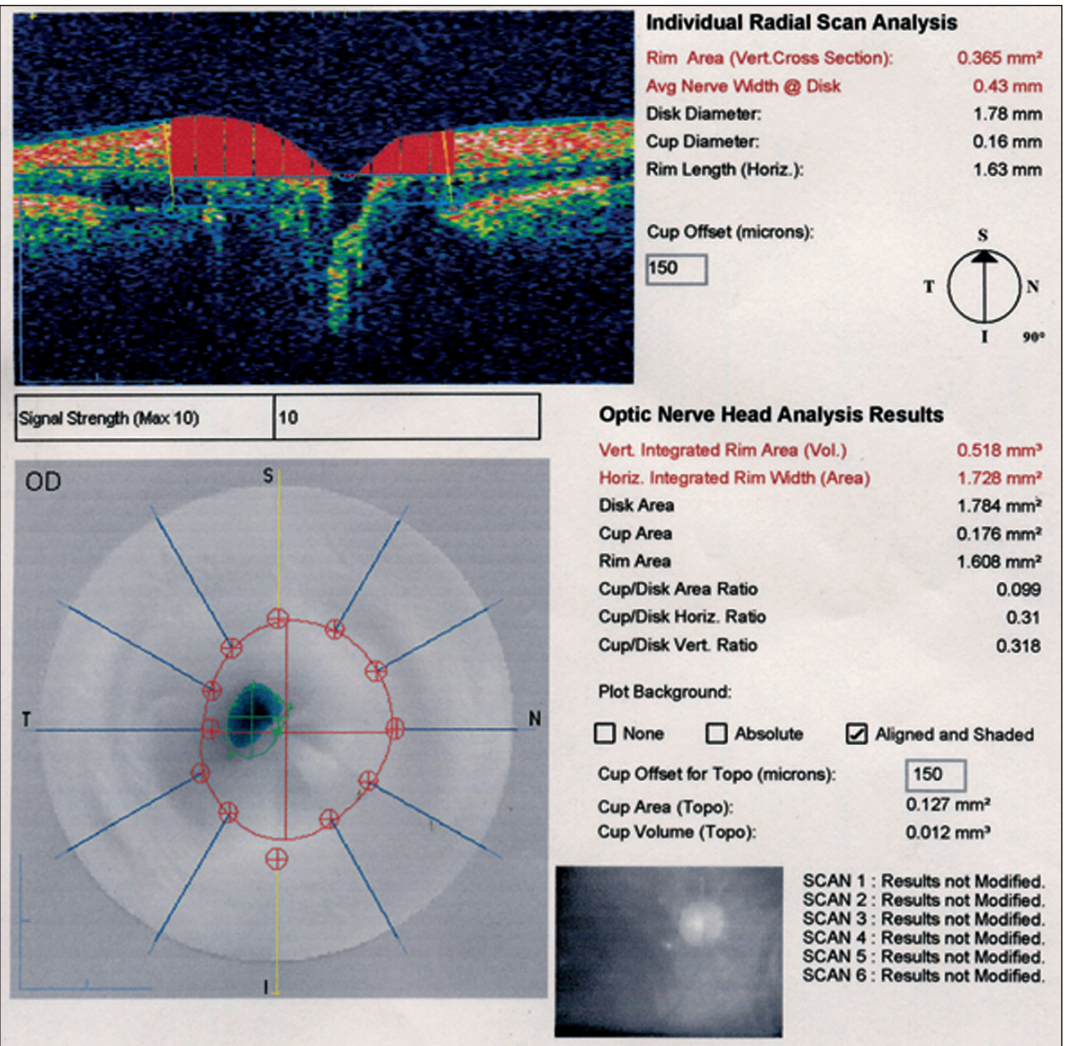


Fig. 2 - Optic nerve head measurements were obtained by the fast optical disk scanning protocol of Stratus optical coherence tomography.

