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ORIGINAL ARTICLE

THE EFFECT OF NORMOBARIC HYPOXIA ON RETINAL SENSITIVITY: A PERIMETRIC STUDY UNDER SIMULATED ALTITUDE OF 4500 M ABOVE SEA LEVEL

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Introduction: Hypoxia is an important factor affecting the function of the nervous system, including the visual pathway. The aim of this study was to evaluate changes in retinal sensitivity to light stimuli under normobaric hypoxia corresponding to an altitude of 4500 m above sea level.

Method: The study involved 26 healthy men (mean age: 20.96 years). Participants breathed a gas mixture containing 9.6% O_2 for 30 minutes (equivalent to staying at an altitude of 4500 m above sea level). Retinal sensitivity was assessed using computerized perimetry with five strategies covering the visual field from the center to 90 degrees, prior to hypoxia exposure, and at the 10th and 25th minute of hypoxia exposure. During the test, peripheral blood oxygen saturation (SpO_2) and heart rate were monitored.

Results: After 25 minutes of exposure to normobaric hypoxia (mean SpO_2: 81.4%), all tests covering the central visual field (0-25 degrees) showed a statistically significant decrease in retinal sensitivity, particularly in the Blue-on-Yellow test, with an average decline of −1.91 dB. The most pronounced changes were observed in the inferotemporal and inferonasal quadrants (up to −2.23 dB). In the 30-60 degree range no significant changes were observed.

Conclusions: Normobaric hypoxia leads to decreased retinal sensitivity, particularly in the central visual field and in the short-wavelength sensitive cone pathway. These results may have operational significance in military aviation, where hypoxia coexists with psychophysical workload, although they require cautious interpretation.

Keywords: normobaric hypoxia, retinal sensitivity, visual field, aviation physiology

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INTRODUCTION

The phenomenon of hypoxia and its impact on the human body remains an important issue in many fields of medicine, such as aviation medicine, sports medicine, diving medicine, high-altitude medicine, and occupational medicine [3,13]. In aviation medicine, hypoxia poses a particular threat in situations involving oxygen system failures, flights at high altitudes in non-pressurized or open cabins (e.g., balloons), and during cabin depressurization [3,6]. In the past, it was the cause of numerous aviation incidents and accidents, especially at a time when knowledge of the effects of hypoxia on human physiological functions was limited [3]. At present, studies on the body's response to hypoxia constitute a standard element of qualification and training of military flying personnel and are routinely conducted under simulated conditions in low-pressure chambers [13,19,24].

Previous research on the impact of hypoxia on retinal function has focused mainly on hypobaric hypoxia [15,42], typical of high-altitude environments or non-pressurized aircraft cabins. It has been demonstrated that under such conditions significant alterations occur in retinal function, both in the central and peripheral regions, with peripheral retinal sensitivity decreasing more than macular sensitivity [4,15,25,28,46]. This effect is attributed, among other things, to the greater susceptibility of rods located in the peripheral parts of the retina to hypoxia, in contrast to the cones that dominate in the macula, which exhibit higher metabolic resistance [7].

At the same time, results from studies performed under conditions of moderate hypoxia (3000-4000 m above sea level) remain inconclusive. Fulk et al. [12] did not find significant changes in retinal sensitivity in computerized perimetry at 3000 m, whereas Osypov [31] demonstrated a narrowing of the visual field in subjects exposed at 3700 m. These data suggest the existence of a threshold level of hypoxia, beyond which measurable disturbances in visual function occur. Furthermore, most earlier studies investigated hypobaric models of hypoxia rather than normobaric hypoxia, which is increasingly being applied in aviation training and simulation research [21-23,38].

In studies of retinal sensitivity, assessment may be performed with static methods (determining threshold sensitivity at individual retinal points) or dynamic methods (analyzing isopters of the visual field) [39,47]. Static methods, particularly when using automated testing strategies, enable quantitative assessment of threshold sensitivity and currently represent the standard in retinal function diagnostics. Thanks to the development of advanced testing strategies such as SITA Standard, SITA Fast, and SITA Faster, it is possible to significantly shorten examination time while maintaining high precision and reproducibility [39]. These strategies optimize the sequence and location of stimuli based on patient responses, making the examination more efficient and less burdensome. The results obtained are automatically compared with age-adjusted normative values derived from large population databases, allowing identification of even subtle deviations from the norm and enabling detection of early retinal dysfunctions that may remain undetectable in structural studies.

Despite the existence of numerous studies employing electroretinography (ERG) or visual acuity testing, there is a lack of data on the influence of normobaric hypoxia on retinal sensitivity in different regions of the visual field, as assessed by computerized perimetry. It remains unclear whether normobaric hypoxia equivalent to an altitude of 4500 m above sea level, comparable to that used in aviation training, induces significant changes in retinal sensitivity, and if so, whether these changes are spatially differentiated (central vs. peripheral).

Therefore, the aim of the present study was to evaluate changes in retinal sensitivity to light stimuli in different regions of the visual field under normobaric hypoxia equivalent to an altitude of 4500 m above sea level. For this purpose, computerized perimetry was used, a standard diagnostic tool in ophthalmologic widely applied in the assessment of glaucoma, optic neuropathies, and other neurological disorders [47].

MATERIAL AND METHODS

Subjects

The study included 26 men aged 19–23 years (mean age: 20.96 ± 1.12 years), recruited from candidates applying for admission to a military university. Exclusion criteria comprised the presence of at least one of the following factors:

- chronic cardiovascular, respiratory, or neurological disease (e.g., heart defects, arrhythmias, uncontrolled hypertension, asthma, history of syncope),
- acute infection (e.g., fever, respiratory tract infection) or conjunctivitis on the day or in the week of the study,
- uncontrolled metabolic or endocrine disorders (e.g., hyperthyroidism),

Table 1. Characteristics of the perimetric programs used.

Program name	Visual field range	Number of test points	Stimuli	Strategy	Stimulus size (Goldmann)	Background [ASP]	Mean test time [s]
Macula White-on--White (W/W)	5° (central)	16	White on a white background	Threshold	Size III (4 mm², 0.43°)	31.5	211
Macula Blue-on-Yellow (B/Y)	5° (central)	16	Blue on a yellow background	Full Threshold	Size V (64 mm², 1.72°)	31.5	225
FASTPAC	5-25° (paracentral field)	52	White on a white background	FASTPAC	Size III	31.5	347
Peripheral 60-4	30-60° (peripheral field)	60	White on a white background	SITA-Standard	Size III	31.5	365
Author's original (temporal field)	60-90° (temporal peripheral)	14	White on a white background	Full Threshold	Size III (4 mm², 0.43°)	31.5	178

ASP – apostilb (1 asp = 1 cd/m² / π)

- prolonged exposure to hypoxic conditions within the previous 2 weeks (e.g., stay above 1500-2000 m above sea level),
- use of medications affecting cardiovascular, respiratory, or central nervous system function (e.g., β-blockers, sympathomimetics, benzodiazepines),
- use of ophthalmic medications that may influence intraocular pressure or pupillary response (e.g., sympathomimetics, prostaglandins),
- intake of supplements enhancing performance or hypoxia tolerance (e.g., nitrates, caffeine in ergogenic doses),
- ophthalmic surgery within the previous 6-12 months (e.g., laser vision correction), presence of corneal scars, or history of ocular trauma,
- smoking tobacco or using e-cigarettes within the previous week,
- failure to comply with pre-examination requirements (intense physical exercise, alcohol consumption, or sleep deprivation within 24 hours).

