Electroretinographic assessment of retinal function at high altitude

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Every year millions of alpinists are subject to hypobaric hypoxia at high altitude with so far objectively unreported consequences for retinal function. Climbers at high altitude are, in addition to hypoxia, challenged by exercise, which has been reported to aggravate retinal alterations at high altitude (33). However, electrophysiological field studies under hypobaric hypoxia at high altitude are inherently difficult to perform due to immense logistical challenges with the necessity to deploy sophisticated equipment requiring stable electrical power supply in a “low electrical noise” environment. Moreover, for sophisticated ERG protocols, strict dark adaptation is required, which demands completely controllable conditions, which can only be ensured in a hut. Probably due to these restrictions, so far no such study has been performed. A recent study has only assessed changes of the multifocal ERG (mfERG) in three subjects before and 1 wk after exposure to 5,600 m (40). In this study, the authors described a decrease of amplitudes in the mfERG. This finding has also been confirmed under simulated normobaric hypoxia (26).

In the past decades, numerous comprehensive studies have been performed to investigate the pathomechanism of acute mountain sickness (AMS), high-altitude pulmonary edema (HAPE), and high-altitude cerebral edema (HACE). Although much insight has been gained into the mechanisms of HAPE and HACE, the relevant pathophysiological mechanisms of AMS still remain heavily debated. Since the retina is a visible part of the brain, with the retina embryologically being a protrusion of the diencephalon, this organ represents a unique opportunity to directly study altitude-related changes of the central nervous system (CNS). Examination of correlations with scores of AMS and incidence of related diseases might be able to shed light onto underlying pathophysiological mechanisms.

The aim of the present study was to investigate the effect of high-altitude hypoxia on retinal function using a comprehensive ERG protocol after controlled ascent and descent, and to correlate the findings to general clinical findings and severity
of AMS. This work is related to the Tübingen High Altitude Ophthalmology (THAO) study.

MATERIALS AND METHODS

This study was performed in accordance with the tenets of the Declaration of Helsinki 1975 (1983 revision) and Title 45 of U.S. Code of Federal Regulations (Part 46, Protection of Human Subjects, Revised June 23, 2005, effective June 23, 2005). All procedures were approved by the local Institutional Review Board (ethics committee of the University of Tübingen Medical Faculty, IEC project no. 258/2010B01). All participants gave written, informed consent after being informed about the nature of the study.

Subjects

Nineteen healthy subjects were included in the study. Due to extreme weather conditions, only 14 subjects (7 men and 7 women; age 25–54 yr) could be guided to the summit; one subject had to be excluded due to strong blepharospasm and eye movements; therefore, results from these 13 subjects are described.

Ophthalmological exclusion criteria were spherical ametropia greater than ±5 dpt and/or cylindrical ametropia greater than ±2 dpt, and any kind of confounding ophthalmological disease such as cataract, vitreous, or corneal opacities and retinal diseases.

Study Design

Baseline ERG recordings were performed at the Centre for Ophthalmology in Tübingen (Germany) at 341 m above sea level. Before and after altitude exposure, subjects had to spend at least 14 days below 2,000 m. Subjects ascended to La Capanna Regina Margherita (CM; Valais Alps, Italy; Fig. 1), according to a previously described ascent profile (58). Day 0 was composed of the ascent to Gressoney (Italy; 1,635 m) to Punta Indren (3,260 m) by cable car followed by ~2 h hiking to the Capanna Gnifetti at 3,647 m, where 1 night was spent. Day 1 was composed of the ascent to the CM (4,559 m) in 4–6 h. Days 2–4 were composed of the stay at CM. Day 4 was composed of the descent to Gressoney in 4–6 h. In the morning of day 2 at high altitude, subjects took part in the ERG session. Assessment of AMS was performed using the Lake-Louise (LL) and the cerebral score of AMS (AMS-C) immediately before ERG examination (43, 47). If AMS-C of >0.7 and LL of >5 was noted, subjects were considered as being mountain sick (2). Vital parameters [oxygen saturation (SpO2) and heart rate (HR)] were assessed as previously described (58).