Statistical analysis

Data analysis was performed with SPSS software version 15.0 (SPSS, Inc., Chicago, Illinois, USA). Values were presented as mean ± SD and expressed in μm for the peripapillary RNFL thickness and macular retinal thickness, and in mm³ for macular volume. Because of the small sample size, for statistical analyses, nonparametric tests were used. The Wilcoxon signed rank test for matched pairs was used to compare OCT measures obtained at baseline and postexpedition examination. Correlations between OCT data and LLS were evaluated by nonparametric Spearman correlation analysis. A 2-sided α error (p value) of <0.05 was considered statistically significant.

RESULTS

Clinical symptoms

Demographic and ascent-related characteristics of the 12 mountaineers are presented in Table I. Regarding acclimatization parameters, all climbers experienced symptoms of AMS (LLS: 5.1±1.1 [range 4-7]). In 11 subjects, AMS was mild (LLS: 4-6), and only one climber developed severe AMS (LLS = 7). Nevertheless, none complained of HACE symptoms. There was no correlation between LLS and OCT parameters (p>0.05, nonparametric Spearman correlation coefficient, rho). Two climbers were treated for frostbite in-

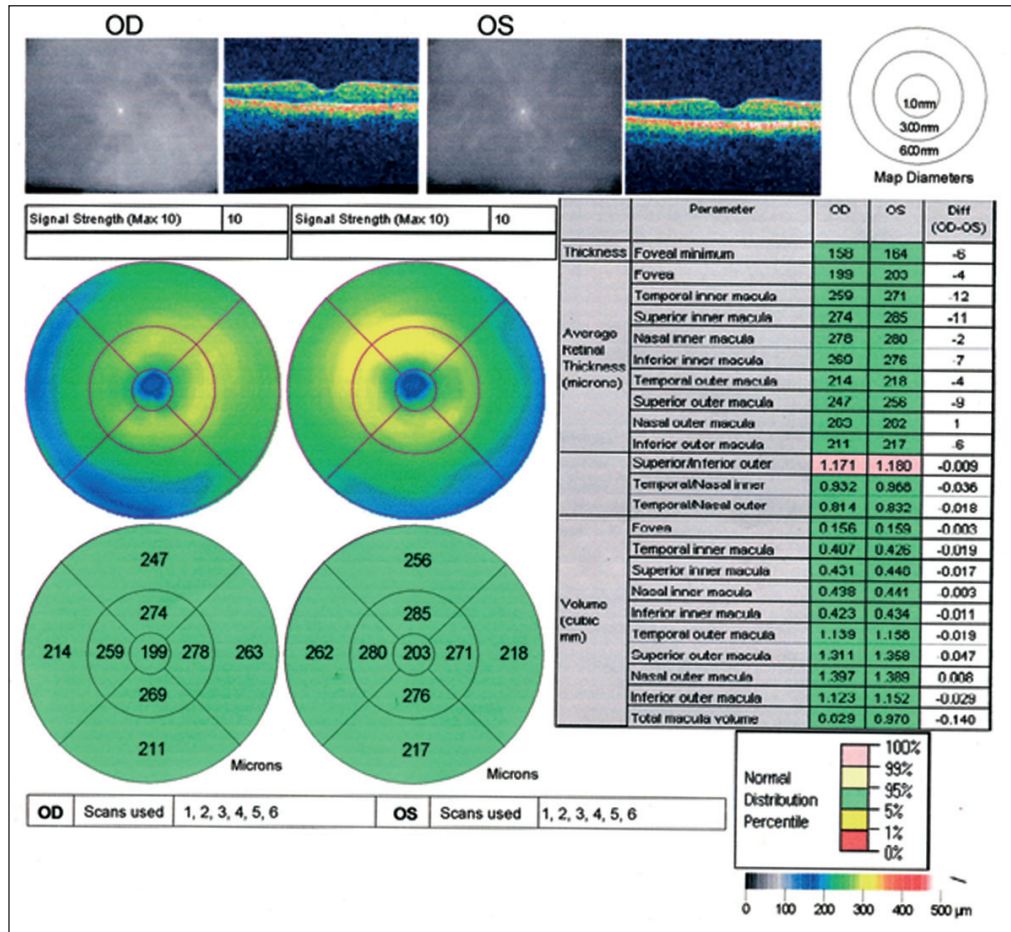


Fig. 3 - Macular thickness measurements were obtained by the fast macular thickness protocol of Stratus optical coherence tomography.

