The effect of hypoxia on visual function
Psychophysical studies

J. Terry Ernest and Alex E. Krill

The effect of the inspiration of a mixture of 10 per cent oxygen and 90 per cent nitrogen on several aspects of dark adaptation was studied in three highly trained observers. Arterial oxygen saturations were monitored during all experiments. The necessity of using highly trained subjects and particularly of monitoring arterial oxygen saturations in such studies was emphasized. Hyperventilation effects, seen initially in all subjects, were eliminated by training. Such effects, as well as other possible changes in oxygen saturation, may be missed unless careful monitoring is done. Hypoxia raised both cone and rod absolute visual thresholds. However, cone thresholds were elevated to a greater degree than rod thresholds at a 5° retinal eccentricity where both were studied. Hypoxia had a greater effect on peripheral rod thresholds (measured at 45° eccentricity) than on central rod thresholds (measured at 5° eccentricity). Only the later portions of rod and cone dark adaptation curves were affected by hypoxia. The first four minutes of either type of curve was unaffected.

Key words: hypoxia, absolute visual thresholds, dark adaptation, rods vs cones, oximetry, trained subjects, hyperventilation.

The retina is markedly susceptible to a decrease in available oxygen (termed hypoxia) because of its relatively high metabolic rate. It has been demonstrated by several workers that hypoxia results in a decrease in white- and colored-light absolute thresholds. Experiments comparing rod and cone functions, however, have been inconclusive. Furthermore, in no previous experiment was an attempt made to measure the actual degree of oxygen deprivation in a subject.

The purpose of this report is to describe the effects of hypoxia on several aspects of dark-adaptation in highly trained, sophisticated observers in whom hemoglobin oxygen saturations were carefully monitored.

Materials

The study was conducted on three subjects aged 24 to 34 years (J. S., E. B., T. E.) during a period of nine months. A modified Goldmann-Weekers adaptometer was used for all dark-adaptation studies. The fixation target was a projected circular red light which subtended one-third degree on the retina. The fixation light was adjustable so that the test area eccentricity could be varied.

Five test target sizes were employed, subtending 12°, 1°, 3°, and 5° of arc on the subject's retina. Nasal field eccentricities at 5° or 45° from foveal fixation on the horizontal
The color of the test light was either white, yellow, red, or blue. The yellow test light was obtained with a Wratten No. 70 filter, and the blue test light with a Wratten No. 47B filter. The Wratten No. 12 filter does not pass the shorter blue wavelengths of the visible spectrum but has a percentage transmission of greater than 50 per cent for wavelengths longer than 520 nm. The Wratten No. 70 filter has a peak transmittance at 430 nm and a half bandwidth of less than 60 nm.

The subjects were made hypoxic by breathing a tank mixture of 90 per cent nitrogen and 10 per cent oxygen. The tank mixture was conducted through reducing valves to a rubber bladder. The subjects inspired the gas mixture from the bladder through a one-way valve into a nasal mask. The expiratory port of the mask was a second one-way valve which opened to the atmosphere.

We monitored arterial blood oxygen saturation with an ear oximeter (Waters Corporation, Rochester, Minn., model XE-60A) operated by an oximeter control circuit (Grass Instruments Company, Quincy, Mass., model OC-2). A permanent record of oxygen saturation was obtained with a direct writing recording instrument (Offner Electronics Inc., Chicago, Ill., Type R Dynograph).

Pupil size was measured either by observing the pupil directly with an infrared light and viewer (Varo, Inc., Varo, Texas, Metascope) or by infrared photography. A Wratten No. 87c filter was placed over the light source of the camera and infrared sensitive film utilized.

**Experiment I: Central retina versus peripheral retina**

**Method.** In this part of the study, the effect of hypoxia on the absolute white light threshold was measured at the two retinal eccentricities using 12°, 1°, 3°, and 5° targets. Each subject was given a minimum of ten three-hour training sessions before measurements were accepted. The three-hour test sessions were separated by a minimum of 48 hours. The sessions were divided randomly into control and hypoxic test periods. At the end of this training period, none of the subjects hyperventilated when they were made hypoxic and their blood pressures remained in the normal range. During the control test period, the subjects were dark adapted 30 minutes. This period was found to be sufficient to produce a stable absolute threshold. The absolute visual thresholds were then measured by starting with a test light intensity which was not visible and increasing its intensity until it was just visible.

The intensity of the test light was then decreased until it was no longer visible. Two such ascending and descending thresholds were obtained, then the subject rested for 1 minute, and the sequence was repeated. Different initial light intensities were used on a random basis. The threshold intensity was mechanically recorded on a logarithmic (log.) scale. The absolute visual threshold for each sequence was measured as the arithmetic mean of the upper and lower log. values.