ERG

All measurements were performed using the identical Ganzfeld light-source and computer-based recording system (ColorDome and Espion E2, Diagnosys, Cambridge, UK) at baseline and at high altitude. The equipment was transported by helicopter from Zermatt (Air Zermatt, Zermatt, Switzerland) to CM and back. Particular care was taken to position the ERG setup to ensure insulation from the huts’ proprietary equipment, such as radio antennas (Fig. 1). After dark adaptation for 30 min and administration of two drops of tropicamide 0.5% (Mydriatikum Stulln, Stulln, Germany), gold cup-electrodes (Viasys Healthcare, Madison, WI) were placed on both temples as counter electrode and the forehead as ground under dim red light after careful cleaning of the skin using abrasive paste and alcohol pads. A drop of 0.4% oxybuprocaine (Novesine, OmniVision, Puchheim, Germany) was applied for corneal anesthesia before the self-constructed DTL-electrodes were positioned as described before (11, 15). An impedance level of <5 kΩ at 25 Hz (manufacturer’s recommendation) was ensured continuously throughout the measurements. After completion of the dark-adapted protocol, light adaptation was achieved by exposure to 30 cd/m² (white 6,500 K background) for 10 min.

ERG protocol. An extended International Society for Clinical Electrophysiology of Vision (ISCEV) protocol was used, which includes stimuli covering a larger range of parameters compared with standard protocols. The dark-adapted ERG protocol consisted of 11 steps (10⁻⁴ to 10 cd/s/m², in increments of 0.5 log units) using a 4-ns white flash (6,500 K); all flashes were delivered with interstimulus intervals of 10 s for dim flashes and 15 s for bright flashes (≥0.3 cd/s/m²). Responses from each stimulus were averages of five sweeps. The light-adapted ERG protocol consisted of three single flashes of 1, 3, and 10 cd/m² in the same white flash on a white background of 30 cd/m², followed by four flicker frequencies (5, 15, 31, and 45 Hz) with a stimulus strength of 3 cd/s/m². Ten sweeps were averaged for single flash responses, 20 sweeps for 5 Hz, 30 sweeps for 15 and 30 Hz, and 60 sweeps for 45 Hz. Band-pass filtering was applied from 0.3 to 300 Hz using the machine’s built-in software algorithm.

Data Retrieval

A-wave amplitudes, as a criterion for photoreceptor function, and b-wave amplitudes, as a criterion for rod- and cone-driven bipolar and Müller cell function, and their respective implicit times were determined according to ISCEV recommendations (31) using our previously described software (34). For low stimulus strengths (up to 0.1 cd/s/m²), a scotopic sensitivity model was fitted using the function of Naka-Rushton (38) to retrieve the parameters Vmax as asymptotic saturation and k as stimulus strength needed for 50% of Vmax, considered as a criterion for scotopic sensitivity (Fig 2A). Oscillatory potentials were analyzed after offline band-pass frequency filtering (75–300 Hz) of ERG responses elicited by stimulus strengths from 0.3 to 10 cd/s/m². The area-under-the-curve (AUC) between the trough of the a-wave and the peak of the b-wave was determined as reported previously (48) to serve as a measure of inner retinal layer function (16). The slope of the initial part of the a-wave was determined by a linear function fitted to the leading edges of the a-wave to evaluate the phototransduction and photoreceptor function (6, 18). The light-adapted standard flash response (3 cd/s/m²) was used to derive the
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**RESULTS**

**Clinical Examinations and AMS Scores**

Mean AMS-C and LL scores were both 0 at baseline and 1.06 ± 0.77 (mean ± SD) and 5.2 ± 2.7, respectively, at high altitude. HR was 60 ± 7 beats/min at baseline and 83 ± 11 beats/min at high altitude; SpO₂ was 98.5 ± 1.3% at baseline and 71.5 ± 5.6% at high altitude. Seven subjects were above the cut-off value for AMS with a mean AMS-C score of 1.62 ± 0.59; LL score of 6.7 ± 2.1; HR of 89 ± 8 beats/min; SpO₂ of 69.9 ± 6.2%. Subjects without AMS at high altitude had a mean AMS-C of 0.40 ± 0.19; LL of 3.5 ± 2.2; HR of 77 ± 9 beats/min; SpO₂ of 73.5 ± 4.6%. HR differed significantly between subjects with and without AMS ($P = 0.028$), but there was no significant difference in SpO₂ ($P = 0.26$).