TABLE I - DEMOGRAPHIC, CLINIC, AND ASCENT-RELATED CHARACTERISTICS OF THE CLIMBERS

Characteristics	Values
No. of eyes (climbers)	24 (12)
Age, y, mean \pm SD (range)	43.0 \pm 5.6 (31-48)
Male/female	12/0
BCVA	20/20
IOP, mmHg, mean \pm SD	13.3 \pm 2.8
Maximum height reached, m, mean \pm SD (range)	7245 \pm 681 (6500-8163)
Time at more than 5500 m, d, mean \pm SD (range)	8.0 \pm 4.4 (3-13)
Summit examination time, d, mean \pm SD (range)	18.4 \pm 4.2 (13-24)
Lake Louise Score	5.1 \pm 1.1 (4.0-7.0)

BCVA = Best-corrected visual acuity; IOP = intraocular pressure measurement.

injuries with enoxaparin (a low molecular weight heparin) and acetylsalicylic acid. Another subject was treated for severe headaches with acetazolamide and dexamethasone.

Eye-related changes

No significant decrease in BCVA was noted during the course of the expeditions. No changes in either slit-lamp biomicroscopy or IOP measurements were found after the expedition compared with initial examinations. No vascular lesions (vessel engorgement and tortuosity) or retinal hemorrhages were noted during the pre-expedition and postexpedition ophthalmic evaluation in any mountaineer. Neither retinal vascular occlusion nor optic disc hyperemia was found in any subject.

OCT results

Table II shows the mean data and statistical results of OCT measurements. The average peripapillary RNFL thick-

TABLE II - BASELINE AND POSTEXPEDITION DATA OF OCT EXAMINATION

	Baseline values, mean \pm SD (range)	Postexpedition values, mean \pm SD (range)	p value ^a
RNFL thickness, μm			
Average	89 \pm 19 (45-114)	94 \pm 23 (47-115)	0.034
Superior	111 \pm 26 (55-139)	121 \pm 31 (54-166)	0.036
Nasal	70 \pm 18 (39-100)	69 \pm 17 (38-100)	0.649
Inferior	111 \pm 31 (40-138)	117 \pm 35 (45-151)	0.103
Temporal	62 \pm 12 (42-83)	71 \pm 16 (48-100)	0.010
Optic nerve head parameters			
VIRA, mm ³	0.51 \pm 0.26 (0.11-1.00)	0.71 \pm 0.43 (0.14-1.50)	0.002
HIRW, mm ²	1.77 \pm 0.27 (1.27-2.08)	1.90 \pm 0.32 (1.37-2.34)	0.004
Disc area, mm ²	2.56 \pm 0.35 (2.04-3.21)	2.41 \pm 0.35 (1.78-2.90)	0.638
Cup area, mm ²	0.54 \pm 0.35 (0.12-1.18)	0.48 \pm 0.30 (0.18-1.10)	0.438
Rim area, mm ²	2.02 \pm 0.40 (1.35-2.77)	1.93 \pm 0.34 (1.45-2.51)	0.388
C/D area ratio	0.21 \pm 0.13 (0.04-0.47)	0.19 \pm 0.11 (0.07-0.39)	0.480
C/D horizontal ratio	0.45 \pm 0.14 (0.20-0.67)	0.43 \pm 0.10 (0.29-0.61)	0.480
C/D vertical ratio	0.42 \pm 0.16 (0.21-0.70)	0.43 \pm 0.15 (0.24-0.71)	0.754
OCT macular parameters			
Fovea, μ m	216 \pm 10 (206-238)	217 \pm 22 (195-290)	0.582
TIM, μ m	276 \pm 15 (258-304)	271 \pm 12 (202-294)	0.816
SIM, μ m	289 \pm 15 (270-316)	286 \pm 29 (228-306)	0.365
NIM, μ m	295 \pm 18 (264-323)	286 \pm 29 (190-313)	0.679
IIM, μ m	285 \pm 17 (266-315)	281 \pm 15 (252-305)	0.306
TOM, μ m	221 \pm 13 (200-248)	217 \pm 16 (170-249)	0.289
SOM, μ m	238 \pm 17 (214-264)	240 \pm 16 (205-258)	0.877
NOM, μ m	261 \pm 14 (244-290)	257 \pm 23 (179-283)	1.000
IOM, μ m	224 \pm 16 (198-247)	224 \pm 16 (189-244)	0.816
MV, mm ³	7.00 \pm 0.40 (6.49-7.63)	6.90 \pm 0.49 (5.47-7.53)	0.469