Ophthalmological inclusion criteria were as follows:

- full visual acuity for distance and near vision (at least 1.0 Snellen),
- absence of refractive errors (±0.5 D),
- normal color vision (Ishihara test),
- normal findings on preliminary ophthalmic examination: evaluation of the anterior segment of the eye, intraocular pressure (contact tonometry), and fundus (indirect ophthalmoscopy).

All participants were informed about the purpose and course of the study, and each provided written informed consent to participate in the experiment. The study was approved by the Ethics Committee for Scientific Research at the Military Institute of Aviation Medicine in Warsaw.

Apparatus

To quantitatively assess retinal function in different regions of the visual field, a Humphrey Field Analyzer 750i (Carl Zeiss Meditec AG, USA) computerized perimeter was used. Although computerized perimetry is a precise method for visual field assessment, it remains a subjective test and is sensitive to factors such as fatigue, motivation, learning effect, and the participant's level of attention [11,14,26]. To increase the reliability and reproducibility of measurements, in the present study the visual field was divided into several distinct regions (central 0-5°, paracentral 5-25°, peripheral 30-60°, and far peripheral 60-90°). This approach reduced the duration of a single test and allowed two complete measurements to be performed during the 30-minute exposure to normobaric hypoxia. Analysis of test duration revealed no significant differences between measurements, which suggests a stable level of participant concentration and reliability of the results obtained.

Five test programs differing in scope and strategy were used in the study, their characteristics being presented in Table 1. The perimetric strategies applied, including FASTPAC and SITA-Standard, despite their shorter testing time, are considered sufficiently sensitive and comparable to full threshold strategies in the assessment of mean retinal sensitivity [39].

To induce hypoxia under constant atmospheric pressure conditions (normobaric hypoxia), a gas mixture containing 9.6 ± 0.2% oxygen and 90.4% nitrogen was used. The proportions corresponded to exposure at a simulated altitude of 4500 m above sea level. This method allows for controlled and safe experimentation, enabling the exposure to be easily terminated in the event of intolerance symptoms, which is particularly important in studies involving young, inexperienced volunteers [23,38].

The nitrogen-oxygen mixture was administered via a KM-32 military oxygen mask at a slight overpressure (7.5 mmHg above atmospheric pressure). The duration of normobaric hypoxia exposure was 30 minutes; in cases of prolonged perimetric testing, this time could be extended by a maximum of 3 minutes.

To assess the effectiveness of the applied procedure for inducing normobaric hypoxia, and to determine the degree of simulated high-altitude hypoxia achieved, two basic physiological parameters were monitored: peripheral blood oxygen saturation (SpO_2) and heart rate (HR). These parameters were measured throughout the experiment using transcutaneous pulse oximetry. The data obtained served as the basis for verifying whether the gas mixture effectively induced an effect comparable to high-altitude exposure, and whether the degree of hypoxia during perimetric testing (Tab. 1) was comparable.

Procedure

The study was conducted in a laboratory located in Warsaw (100 m above sea level). All measurements were performed between 14:00 and 18:00, with a minimum interval of two hours after the last meal. The examination room was darkened; the mean illumination behind the perimeter bowl (area not illuminated by the perimeter light source) was approximately 20 lux. Visual field measurements were conducted only for the dominant eye, determined by the sighting dominance test.

Approximately 60 minutes prior to the start of the experiment involving hypoxia exposure, each participant performed a practice perimetry session using the selected program. This was intended to familiarize participants with the procedure and to minimize learning effects and incorrect responses during the actual measurements.

Participants were randomly assigned to five study groups (15 individuals in each group), with each group performing one of the five perimetric programs described in Table 1. In total, 75 examinations were performed. Due to the group structure and randomization scheme, not all participants were assigned to complete the full set of examinations. This was accounted for in the data analysis by attributing results to measurement groups independently.

The order of perimetric examinations (Tab. 1) was randomized, and each test was performed three times: (1) immediately before breathing the gas mixture, (2) after 10 minutes of exposure to normobaric hypoxia, and (3) after 25 minutes of exposure to normobaric hypoxia.

Perimetric test results were included in the analysis only if the following quality criteria were met: the number of false-positive errors, false-negative errors, and fixation losses did not exceed 15%.

Statistical Analysis

Statistical analysis was conducted using R (version 4.4.2) [36]. Dependent variable – retinal sensitivity (dBs) measured in four visual field regions: superonasal, inferonasal, superotemporal, and inferotemporal, as well as the mean sensitivity ("overall") were analyzed across three time points (independent variable): baseline (before exposure), 10 minutes, and 25 minutes post-exposure).

Data were initially assessed for normality using the Shapiro–Wilk test. Since several distributions significantly deviated from normality ($p < 0.05$), non-parametric methods were applied. For each region, changes over time were evaluated using the Friedman test for repeated measures. When the Friedman test revealed a significant main effect, post-hoc pairwise comparisons were conducted using the Wilcoxon signed-rank test with Bonferroni correction for multiple comparisons. The effect size for each significant result was calculated using the Kendall's W-type measure. A significance threshold of $p < 0.05$ was applied throughout. All visualizations and statistical computations were performed using the ggplot2 [44], ggpubr package version 0.6.1 [17], rstatix package version 0.7.2 [18], and dplyr packages package version 1.1.4 in R [43].

RESULTS

Changes in retinal sensitivity in the central visual field (0–5°)

(B/Y) test. Friedman analysis revealed statistically significant changes in retinal sensitivity during hypoxia exposure in all analyzed quadrants (Fig. 1) superonasal: $\chi^2(2) = 12.20$, $p = 0.002$, $r = 0.408$; inferonasal: $\chi^2(2) = 12.00$, $p = 0.002$, $r = 0.401$; superotemporal: $\chi^2(2) = 11.10$, $p = 0.004$, $r = 0.370$; inferotemporal: $\chi^2(2) = 11.00$, $p = 0.004$, $r = 0.368$ as well as in the pooled analysis of all regions ($\chi^2(2) = 18.90$, $p < 0.001$, $r = 0.631$).

Post hoc analysis demonstrated that in the superonasal quadrant there was a significant decrease in sensitivity after 10 minutes compared with baseline ($p = 0.020$), as well as compared with the 25-minute measurement ($p = 0.013$). A similar effect was observed in the inferonasal quadrant, where differences between baseline and subsequent measurements were also significant ($p = 0.011$ at 10 minutes, $p = 0.015$ at 25 minutes).