**Results.** The results of comparing the effect of hypoxia on two different retinal areas are recorded in Table I. It is evident that the mean percentage increase in the absolute visual threshold secondary to hypoxia was greater in the peripheral retina (45° eccentricity) than in the central retina (5° eccentricity) for all four target sizes.

**Experiment II: Area-summation studies.**

**Method.** The effect of hypoxia on the absolute white-light threshold of two target sizes (1° and 5°) at a retinal eccentricity of 45° was measured. The threshold determinations were made

<table>
<thead>
<tr>
<th>Target size</th>
<th>Eccentricity, 5°</th>
<th>Eccentricity, 45°</th>
</tr>
</thead>
<tbody>
<tr>
<td>12°</td>
<td>0.25 ± 0.09</td>
<td>0.77 ± 0.18</td>
</tr>
<tr>
<td>1°</td>
<td>0.36 ± 0.18</td>
<td>0.54 ± 0.14</td>
</tr>
<tr>
<td>3°</td>
<td>0.30 ± 0.07</td>
<td>0.41 ± 0.06</td>
</tr>
<tr>
<td>5°</td>
<td>0.22 ± 0.04</td>
<td>0.42 ± 0.03</td>
</tr>
</tbody>
</table>

Each number is the mean of six sessions and is entered with the standard error.
random mixing of the red and blue targets was by hypoxia to a greater extent than was the blue (Wratten No. 47B filter) target threshold present, and we believe cone function was evaluated.

<table>
<thead>
<tr>
<th>Session</th>
<th>Mean increase in absolute visual threshold with hypoxia (log. micromicrolamberts)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5°</td>
</tr>
<tr>
<td>701</td>
<td>0.53</td>
</tr>
<tr>
<td>702</td>
<td>0.22</td>
</tr>
<tr>
<td>703</td>
<td>0.98</td>
</tr>
<tr>
<td>704</td>
<td>0.52</td>
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<tr>
<td>705</td>
<td>0.41</td>
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<tr>
<td>706</td>
<td>0.53</td>
</tr>
<tr>
<td>707</td>
<td>0.68</td>
</tr>
<tr>
<td>708</td>
<td>0.56</td>
</tr>
<tr>
<td>709</td>
<td>0.70</td>
</tr>
</tbody>
</table>

*Target size: see table; eccentricity: 45°; color: white.

Results. In Table II, the results comparing the two target sizes in the same retinal area are recorded. The difference between the paired means was not significant.

Experiment III: Rod versus cone vision.

Method. The effect of hypoxia on the absolute blue light threshold versus the absolute red light threshold was measured at an eccentricity of 5° with the use of a 5° target. The subjects in our studies all visualized the red color at threshold. Thus, no photochromatic interval was present, and we believe cone function was evaluated.

Each session consisted of a control period in the fully dark-adapted eye during which three blue (Wratten No. 47B filter) target threshold determinations were mixed randomly with three red (Wratten No. 70 filter) target threshold determinations. Each of the six threshold determinations consisted of the average of one ascending and one descending measurement. The same random mixing of the red and blue targets was used during the hypoxia testing period.

Results. It is evident from Table III that the difference between the paired means was significant. The red target threshold was affected by hypoxia to a greater extent than was the blue target threshold.

Experiment IV: Course of dark adaptation.

Method. The effect of hypoxia on the course of dark adaptation was analyzed. To secure the largest range of cone adaptation, the subject’s eye was preadapted for 7 minutes with blue light (Wratten No. 47B filter) having a luminance of 1,000 millilamberts to decrease the response of the rods further. A red target was not used because we wanted to emphasize the rod-cone break. To obtain the rod curves, the subject’s eye was preadapted for five minutes with red light (Wratten No. 70 filter) having a luminance of 1,000 millilamberts to decrease the response of the cones. Testing was then carried out with a 1° blue (Wratten No. 47B filter) target to which the rods were more sensitive than the cones. All the adaptation curves were obtained at an eccentricity of 5° in the nasal field on the horizontal meridian.

The effective brightness of the blue and yellow filters relative to white light was determined by flicker photometry. Our method consisted of placing a sector disk which had a constant rate of 40 cycles per second in the path of the white light and of each colored filter, one at a time. The intensity of each light stimulus was then adjusted with neutral density filters until the critical flicker frequency was reached. The relative brightness of the colored and the white light stimuli were equated. As the filters were balanced on the basis of photopic luminosity, absolute visual thresholds obtained from the dark-adapted eye (scotopic) were relatively lower with blue than with yellow light.