HIRW = horizontal integrated rim width; IIM = inferior inner macular thickness; IOM = inferior outer macular thickness; NIM = nasal inner macular thickness; NOM = nasal outer macular thickness; OCT = optical coherence tomography; RNFL = retinal nerve fiber layer; SIM = superior inner macular thickness; SOM = superior outer macular thickness; TIM = temporal inner macular thickness; TOM = temporal outer macular thickness; VIRA = vertical integrated rim area.

^a The Wilcoxon signed rank test for matched pairs was used to compare OCT measures obtained at baseline and postexpedition examination.

ness showed a significant increase in the postexpedition examination (94 \pm 23 μ m, range 47-115) compared with baseline values (89 \pm 19 μ m, range 45-114) ($p=0.034$, Wilcoxon signed rank test). Superior ($p=0.036$) and temporal ($p=0.010$) quadrants also showed an increased RNFL thickness following exposure to high altitude. With respect to ONH analysis results, vertical integrated rim area (VIRA) was significantly higher in postexpedition examination (0.71 \pm 0.43 mm³, range 0.14-1.50) than in baseline examination (0.51 \pm 0.26 mm³, range 0.11-1.00) ($p=0.002$, Wil-

coxon signed rank test). Likewise, horizontal integrated rim width was significantly higher in postexpedition examination (1.90 \pm 0.32 mm², range 1.37-2.34) than in baseline examination (1.77 \pm 0.27 mm², range 1.27-2.08) ($p=0.004$, Wilcoxon signed rank test). The remaining ONH parameters did not show significant differences between baseline and postexpedition examinations. Mean values of macular thickness and volume are shown in the same table and no statistically significant differences were observed between baseline and postexpedition values ($p>0.05$, Wilcoxon signed rank test).

DISCUSSION

Acute mountain sickness represents a syndrome which consists of headache as well as gastrointestinal symptoms (anorexia, nausea, or vomiting), fatigue or weakness, dizziness or light-headedness, and sleep disturbance. The occurrence of AMS is dependent upon the altitude, the ascent rate, and individual susceptibility. Many people will experience mild AMS during the acclimatization process. Symptoms usually start 12 to 24 hours after arrival at altitude and begin to decrease in severity around the third day (9, 11). The HACE involves a global encephalopathy with the presence of headache, impaired cortical function, confusion, ataxia, depressed sensorium, and coma (16). Acute mountain sickness and HACE might be manifestations along a spectrum of the same clinical entity, and a rapid progression from AMS to HACE may occur in the setting of severe hypoxemia (17). The exact pathophysiologic basis of AMS and HACE remains unknown, but seems multifactorial, with altitude-related hypoxia leading to neurohormonal and hemodynamic processes at the vascular level in the CNS. These include impaired autoregulation, vasodilation, increased blood flow, and capillary permeability, leading to capillary leakage and edema (11, 16, 18). There is a close anatomic correlation between the vascular blood supply to the brain and the retina, due to similar vascular regulatory processes (19, 20).