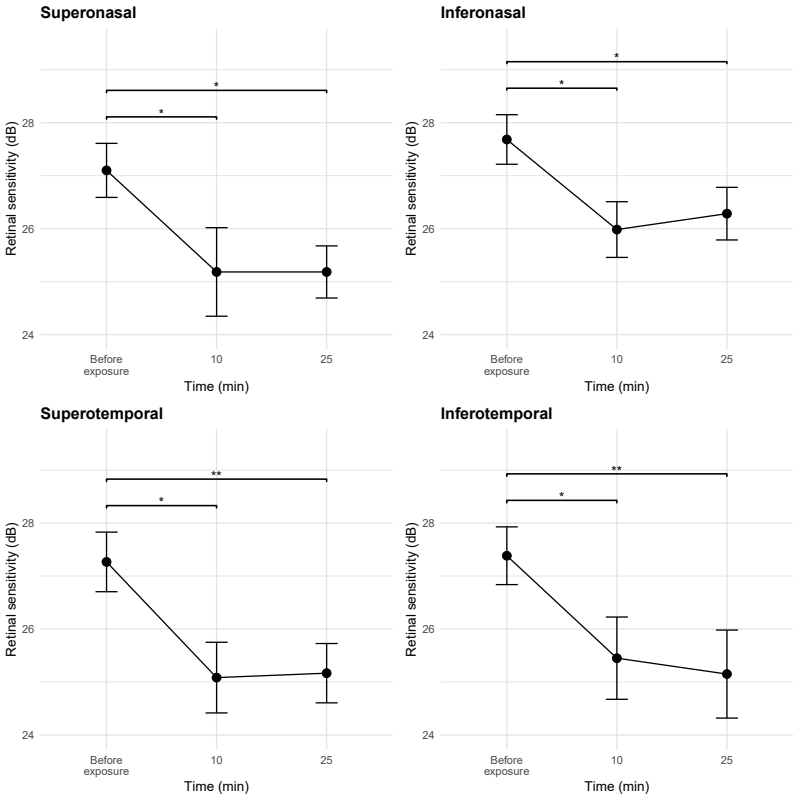

Fig. 1. Changes in retinal sensitivity in the central visual field (0–5°) in the Macula Blue-on-Yellow test. Error bars represent the standard error of the mean; **p < 0.01, *p < 0.05.

In the superotemporal quadrant, sensitivity after 10 minutes was significantly lower than at baseline (p = 0.019), and this difference became more pronounced after 25 minutes (p = 0.005). In the inferotemporal quadrant, sensitivity was also significantly reduced at both 10 minutes (p = 0.018) and 25 minutes (p = 0.006) compared with baseline. In all quadrants, no significant differences were found between the 10- and 25-minute measurements (p > 0.88), suggesting that the decline in sensitivity observed at 10 minutes persisted, with only partial improvement by the 25th minute. For the mean value across all four quadrants, differences compared with baseline were significant both at 10 minutes (p = 0.004) and at 25 minutes (p = 0.002).

Analysis of SpO_2 revealed a significant hypoxia effect (p < 0.001). Post hoc tests showed a significant reduction in SpO_2 at both 10-15 minutes (p = 0.002) and 25-30 minutes (p = 0.002) compared with baseline (before exposure) (Fig. 2). No significant changes in HR were observed at any time point.

Macula White-on-White (W/W) test. Significant differences in retinal sensitivity were found in the superonasal quadrant ($\chi^2(2) = 7.58$, p = 0.022) and the inferonasal quadrant ($\chi^2(2) = 6.42$, p = 0.040). In both cases, the effect size was small (r = 0.253 and r = 0.214, respectively). Post hoc analysis showed that in the superonasal quadrant retinal sensitivity was significantly lower both after 10 minutes of hypoxia (p = 0.028) and after 25 minutes (p = 0.047) compared with baseline (Fig. 3). In the inferonasal quadrant, a significant difference was observed only after 10 minutes compared with baseline (p = 0.047).

Significant changes in SpO_2 were also observed (p < 0.01). Post hoc tests confirmed a significant decrease in SpO_2 both after 10-15 minutes (p = 0.002) and after 25-30 minutes (p = 0.002) compared with baseline (before exposure) (Fig. 4). No significant changes in HR were observed across time points.

Changes in Retinal Sensitivity in the Paracentral Visual Field (5-25°)

Results from the FASTPAC test showed a statistically significant decrease in retinal sensitivity in the inferonasal quadrant ($\chi^2(2) = 8.53$, p = 0.014) and the inferotemporal quadrant ($\chi^2(2) = 10.5$, p = 0.005). In the superonasal quadrant ($\chi^2(2) = 5.53$, p = 0.063) and the superotemporal quadrant ($\chi^2(2) = 5.73$, p = 0.057), only a trend toward significance was observed. Effect size analysis indicated that the effects in the superonasal, inferonasal, and superotemporal quadrants were

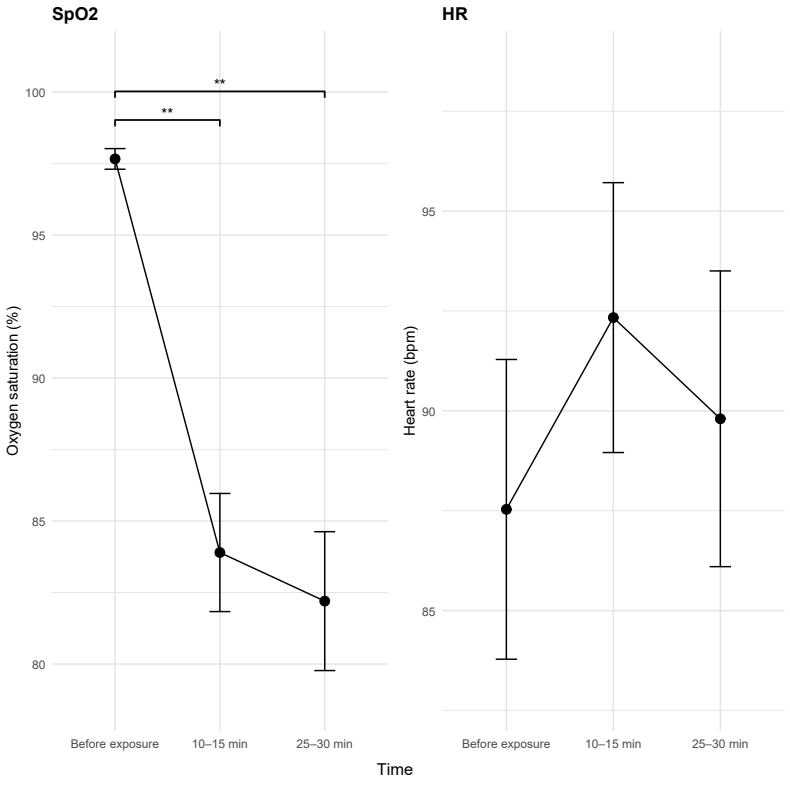

Fig. 2. Changes in blood oxygen saturation (SpO_2) and heart rate (HR) during the Macula Blue-on-Yellow test. Error bars represent the standard error of the mean; **p < 0.01.