**Dark-Adapted ERG**

Results of the standard and extended ISCEV protocols are shown separately in Figs. 2 and 4, but all parameters that are relevant to a particular component of the ERG are described together below.

**Scotopic sensitivity function.** $V_{max}$ was significantly lower at high altitude compared with baseline (Fig. 2; $P < 0.01$), but no significant differences were seen for $k$ (Fig. 2; $P = 0.71$).

**b-Wave amplitudes and implicit times.** Analysis of rod-driven b-wave amplitudes and implicit times (0.01 cd·s/m²) revealed no significant changes at high altitude (Fig. 2; $P = 0.23$ and $P = 0.91$, respectively). For stimulus strengths of 0.3 and 1 cd·s/m², with low cone contributions to the rod-dominated ERG, a tendency for reduced amplitudes was noticed at high altitude (Fig. 4; $P = 0.16$ and $P = 0.05$, respectively). A significantly prolonged implicit time was found for 1 cd·s/m², but for 0.3 cd·s/m² it remained unchanged (Fig. 4; 0.3 cd·s/m² $P = 0.97$ and 1 cd·s/m² $P < 0.01$). For the mixed rod-cone response (3 and 10 cd·s/m²), where cone contributions become evident, amplitudes were significantly reduced (Figs. 2 and 4; 3 cd·s/m², $P < 0.05$; 10 cd·s/m², $P < 0.01$) and implicit times

Fig. 2. A: fit of b-wave amplitudes vs. stimulus strength showing the scotopic sensitivity function at baseline (Tübingen, Germany, 341 m) and at high altitude. Analyzed parameters [asymptotic saturation amplitude ($V_{max}$) and stimulus strength needed for 50% of $V_{max}$ ($k$)] are marked by dotted lines. The $V_{max}$ was significantly reduced at high altitude ($P < 0.01$). B: corresponding electroretinography (ERG) traces for the amplitudes in A and illustrations of a- and b-waves. C: comparison of all International Society for Clinical Electrophysiology of Vision (ISCEV) standard ERG parameters and of the scotopic sensitivity function at baseline and high altitude with means and confidence intervals (95%) for dark- and light-adapted measurements. ampl., Amplitude; impl., implicit time.

Statistical Analysis

JMP was used for all statistical analyses (version 8.0.2, SAS Institute, Cary, NC). A paired $t$-test was used for comparison of baseline and high-altitude ERG recordings. For comparison of HR and SpO₂ between subjects with and without AMS, an unpaired $t$-test was used. The significance level was set at $P < 0.05$. Pearson’s correlation coefficient (significance level, $P < 0.05$) was calculated to evaluate possible correlations between ERG and clinical parameters (SpO₂, HR) and AMS-C.
of b-waves were prolonged at high altitude (Figs. 2 and 4; \( P < 0.01 \) and \( P = 0.12 \), respectively).

**a-Wave amplitudes, implicit times, and slopes.** a-Wave amplitudes at high altitude showed a tendency for reduction at 3 cd·s/m² (\( P = 0.08 \)) and 10 cd·s/m² (\( P = 0.06 \)) but not at 0.3 cd·s/m² (\( P = 0.48 \)) and 1 cd·s/m² (\( P = 0.35 \); Figs. 2 and 4). A-wave implicit times were significantly prolonged at high altitude for 0.3 and 1 cd·s/m² but not for 3 and 10 cd·s/m² (Figs. 2 and 4; 0.3 cd·s/m², \( P < 0.01 \); 1 cd·s/m², \( P < 0.05 \); 3 cd·s/m², \( P = 0.34 \); 10 cd·s/m², \( P = 0.67 \)). The a-wave slope was significantly reduced at high altitude for 1 and 3 cd·s/m² but not for 0.3 and 10 cd·s/m² (Fig. 3; 0.3 cd·s/m², \( P = 0.64 \); 1 cd·s/m², \( P < 0.05 \); 3 cd·s/m², \( P < 0.05 \); 10 cd·s/m², \( P = 0.14 \)).