Several authors think that high-altitude hypoxia induces cerebral edema and consequently increased ICP (9, 11, 17). However, no correlation has been found between increased ICP and AMS symptoms (1, 3, 21-27). Recently, Fagenholz et al, using optic nerve sheath ultrasonography, measured the optic nerve sheath diameter (22). Optic nerve sheath diameter was correlated with ICP, providing compelling evidence for the long-suspected but never demonstrated association between increased ICP and the symptoms and severity of AMS. Thus, increases in ICP would be transmitted by the cerebrospinal fluid down the perineural subarachnoid space of the optic nerve, causing an expansion of the nerve sheath that can be measured by ultrasound.

The retina is the most metabolically active tissue on a weight basis in the human body (28). The retinal blood flow is tightly regulated by tissue oxygen tension (PO_2) (29); thus, a drop in arterial oxygen partial pressure (PaO_2) induces an immediate increase in retinal blood flow. Muller and Deck demonstrated from necropsy studies the effu-

sion of cerebrospinal fluid into the optic nerve sheath in cases of sudden increase in ICP (30).

The HAR in the form of retinal hemorrhages often goes unnoticed, unless they are large enough to impair vision or occur near the macula. In our study, several weeks after the ascent to summit, we observed neither ophthalmoscopic signs of HAR (retinal hemorrhages or optic disc swelling) nor cerebral edema in MRI studies in the examined climbers. Probably, the fundusoscopic signs of retinal involvement disappeared due to the long period of time (2 weeks) between high altitude exposure and the time of examination at hospital. According to Wiedman and Tabin, the development of HAR seems to be an earlier phenomenon than HACE, and the finding of HAR should be thought of as a forewarning to the possible development of the more life-threatening HACE (31). However, a differentiation must be made between the clinical signs and OCT findings. The last ones are a result of neuro-ophthalmologic changes. In fact, in the present series patients neither showed HAR nor OCT macular changes.

Currently, direct visualization of the retina, which is a contiguous part of the CNS, allows for potential new insights into the pathophysiology of AMS and HACE. The development of AMS symptoms is correlated with a higher increase in retinal capillary blood flow and with optic disc swelling (21). Papilledema could be related to an increase in retinal blood flow and AMS with early stages of cerebral edema (17, 32). Whether an increase in cerebral blood flow (CBF) plays a pathogenic role in AMS continues to be a matter of debate. However, an altered autoregulation of CBF, allowing for an increased blood flow in the cerebral capillary bed, which then leads to a vasogenic brain edema, has been suggested to be the main cause of AMS or HACE symptoms (33).

Papilledema is thought to occur when an increased perineural pressure produces axoplasmatic flow stasis and thus swelling of the nerve fibers at the level of the optic disc (30). Histologic findings show that peripapillary RNFL is commonly thickened in patients with papilledema (10). Ophthalmoscopic identification of hyperemia of the optic disc, blurring of the peripapillary nerve fiber layer, and absent spontaneous venous pulsation are considered as indications of early swelling but they may be difficult for untrained physicians (20, 34).