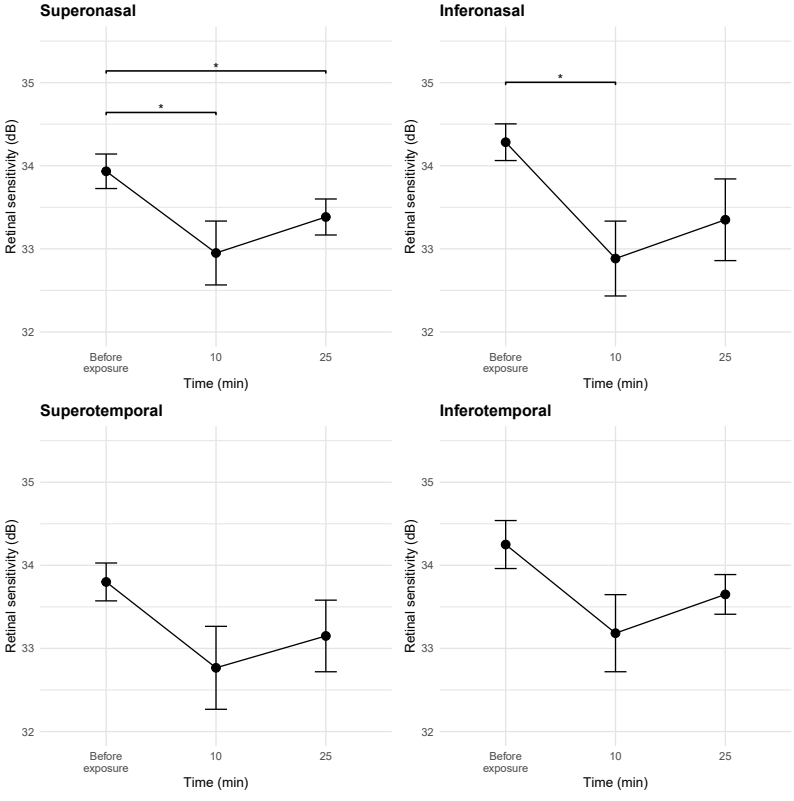

Fig. 3. Changes in retinal sensitivity in the central visual field (0-5°) in the Macula White-on-White test. Error bars represent the standard error of the mean; *p < 0.05.

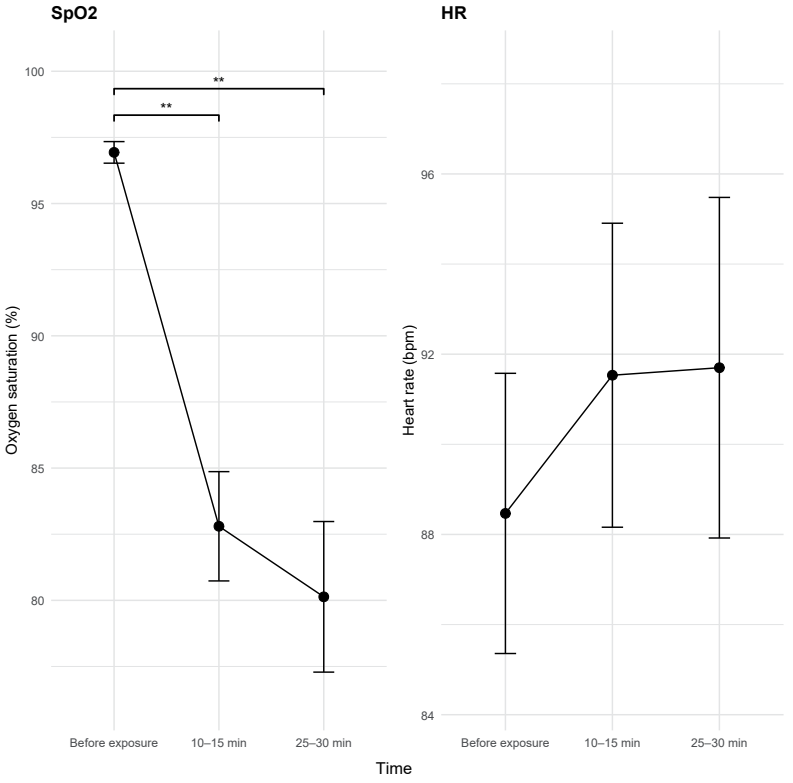

Fig. 4. Changes in blood oxygen saturation (SpO_2) and heart rate (HR) during the Macula White-on-White test. Error bars represent the standard error of the mean; **p < 0.01.

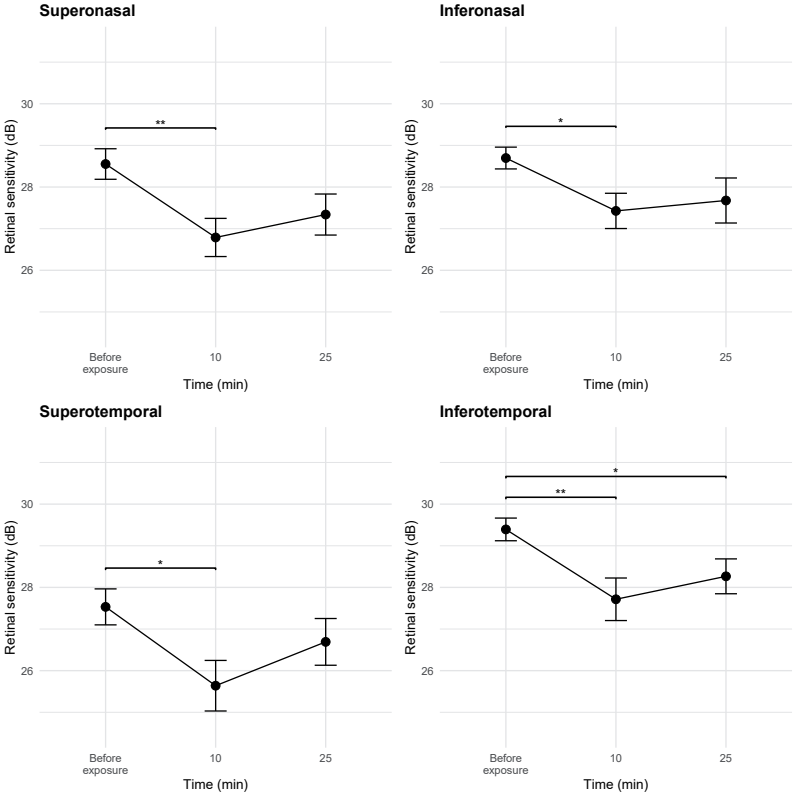

Fig. 5. Changes in retinal sensitivity in the paracentral visual field (5-25°) in the FASTPAC test. Error bars represent the standard error of the mean; **p < 0.01, *p < 0.05.