**Oscillatory potentials.** Oscillatory potentials (OPs) were not significantly altered at high altitude at any step (Fig. 4; 0.3 cd·s/m², \( P = 0.68 \); 1 cd·s/m², \( P = 0.79 \); 3 cd·s/m², \( P = 0.54 \); 10 cd·s/m², \( P = 0.82 \)).

**Light-Adapted ERG**

**b-Wave amplitudes and implicit times.** Single flash b-wave amplitudes showed a tendency for reduction at high altitude (Figs. 2 and 4; 1 cd·s/m², \( P = 0.06 \); 3 cd·s/m², \( P = 0.08 \); 10 cd·s/m², \( P = 0.14 \)) without reaching significance. No differences were observed for corresponding implicit times (Figs. 2 and 4; 1 cd·s/m², \( P = 0.75 \); 3 cd·s/m², \( P = 0.39 \); 10 cd·s/m², \( P = 0.06 \)). The flicker series with increasing frequencies from 5 to 45 Hz revealed no significant differences of amplitudes or phases at high altitude (Figs. 2 and 4; amplitude 5 Hz, \( P = 0.39 \); 15 Hz, \( P = 0.39 \); 31 Hz, \( P = 0.64 \); 45 Hz, \( P = 0.33 \); phases 5 Hz, \( P = 0.88 \); 15 Hz, \( P = 0.34 \); 31 Hz, \( P = 0.17 \); 45 Hz, \( P = 0.75 \)).

**b-Wave amplitudes and implicit times.** Amplitudes (Figs. 2 and 4; 1 cd·s/m², \( P = 0.21 \); 3 cd·s/m², \( P = 0.17 \); 10 cd·s/m², \( P = 0.36 \)) and implicit times were not significantly different at high altitude (Figs. 2 and 4; 1 cd·s/m², \( P = 0.25 \); 3 cd·s/m², \( P = 0.75 \); 10 cd·s/m², \( P = 0.10 \)).

**PhNR and i-wave.** Implicit times of the PhNRs were significantly longer at high altitude (Fig. 4; \( P < 0.05 \)); amplitudes remained unaltered (Fig. 4; \( P = 0.28 \)). The i-wave showed a significant decrease of amplitudes at high altitude (Fig. 4; \( P < 0.01 \)). No changes were observed for i-wave implicit times (Fig. 4; \( P = 0.37 \)).

**OPs.** No significant changes were detected for cone-derived OPs (Fig. 4; 1 cd·s/m², \( P = 0.23 \); 3 cd·s/m², \( P = 0.35 \); 10 cd·s/m², \( P = 0.16 \)).

**Correlation of Electrophysiological Parameters with Clinical Tests and Scores of AMS**

Pearson’s correlation coefficient between electrophysiological parameters and HR, \( \text{SpO}_2 \), and AMS-C yielded only eight significant (of 165 possible) correlations: the highest significant correlation was observed between \( \text{SpO}_2 \) and PhNR (Fig. 5; \( r = 0.68 \) \( P < 0.05 \)). Furthermore, \( \text{SpO}_2 \) correlated with the light-adapted a-wave amplitude (Fig. 5; 10 cd·s², \( r = 0.64 \); \( P < 0.05 \)). Another strong correlation was detected for HR and b-wave amplitude of the rod response (Fig. 5; 0.01 cd·s/m² under dark adaptation, \( r = 0.64 \) \( P < 0.05 \)). Other moderately strong but significant correlations for HR were found with Vmax (Fig. 5; \( r = 0.55 \) \( P < 0.05 \)), a-wave amplitude of 3 cd·s/m² (Fig. 5; \( r = -0.57 \) \( P < 0.05 \)), a-wave slope of 0.3 cd·s/m² (\( r = 0.55 \) \( P < 0.05 \)), and the light-adapted a-wave implicit time of 1 cd·s/m² (\( r = 0.56 \) and \( P < 0.05 \)). Only one significant correlation was found with AMS-C: the light-adapted b-wave implicit time of 10 cd·s/m² (Fig. 5; \( r = 0.57 \) and \( P < 0.05 \)).
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DISCUSSION

Electroretinography is the most widely used modality that can provide objective information about the integrity of the retina and its various cell types; it has greatly contributed to our understanding of physiological and pathophysiological processes of the visual system (5, 25, 27, 35). Exposure to high altitude constitutes a systemic hypoxic challenge, and effects of high altitude on the visual system have been studied; studies have also detected a possible pathophysiological link to high-altitude illnesses such as AMS and HACE. Since the eye is considered a visible part of the brain, it is often used as a correlate for alterations of the CNS (3, 13, 17, 19, 50, 51).