The retina represents the only part of the CNS where nerve fibers are visible and can be measured by noninvasive means. Thus, several studies have demonstrated the ca-

pability of OCT to detect alterations in the peripapillary RNFL thickness in various neurologic disorders, such as multiple sclerosis, Alzheimer disease, Parkinson disease, and schizophrenia, suggesting that this technology might also prove useful in other neurodegenerative conditions (12-15). However, there are few studies evaluating ability of OCT to identify and quantify papilledema (7, 34, 35). To our knowledge, this is the first time that peripapillary RNFL thickness has been measured by OCT following a sojourn to very high altitude. The advantages of OCT compared with ophthalmoscopic observation of the optic disc are its reliability at lower grades of optic disc swelling and the possibility to quantify using a continuous as opposed to ordinal measurement scale. Application of a cross-sectional imaging technique as OCT in order to determine if this technique provides additional information to detect optic disc swelling in these subjects is therefore theoretically attractive. The possible ability of OCT to detect subclinical disc changes following a sojourn to extreme altitude has to our knowledge never been evaluated before. Our study suggests that OCT is superior to clinical disc evaluation for RNFL changes detection in subjects exposed to high altitude without clinical swelling (20). This technique could provide a quantitative, objective, and noninvasive adjunctive tool to assess the effect of exposition to high altitude on RNFL thickness. The mean RNFL was significantly thicker in the postexpedition examination than in baseline examination.

Subclinical optic disc swelling was observed 2 weeks after coming back from the expedition at the time that OCT examination was done. Under these circumstances, an already partial resolution of the RNFL concomitant with a diminution in disc swelling could be expected, either secondarily to therapy with dexamethasone, as initiated in one subject, and/or possibly secondarily to the natural course of papilledema.

Regarding OCT peripapillary measurements, average, superior quadrant, and temporal quadrant RNFL thickness values revealed a significant increase following exposure to extreme altitude. However, we cannot demonstrate a correlation between these changes in OCT measurements and the severity of AMS measured by the LLS system for acclimatization grading. Recently, Seth and Adelman [QUERY: Please clarify: ref. 23 is Fischer et al] reported the first case demonstrating the OCT findings of a patient with HAR, confirming the location of the hemorrhages in the superficial retina (23). However, the authors did not ex-

plore any change in the peripapillary RNFL thickness, ONH parameters, or in the macular thickness and volume. The present study is the first time that peripapillary RNFL thickness, macular thickness and volume, and selected morphologic parameters of the ONH have been measured following a sojourn to extreme altitude. The RNFL thickness measured by OCT could be a sensitive parameter in physiologic acclimatization and in the pathogenesis of AMS.

Disc edema results in a large disc area and vertical disc diameter because the presence of subretinal fluid masks the retinal pigment epithelium (RPE) near the ONH, leading to measurement artifacts caused by the failure of the scan to detect the RPE. Following papilledema resolution and the consequent RPE reappearance, ONH can be measured more accurately, showing a decrease in optic disc area and vertical disc diameter. Regarding ONH parameters, we did not find a difference in disc area and disc diameters between baseline and postexpedition examination values. However, VIRA was significantly higher after high-altitude exposure compared with the baseline values, even in the presence of similar disc areas and vertical disc diameters, which suggests more crowding in these eyes with hypoxia. This fact has been previously reported in nonarteritic anterior ischemic optic neuropathy, whose patients have a higher level of nerve fiber crowding (high VIRA) (36). Therefore, measurement of peripapillary RNFL thickness and ONH parameters by OCT might show subtle changes although fundus photographs and MRI studies are not able to demonstrate any sign of edema.

The present study has certain limitations that need to be taken into account when considering the study and its contributions. However, some of these limitations can be seen as fruitful avenues for future research under the same theme. The main limitation is the relatively small series. Nevertheless, due to obvious recruiting difficulties, a large number of AMS cases are difficult to collect at one site. Despite the logistical and technical difficulties associated with medical research in such a challenging environment, we were able to collect novel data in a group of mountaineers after ascending to extreme altitudes. Although it would have been preferable if the climbers had been from the same expedition team climbing to the same peak at the same time, recruiting climbers in real extreme environments is not an easy task. In any case, 2 of the climbers (C.P. and J.P.) participated in 3 of the 4 expeditions, and therefore both mean 50% of the 12 examined mountaineers [QUERY: Please clarify "and therefore both mean

50% of the 12 examined mountaineers"]. Likewise, half of the expeditions (2/4) were to Manaslu (8163 m) and the other mountains (Anapurna and Cho-Oyu are in the same Himalayan area and have a similar altitude, 8091 m and 8201 m, respectively). Another limitation of this study is that OCT measurements were performed 2 weeks after high altitude exposure.