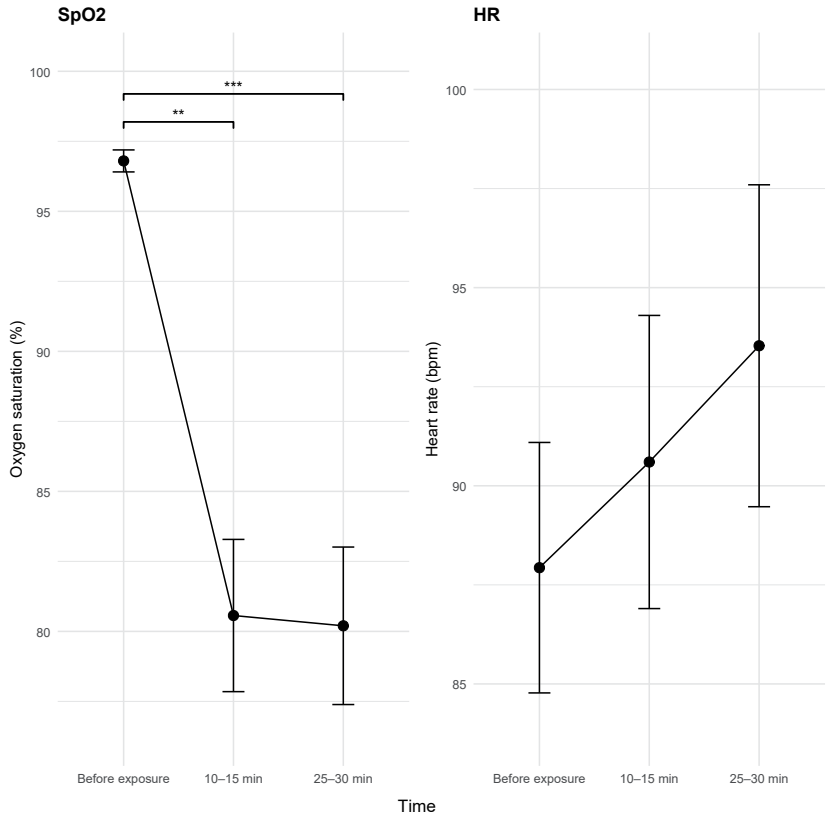

Fig. 6. Changes in blood oxygen saturation (SpO_2) and heart rate (HR) during the FASTPAC test. Error bars represent the standard error of the mean (SE); ** $p < 0.01$, *** $p < 0.005$.

small (r = 0.184, 0.284, and 0.191, respectively), while the effect in the inferotemporal quadrant was moderate (r = 0.351).

Post hoc tests (Fig. 5) revealed that in the superonasal, inferonasal, and superotemporal quadrants, significant decreases in sensitivity occurred only after 10 minutes compared with baseline (p = 0.003, p = 0.013, and p = 0.031, respectively). In the inferotemporal quadrant, retinal sensitivity significantly decreased after 10 minutes (p = 0.006) and remained lower after 25 minutes (p = 0.044).

Analysis of SpO_2 changes during breathing with the gas mixture in the FASTPAC test revealed significant differences ($\chi^2(2) = 23.4$, $p < 0.001$). In the case of HR, only a trend toward significance was observed ($\chi^2(2) = 5.93$, $p = 0.0516$). Post-hoc analysis confirmed that SpO_2 values decreased significantly after 10–15 minutes (p = 0.002) and after 25–30 minutes ($p < 0.001$) compared to baseline (before exposure) (Fig. 6). No significant differences were found between 10–15 and 25–30 minutes, suggesting that the lowered saturation level persisted after the initial decline.

Changes in retinal sensitivity in the peripheral visual field (30-90°)

Peripheral 60–4 test. In the peripheral visual field (30-60°), no statistically significant changes in retinal sensitivity were observed across the four analyzed quadrants (Fig. 7). This result indicates stability of retinal sensitivity in the peripheral visual field during the study period.

During breathing with the hypoxic gas mixture, a statistically significant decrease in SpO_2 was observed ($\chi^2(2) = 20.5$, $p < 0.001$). Post-hoc tests showed that blood oxygen saturation was significantly lower after 10–15 minutes (p = 0.005) and after 25-30 minutes (p = 0.005) compared to baseline values (Fig. 8). No significant differences were observed between SpO_2 values at 10-15 and 25-30 minutes, indicating that the decreased saturation level persisted after the initial decline.

It is noteworthy that in none of the analyzed regions (quadrants) in any of the tests (Figs. 2, 4, 6, and 8) were significant differences observed between the 10-minute and 25-minute measurements. This suggests no further improvement or deterioration in sensitivity after the initial decline (from baseline to 10 minutes of exposure to hypoxia).

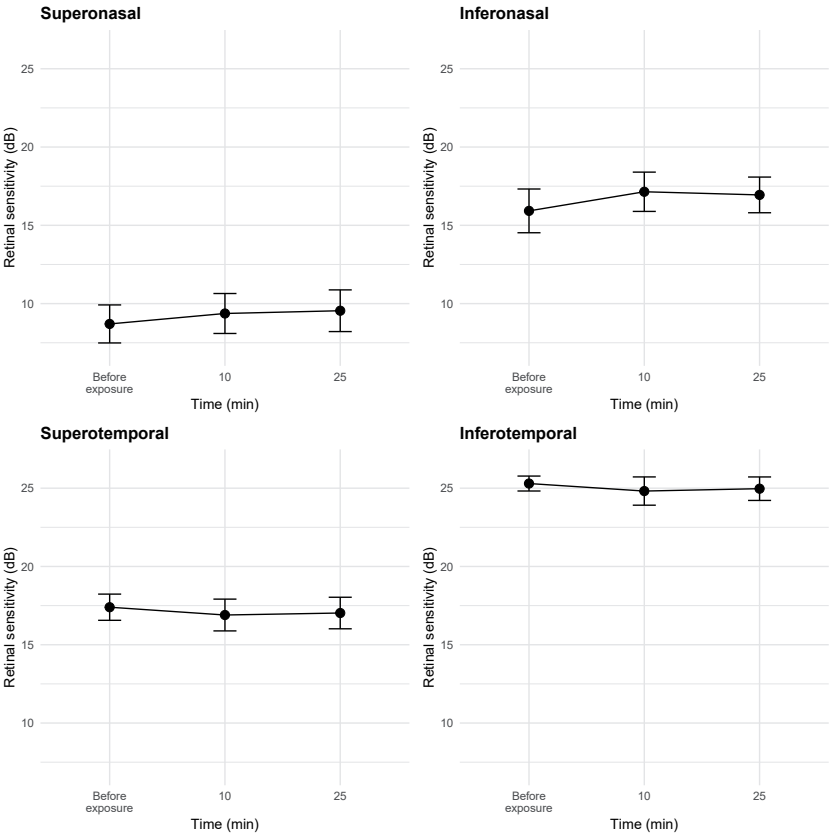

Fig. 7. Changes in retinal sensitivity in the peripheral visual field (30-60°) in the Peripheral 60–4 test.