Besides logistical difficulties (size and sensitivity of ERG equipment) with the necessity of helicopter delivery to the hut, the cold, the wind, the altitude, and the electrical noise were challenging tasks for our setup. By equipping the room with the best of the-art ERG equipment and extended ISCEV protocols. physiological recordings of the retina at high altitude using state-of-the-art ERG equipment and extended ISCEV protocols.

Studies using hypobaric or normobaric systemic hypoxia using chambers or ventilation masks have shown that, in healthy subjects, outer retinal function is more resistant to hypoxia than inner retinal function (21, 53). This is explainable by the predominant supply of the inner retina through retinal vessels, whereas the outer retina is mostly nourished by the choroid (56).

The saturated response of the scotopic sensitivity function (Vmax of Naka and Rushton fit; Fig. 2) was significantly reduced in our study, without significant changes of a-wave amplitudes of the outer retina, supporting an impaired inner retinal function (rod bipolar and Müller cells). However, we found no significant changes of the rod responses at 0.01 cd·s/m². At the highest stimulus strengths used for the scotopic sensitivity function (0.03 and 0.1 cd·s/m²), an a-wave was clearly visible in the ERG (Fig. 2). Since ERG recordings with marked a-wave amplitudes under dark-adapted condition are declared as combined rod-cone responses, the beginning interaction of both photoreceptors may be present at these stimulus strengths. Even if rods are predominant in the ERG recordings of the scotopic sensitivity function, a cone contribution cannot

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be excluded. This may explain the fact that the isolated rod responses (0.01 cd·s/m²), which presented no marked a-wave and therefore no beginning rod-cone interaction, showed no significant changes at high altitude and was supported by reduction of b-wave amplitudes and prolongation of implicit times of the mixed rod-cone responses (3 and 10 cd·s/m²).

Furthermore, the interaction of rods and cones, as expressed by the dark-adapted combined responses (1–10 cd·s/m²), showed one of the highest changes under hypobaric hypoxia of all parameters. In conclusion, high-altitude hypoxia causes an impairment of post-photoreceptorial signaling pathways, most marked under conditions where interaction of rods and cones is present.

Notably, not only inner retinal function was impaired under dark-adapted conditions as shown by a prolonged a-wave implicit time and decreased a-wave slopes (there was only a tendency for a reduction of a-wave amplitudes). Both findings indicate an impairment of the photoreceptor function at high altitude. Previous studies utilizing specific ERG protocols to separate the early and late a-wave components as stated, e.g., by Bradshaw et al. (4, 7, 44), could investigate the impairment of the a-wave under hypoxia in more detail. Unfortunately, we were not able to include them in the presented study due to the screening character and lack of previous ERG data under such specific conditions, but further studies might be conducted to clarify this point.

In contrast to previous studies under simulated hypobaric hypoxia in a chamber (21), we found no significant differences in OPs, which are considered to represent function of amacrine cells, depolarizing and hyperpolarizing bipolar cells, and interplexiform cells. These groups of cells are responsible for modulation of signal processing between different types of bipolar cells and ganglion cells, contributing to adjustment of retinal sensitivity. One explanation might be that OP alterations only occur acutely and at higher altitudes since the simulated altitude in the cited study corresponds to 5,500 m (21) with 10.5% O₂ content and was observed after 15 min of hypoxia compared with 11.7% in our study at 4,559 m observed 24 h after ascent. Another plausible explanation might be that OPs are impaired more in early stages of hypoxic exposure and that these cells, which are represented by OPs, might acclimatize faster than other retinal cells. However, due to the short-term hypoxia used in previous studies with missing evaluation on incidence of AMS, we are not able to perform any comparisons to this previous study.