Nevertheless, to our knowledge, this is the first prospective, controlled study to compare RNFL thickness and ONH parameters in subjects exposed to extreme altitude by means of clinical direct ophthalmoscopy and OCT. Our study provides additional cumulative data regarding OCT findings and its benefits as an objective, micron-resolution quantitative and noninvasive adjunctive tool in the diagnosis of subclinical optic disc swelling secondary to AMS, but larger validation studies are needed.

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REFERENCES

- Honigman B, Theis MK, Koziol-McLain J, et al. Acute mountain sickness in a general tourist population at moderate altitudes. *Ann Intern Med* 1993; 118: 587-92.
- Clarke C. Acute mountain sickness: medical problems associated with acute and subacute exposure to hypobaric hypoxia. *Postgrad Med J* 2006; 82: 748-53.
- Honigman B, Noordewier E, Kleinman D, Yaron M. High altitude retinal hemorrhages in a Colorado skier. *High Alt Med Biol* 2001; 2: 539-44.
- Lubin JR, Rennie D, Hackett P, Albert DM. High altitude retinal hemorrhage: a clinical and pathological case report. *Ann Ophthalmol* 1982; 14: 1071-6.
- MacLaren RE. Retinal haemorrhage in Himalayan mountaineers. *J R Army Med Corps* 1995; 141: 25-8.
- Morris DS, Somner J, Donald MJ, et al. The eye at altitude. *Adv Exp Med Biol* 2006; 588: 249-70.
- Munsen RS, Blodi FC. High-altitude retinal hemorrhages. *JAMA* 1981; 245: 610.
- Schumacher GA, Petajan JH. High altitude stress and retinal hemorrhage: relation to vascular headache mechanisms. *Arch Environ Health* 1975; 30: 217-21.
- Roach RC, Bartsch P, Oelz O, Hackett PH. The Lake Louise AMS scoring system. In: Sutton JR, Houston CS, Coates G, eds. *Hypoxia & Molecular Medicine*. Burlington, VT: Charles S Houston; 1993: 272-4.
- Sutherland AI, Morris DS, Owen CG, Bron AJ, Roach RC. Optic nerve sheath diameter, intracranial pressure and acute mountain sickness on Mount Everest: a longitudinal cohort study. *Br J Sports Med* 2008; 42: 183-8.
- Bartsch P, Bailey DM, Berger MM, Knauth M, Baumgartner RW. Acute mountain sickness: controversies and advances. *High Alt Med Biol* 2004; 5: 110-24.
- Ascaso FJ, Cabezón L, Quintanilla MA, et al. Retinal nerve fiber layer thickness measured by optical coherence tomography in patients with schizophrenia: a short report. *Eur J Psychiatry* 2010; 24: 227-35.
- Berisha F, Feke GT, Trempe CL, McMeel JW, Schepens CL. Retinal abnormalities in early Alzheimer's disease. *Invest Ophthalmol Vis Sci* 2007; 48: 2285-9.
- Hajee ME, March WF, Lazzaro DR, et al. Inner retinal layer thinning in Parkinson disease. *Arch Ophthalmol* 2009; 127: 737-41.
- Henderson AP, Trip SA, Schlottmann PG, et al. An investigation of the retinal nerve fibre layer in progressive multiple sclerosis using optical coherence tomography. *Brain* 2008; 131(Pt 1): 277-87.
- Gallagher SA, Hackett PH. High-altitude illness. *Emerg Med Clin North Am* 2004; 22: 329-55.
- Hackett PH, Roach RC. High-altitude illness. *N Engl J Med* 2001; 345: 107-14.
- Seth RK, Adelman RA. High-altitude retinopathy and optical coherence tomography findings. *Semin Ophthalmol* 2010; 25: 13-5.
- Delaey C, Van De Voorde J. Regulatory mechanisms in the