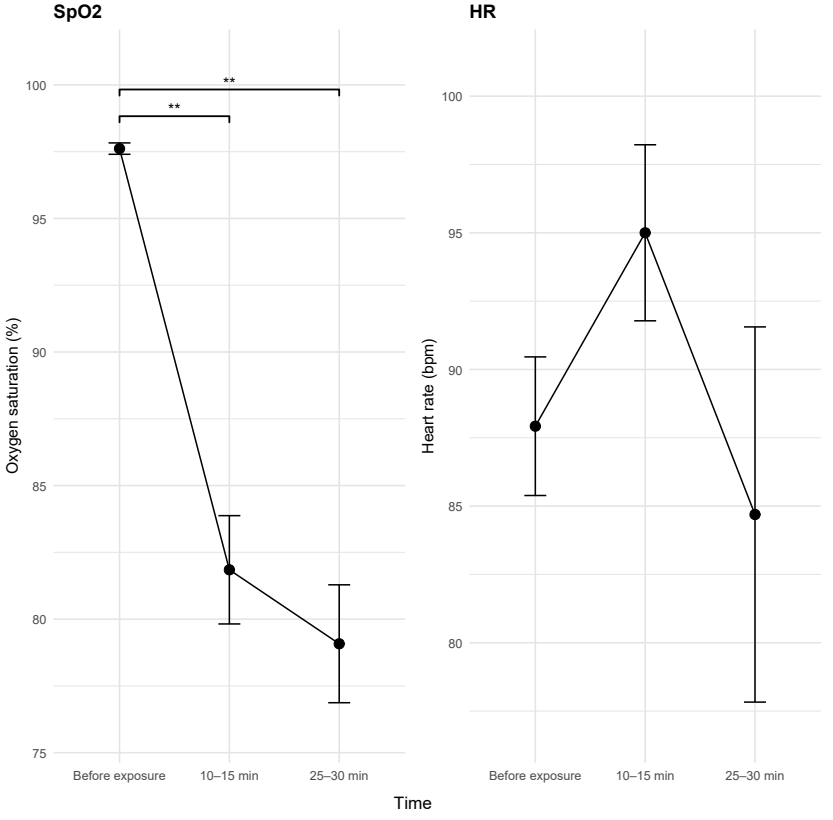

Fig. 8. Changes in blood oxygen saturation (SpO_2) and heart rate (HR) during the Peripheral 60–4 test. Error bars represent the standard error of the mean (SE); ** $p < 0.01$.

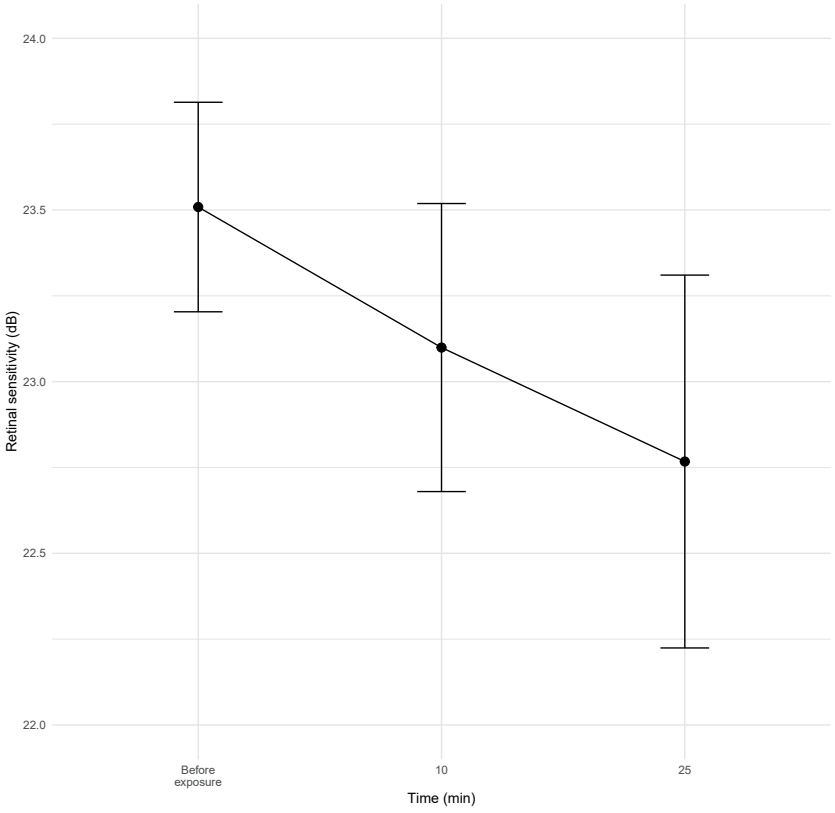

Fig. 9. Changes in retinal sensitivity in the peripheral visual field (60–90°) in the custom test. Error bars represent the standard error of the mean.

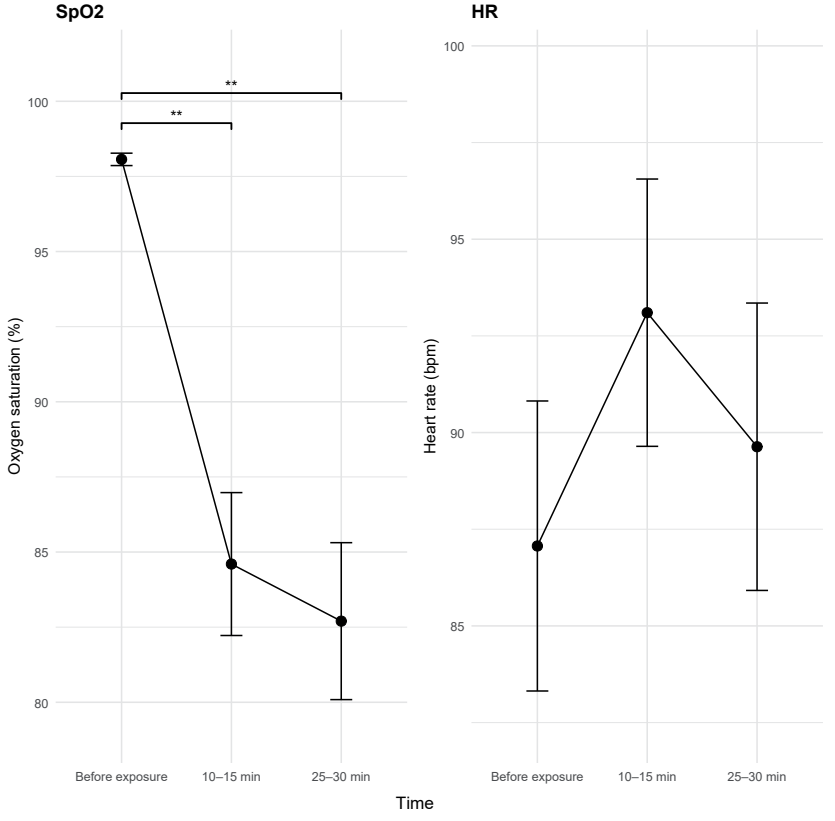

Fig. 10. Changes in blood oxygen saturation (SpO_2) and heart rate (HR) during normobaric hypoxia exposure in the custom test (60-90°). Error bars represent the standard error of the mean; **p < 0.01.