In the light-adapted retinal state, we found changes of the PhNR and the i-wave. Although the exact origin of these potentials is still not entirely clear, it is postulated that both represent ganglion cell function (9, 39, 42, 45, 54, 55). Ganglion cells are responsible for transmission of visual information from retinal cells to the brain by forming the optic nerve. An impairment of ganglion cells might be in accordance with morphological findings in our study population in whom retinal nerve fiber layer swelling has been shown in confocal laser (58).

At high altitude, hypoxia is accompanied by hypocapnia. Although hypoxia is believed to be the key factor of high altitude-related retinal dysfunction, hypocapnia should also be considered to have an impact on retinal function at high altitude. However, difficulties arise when separating the influence of hypoxia and hypocapnia on retinal function. Previous studies have shown that retinal function tends to increase during induced hypocapnia (10, 30, 37). But hypocapnia was accompanied by hyperoxia in these studies due to the study design. Studies examining the special condition of hypocapnia at high altitude have shown a vasoconstrictive effect on the inner retinal circulation and therefore a reduced oxygen supply.
to retinal cells at high altitude (41). Beside the effect of hypoxia, hypocapnia therefore may further intensify the functional impairment of retinal cells. However, hypocapnia is triggered by hypoxia at high altitude, and therefore hypoxia is believed to be the responsible mechanism.

In our study, 7 of 13 subjects were classified as having AMS (AMS-C of ≥0.7 and LL of ≥5). Correlations of AMS-C with ERG parameters of retinal function revealed only one moderate correlation (light-adapted b-wave implicit time of 10 cd·s/m²). Strong and moderate correlations were found for SpO₂, light-adapted a-wave amplitude (10 cd·s/m²), and amplitudes of the PhNR (Fig. 5). Levels of significance were also reached for HR and light-adapted a-wave implicit time (1 cd·s/m²). It has to be pointed out, however, that significant changes in light-adapted ERG potentials were not observed at high altitude. Nevertheless, altered color vision, as a psychophysical parameter of cone function, has been detected at high altitude in previous studies (23, 51, 52, 59). Strong correlations were found for HR with dark-adapted rod b-wave amplitude at 0.01 cd·s/m² and for Vmax of the scotopic sensitivity function and the standard flash a-wave amplitude at 3 cd·s/m² (Fig. 5). All three parameters showed higher ERG amplitudes with higher HR. This may be explained by improved tissue oxygenation via increased cardiac output per time in these subjects. It has to be noted that these subjects also suffered from lower O₂ saturation, and thus increased HR and therefore increased blood supply to the retina would have outweighed the decreased O₂ saturation. Respective correlations found for SpO₂ showed higher amplitudes with lower SpO₂ and may further support this assumption.

Considering all calculated correlations (in total 165), the appearance of eight significant correlations, even if they are plausible, may represent a fortuitous result. Since only 1 of 55 possible correlations with AMS-C has proven significant (light-adapted b-wave implicit time at 10 cd·s/m²), a clear relationship of this score of AMS with retinal function is not supported. Consequently, we have found no predictive capability of retinal function for appearance or severity of AMS. Since high-altitude retinopathy has been shown to be associated with HACE (1) and since the eye is a visible part of the CNS, it might well be postulated that retinal function reflects CNS function in general. However, in our setting, we found no correlation of retinal or CNS function with severity of AMS. This would, in line with the hypothesis of the retina being a part of the CNS, reject a correlation of CNS function and AMS.

In conclusion, our findings indicate that retinal function is moderately and selectively impaired during acute exposure to high altitude. The setting of the study at an altitude of 4,559 m presents an environment that is frequented by millions of trekkers and mountaineers worldwide each year. Although visual function measured by visual acuity remained unaffected (14), alterations of electrophysiological responses were found for rod-cone interaction, in signals of inner and outer retinal functioning, and in retinal ganglion cell function. These findings indicate an impairment of phototransduction and visual processing, especially under conditions with rod-cone interaction. Our results are in line with clinical studies of hypoxia-related retinal diseases and present novel evidence for altered retinal function at high altitude. Correlations in our study showed that low O₂ Saturation was compensated by higher HR and was associated with higher ERG potentials. But significant correlations were few and might be negligible in regard to all nonsignificant correlations. Notably, these missing correlations do not support CNS dysfunction as a pathophysiological mechanism of AMS.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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