- retinal and choroidal circulation. *Ophthalmic Res* 2000; 32: 249-56.
20. Møller K, Paulson OB, Hornbein TF, et al. Unchanged cerebral blood flow and oxidative metabolism after acclimatization to high altitude. *J Cereb Blood Flow Metab* 2002; 22: 118-26.
 21. Bosch MM, Barthelmes D, Merz T, et al. High incidence of optic disc swelling at very high altitudes. *Arch Ophthalmol* 2008; 126: 644-50.
 22. Fagenholz PJ, Gutman JA, Murray AF, Noble VE, Camargo CA Jr, Harris NS. Optic nerve sheath diameter correlates with the presence and severity of acute mountain sickness: evidence for increased intracranial pressure. *J Appl Physiol* 2009; 106: 1207-11.
 23. Fischer R, Vollmar C, Thiere M, et al. No evidence of cerebral oedema in severe acute mountain sickness. *Cephalalgia* 2004; 24: 66-71.
 24. Hartig GS, Hackett PH. Cerebral spinal fluid pressure and cerebral blood velocity in acute mountain sickness. In: Sutton JR, Coates G, Houston CS, ed. *Hypoxia and Mountain Medicine*. Burlington, VT: Queen City; 1992: 60-265.
 25. Levine BD, Yoshimura K, Kobayashi T, Fukushima M, Shibamoto T, Ueda G. Dexamethasone in the treatment of acute mountain sickness. *N Engl J Med* 1989; 321: 1707-13.
 26. Mórocz IA, Zientara GP, Gudbjartsson H, et al. Volumetric quantification of brain swelling after hypobaric hypoxia exposure. *Exp Neurol* 2001; 168: 96-104.
 27. Wiedman M, Tabin GC. High-altitude retinopathy and altitude illness. *Ophthalmology* 1999; 106: 1924-6; discussion 1927.
 28. Anderson B Jr, Saltzman HA. Retinal oxygen utilization measured by hyperbaric blackout. *Arch Ophthalmol* 1964; 72: 792-5.
 29. Pournaras CJ, Rungger-Brändle E, Riva CE, Hardarson SH, Stefansson E. Regulation of retinal blood flow in health and disease. *Prog Retin Eye Res* 2008; 27: 284-330.
 30. Muller PJ, Deck JH. Intraocular and optic nerve sheath hemorrhage in cases of sudden intracranial hypertension. *J Neurosurg* 1974; 41: 160-6.
 31. Wiedman M, Tabin G. High-altitude retinal hemorrhage as a prognostic indicator in altitude illness. *Int Ophthalmol Clin* 1986; 26: 175-86.
 32. Bosch MM, Merz TM, Barthelmes D, et al. New insights into ocular blood flow at very high altitudes. *J Appl Physiol* 2009; 106: 454-60.
 33. Tso MO, Fine BS. Electron microscopic study of human papilledema. *Am J Ophthalmol* 1976; 82: 424-34.
 34. Skau M, Milea D, Sander B, Wegener M, Jensen R. OCT for optic disc evaluation in idiopathic intracranial hypertension. *Graefes Arch Clin Exp Ophthalmol* 2011; 249: 723-30.
 35. Walsh FB, Hoyt WF. The ophthalmoscopic diagnosis of papilledema. In: Walsh FB, Hoyt WF, ed. *Clinical Neuroophthalmology*. Baltimore, MD: Williams & Wilkins; 1969: 576-83.
 36. Contreras I, Rebolledo G, Noval S, Muñoz-Negrete FJ. Optic disc evaluation by optical coherence tomography in nonarteritic anterior ischemic optic neuropathy. *Invest Ophthalmol Vis Sci* 2007; 48: 4087-92.