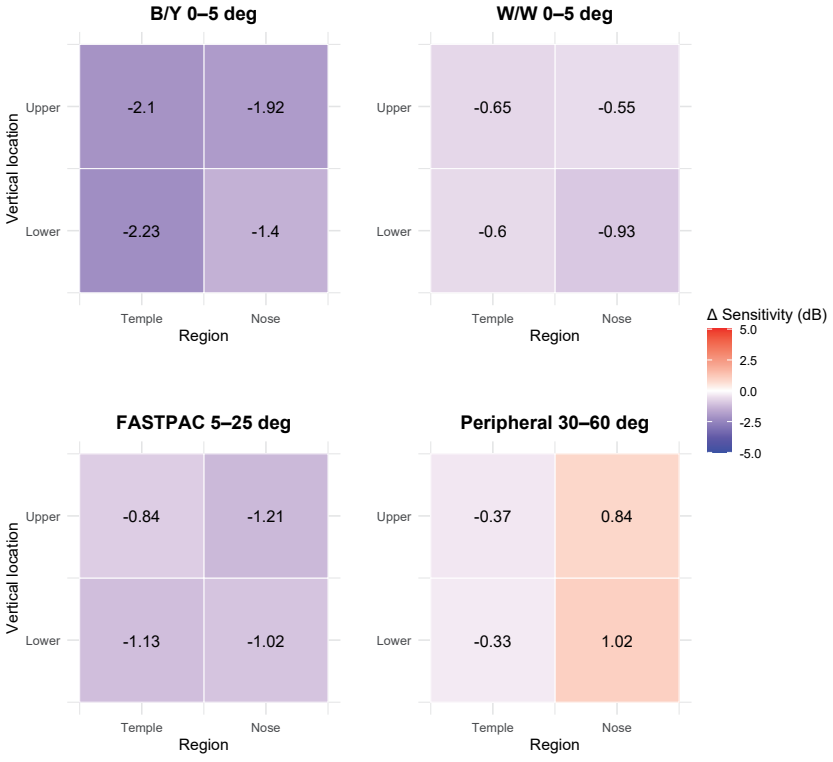

Fig. 11. Heat map showing changes in retinal sensitivity in each quadrant relative to baseline before hypoxia exposure. B/Y – Macula Blue-on-Yellow test; W/W – Macula White-on-White test.

Author's Original Test (60-90°). Although exposure to normobaric hypoxia caused a decrease in retinal sensitivity in the peripheral visual field (60-90°), these changes were not statistically significant (Fig. 9).

During the test, significant changes in SpO_2 were observed ($\chi^2(2) = 25.1$, $p < 0.001$), corresponding to a 13% decrease after 10-15 minutes ($p = 0.002$) and a 16% decrease after 25-30 minutes ($p = 0.002$) compared with baseline (97.6%) before hypoxia exposure (Fig. 10). No significant changes in HR were observed during exposure to simulated altitude hypoxia ($\chi^2(2) = 6.14$, $p = 0.046$).

Changes in retinal sensitivity across visual field regions during normobaric hypoxia, relative to baseline (pre-exposure), are also shown in Figure 11 as a heat map (Δ sensitivity in dB). The greatest reductions in sensitivity were observed in the central retina (0–5°) in the Blue-on-Yellow test, particularly in the inferotemporal quadrant (−2.23 dB) and inferonasal quadrant (−1.40 dB). In the corresponding area in the White-on-White perimetry, changes were much smaller and did not exceed −0.93 dB. In the paracentral region (5–25°), sensitivity decreases were also observed, especially in the inferotemporal quadrant (−1.13 dB) and the superonasal quadrant (−1.21 dB).

In the 30-60° visual field, corresponding to peripheral retina, no significant deterioration was noted. Moreover, in the nasal regions (both supero and infero), a slight increase in sensitivity was observed (+0.84 and +1.02 dB, respectively). The distribution of changes indicates selective sensitivity of certain retinal regions to hypoxia, particularly within the central 5° and along the blue-yellow pathway.

DISCUSSION

During breathing with the hypoxic gas mixture, a statistically significant decrease in SpO_2 ($p < 0.05$) was observed in all tests (Figs. 2, 4, 6, 8), from a mean baseline value of 97.61% before the experiment to 82.82% between 10 and 15 minutes (a 16% decrease) and 81.40% between 25 and 30 minutes (a 17% decrease). These results clearly confirm the effectiveness of the applied procedure in inducing normobaric hypoxia equivalent to an altitude of 4500 m above sea level. The observed SpO_2 decrease during each exposure indicates that a hypoxic state comparable to conditions at approximately 4500 m was achieved [29,40]. It is also important that the SpO_2 levels reached during the 10-15 minute and 20-25 minute intervals of hypoxic exposure

were stable and comparable. This indicates that a plateau in the physiological response to the applied hypoxia was achieved, allowing the results obtained at these two time points to be considered equivalent in terms of oxygen conditions. Therefore, comparing the results of perimetry tests performed after 10 and 25 minutes of exposure is justified and methodologically sound.

During normobaric hypoxia exposure, a typical increase in HR was observed after 10 minutes (Figs. 2, 4, 6, 8), further confirming the effectiveness of the procedure in eliciting a physiological response to hypoxia. An increase in HR is a well-known compensatory mechanism aimed at enhancing blood flow and improving oxygen delivery to tissues under conditions of reduced saturation [27,30]. In the next stage of exposure (20-25 minutes), a slight decrease in HR was observed, which may result from partial adaptation of the autonomic nervous system or reduced activation of the cardiovascular stress response [2]. Such a biphasic cardiovascular response pattern is consistent with previous studies conducted under both normobaric and hypobaric hypoxia conditions [1,27]. It is also noteworthy that high variance was observed in SpO_2 and HR values. It may reflect substantial individual differences in physiological responses to hypoxia, possibly due to variation in compensatory mechanisms among participants.

In the present study, the largest changes in retinal sensitivity under hypoxia were observed in the central 25° of the visual field, with the most pronounced decrease occurring during the first 10 minutes of breathing the hypoxic gas mixture (Fig. 5). This indicates a significant sensitivity of the foveal region and surrounding structures to hypoxia. These results are consistent with observations from PERG studies, contrast sensitivity tests, and color perception assessments [21,23], which suggest transient dysfunction of retinal ganglion cells under acute hypoxia. This points to the potential reversibility of these changes during short-term hypoxia and partial physiological compensation.

Different findings were reported by Benedek et al. [4], who observed a transient increase in contrast sensitivity during exposure to a simulated altitude of 5500 m above sea level. This effect may result from neuroadaptive compensatory mechanisms or short-term stimulation of the retinal system in response to physiological stress. It is worth noting that in their study, visual function returned to baseline within 5 minutes after the end of hypoxia exposure, suggesting that the hypoxia applied there may have been less intense or of shorter duration than in our study.

Particularly interesting are the results obtained using the blue-on-yellow (B/Y) stimulus (Fig. 1), which selectively activates S-cones, a component of the so-called koniocellular pathway. S-cones, which constitute approximately 10% of the cone photoreceptor population, are characterized by wider nerve fibers and larger receptive fields, making them more sensitive to hypoxia [9,37]. In our study, a clear and statistically significant decrease in sensitivity was observed in the central 5° after 10 and 25 minutes of hypoxia. These findings are consistent with the studies by Racette and Sample [37], who showed that changes in B/Y perimetry can appear several years before detectable deficits in standard W/W perimetry in glaucoma. This underscores the high sensitivity of this technique for detecting early dysfunction of retinal ganglion cells.

Retinal sensitivity measured by standard W/W perimetry showed smaller, but still significant reductions (Fig. 3), which may result from the contribution of all three cone types (S, M, L) and partial compensation by the red- and green-cone pathways, which are more tolerant to hypoxia. The mean decreases in sensitivity obtained in our study: −1.12 dB in the central 5° and −1.66 dB in the 5-25° range, are comparable to the results reported by Brandl and Lachenmayr [5], who observed a decrease of approximately −1.25 dB at SpO_2 levels around 82%.

In contrast to the central regions, no statistically significant changes were observed in perimetry across the 30-60° range. This result may be partly related to limitations of the SITA-Standard methodology. However, it is also possible that during short-term hypoxia, the activation of large receptive fields in the peripheral retina allows preservation of responses close to normal. Nevertheless, this contrasts with the findings of Horng et al. [15], who reported significant reductions in retinal sensitivity in peripheral regions (mean 8.3 dB in the 20-30° range) during exposure to hypobaric hypoxia at 7620 m above sea level. Similar conclusions come from the studies by Petrassi et al. [33], who observed a greater reduction in ERG response amplitudes in regions corresponding to the peripheral retina. Connolly et al. [8] reported more pronounced impairment of peripheral vision function (dark adaptation) compared to central visual acuity under simulated hypoxia conditions.

Thus, the discrepancy between our results and those of previous studies may be due to differences in the type of hypoxia applied (normobaric vs. hypobaric), exposure duration, and the methodology used for assessment. Furthermore,

ERG recordings and adaptation tests may be more sensitive to subclinical functional changes than the perimetry tests employed in our experiment.

Despite the detected changes in retinal sensitivity, none of the participants reported subjective visual impairment. The lack of hypoxia effect on visual acuity is also supported by our previous studies [21,23]. It should be noted, however, that the experimental conditions were controlled and do not fully reflect real aviation environments, where multiple additional stressors, such as noise, acceleration forces, and psychological stress may influence overall visual system performance and its functional significance.

Study Limitations

Despite the valuable observations obtained in this experiment, there are several important methodological and physiological limitations that may affect the interpretation of the results. To provide a more complete picture of the physiological impact of hypoxia on retinal function, these limitations must be acknowledged, along with possible approaches for mitigation in future studies.

A potential limitation of our study is the use of the SITA-Standard strategy in perimetry testing. Its insufficient sensitivity in detecting subtle, localized changes in retinal sensitivity may have influenced the results obtained in the peripheral regions (30-60°). Although this strategy is time-efficient, it simplifies analysis at the expense of precision. Future studies should employ more accurate protocols, such as Full Threshold or ZEST adaptive strategies, which allow for more precise mapping of visual sensitivity deficits, particularly when examining the effects of hypoxia.

Another issue is the lack of measurements of rod function. Since hypoxia affects rod function more than cone function, especially under low-light conditions, the absence of assessments of rod activity (e.g., via scotopic ERG or dark adaptation tests) represents a significant limitation. Supplementing studies with full-field ERG and psychophysical dark adaptation tests would enable a more precise evaluation of hypoxia's impact on peripheral vision.

Furthermore, visual system sensitivity under hypoxic conditions is substantially reduced in low-light environments, due to the greater contribution of rods to mesopic and scotopic vision [8]. Performing perimetry and functional tests exclusively under photopic (bright light) conditions may have limited the ability to detect changes in rod function. Future studies should incorporate variable lighting conditions (mesopic and scotopic), particularly since these conditions are more representative of military cockpit environments [32,33,41].

Although no subjective visual impairment was reported, the lack of data on the duration and full recovery of retinal function limits the ability to draw conclusions about the permanence or reversibility of the observed changes. Some studies suggest that certain deficits may persist longer, indicating the need to perform follow-up measurements during the recovery period (e.g., 30 minutes, 1 hour, 6 hours post-exposure) [16,34].

Finally, the normobaric hypoxia model used in this study (hypoxic gas mixture at atmospheric pressure) does not fully replicate altitude conditions, where both the partial pressure of oxygen and total atmospheric pressure are reduced [40]. Research indicates that hypobaric hypoxia produces stronger and more extensive functional changes in the visual system [15]. Therefore, in subsequent studies, the use of hypobaric chambers or field studies at actual altitude is recommended.

It is also worth noting that the effects of hypoxia can be modulated by other factors, such as fatigue, psychological stress, circadian rhythm, or individual tolerance to hypoxia [10,20,35,45]. These interactions were not assessed in the present study, yet they may influence both subjective and objective measures of visual function. Future studies should record and control for additional variables (e.g., fatigue level, cortisol concentration, HR variability indicators) that may modify the physiological response to hypoxia. Moreover, in real flight conditions, additional stressors such as vibration, noise, accelerations, or cognitive load may act synergistically with hypoxia, impairing visual information processing [13]. Therefore, even minor deficits in retinal function under laboratory conditions could translate into significant operational limitations in combat or high-altitude environments.

CONCLUSIONS

Based on the conducted study of changes in retinal sensitivity to light stimuli in different regions of the visual field under normobaric hypoxia equivalent to an altitude of 4500 m above sea level, the following conclusions were formulated:

1. Short-wavelength-sensitive (blue) cones exhibit the highest sensitivity to hypoxia, confirming the effectiveness of the Blue-on-Yellow test as a sensitive method for detecting early functional changes in the retina under hypoxic conditions;

2, Visual function in the macular region was relatively stable, and the observed decrease in sensitivity after 10 minutes of exposure partially improved after 25 minutes, which may indicate the activation of adaptive mechanisms;
3. No significant changes in retinal sensitivity were observed in peripheral regions, which may result from limitations of the perimetry method. Literature reports indicate, however, that more severe hypoxia leads to more pronounced impairments in these regions.
4. The results should be interpreted with caution, especially in the context of operational applications, where hypoxia may occur alongside other stressors, such as fatigue or psychological stress.

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AUTHORS' DECLARATION

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