Measurements were obtained by starting with a test light intensity above threshold and decreasing the intensity until it was no longer visible. An ascending threshold was then determined and the threshold value was taken as the mean of the descending and the ascending values. After a one-minute rest period the sequence was repeated starting with the previous ascending threshold value. The control testing was continued at one-minute intervals for 30 minutes. Hypoxia testing was performed in exactly the same fashion each day. The data col-
Fig. 1. The upper two dark adaptation curves represent composites (see text) obtained with a 1° circular yellow target at an eccentricity of 5° in the nasal field on the horizontal meridian. The subject's eye was preadapted with blue light having a luminance of 1,000 millilamberts. The lower two dark adaptation curves are composites recorded with a 1° circular blue target at the same 5° eccentricity. The subject's eye was preadapted with red light having a luminance of 1,000 millilamberts.

lected during the last five minutes of the 20 minute period of breathing the 10 per cent oxygen and 90 per cent nitrogen mixture was used. The 20 minute period of breathing the hypoxic mixture was shifted so as to span the entire dark-adaptation curve. A different five-minute segment of the 30 minute dark-adaptation curve was measured each day until six segments spanning the entire curve had been recorded. The segments were then fitted together by matching their respective control curves. In Fig. 1, the curves represent composites of five-minute control values (solid lines) fitted together plus their respective hypoxia values (dotted lines).

Results. The effect of hypoxia on the course of dark adaptation is shown by the upper curve of each pair in Fig. 1. The “Purkinje-break” in the yellow-light curve occurred at approximately 12 minutes. Hypoxia elevated the cone segment of the dark-adaptation curve, but only after the first four minutes. The time at which

the rod-cone break occurred was not affected by hypoxia. The blue-light rod curve was affected by hypoxia in a fashion similar to the yellow-light curve. During the early four minutes there was no change in either curve, but hypoxia elevated the later curve segments.

In all four experiments there was an increase (25 to 100 per cent) in the amplitude of the ascending and descending threshold excursions during hypoxia (Fig. 2). This was true of the hypoxia tests for all target sizes and colors and for both eccentricities examined.

Discussion

The retina is extremely sensitive to hypoxia because of its relatively high metabolic rate. In a study of hypoxic effects on visual function it is absolutely necessary to measure the level of oxygen deprivation throughout the period of data collection. In our study the subjects' hemoglobin oxygen saturations remained constant after 15 minutes unless they hyperventilated. Hyperventilation is undesirable as it causes an elevation in the subjects' hemoglobin oxygen saturations and may lead to hypocapnea and alkalosis, even though the partial pressure of oxygen in the inspired air remains constant. Visual performance thus may be compromised and eventually a loss of consciousness may occur even with 100 per cent oxygen. The major reason for hyperventilation in our
study was anxiety occurring when the subjects were breathing through the nasal mask, not hypoxia. Training sessions were successfully utilized to overcome anxiety and thereby eliminate hyperventilation during the experiments. In our opinion, experiments of this type must include training periods to overcome hyperventilation and must include measurements of the subjects' arterial oxygen saturations to detect variability due to various factors. For example, data reflecting cumulative effects of hypoxia were avoided by continuous monitoring.

The data recorded in Table I demonstrate that hypoxia has a greater effect on peripheral rod thresholds than on central rod thresholds. Possibly, differences in neural organization explain the differential sensitivity to hypoxia of central and peripheral retinal areas. Peripheral receptive fields are larger than central receptive fields. Should hypoxia have a primary depressant effect on transmission over the polysynaptic connections of the summation receptive field, then the larger peripheral receptive fields would be more affected. Our area-summation data, however, did not support this hypothesis, rather it suggested a direct effect on the receptors of each area.

A second possible explanation for our finding that hypoxia has a greater effect on peripheral (45° eccentricity) rod thresholds than on central (5° eccentricity) rod thresholds is that hypoxia may cause a greater ischemia of the peripheral retina than of the central retina. The blood in the central retinal artery, supplying oxygen to the inner retinal layers, presumably has a lower oxygen concentration the further from its origin at the disk one goes. Furthermore, the inner retinal volume, which is supplied by the central retinal artery, increases with increasing distance from the optic disk. If this explanation is correct then the site of action of hypoxia would be the inner retinal layers rather than the receptors as the choriocapillaris, nourishing the outer retinal layers, is augmented in the periphery by anterior ciliary artery anastomoses.

Red-light absolute thresholds thought to relate mostly to cone function at 5° retinal eccentricity, were affected more by hypoxia than blue-light absolute thresholds, thought to relate mostly to rod function in this area. Why cones should be affected more than rods by hypoxia in this retinal area is not clear.

Sheard reported that hypoxia had a greater effect on peripheral rods tested at 10° and 15° eccentricities than on cones tested at a 1° retinal eccentricity. Our data, on the other hand, showed that cone function at 5° retinal eccentricity tested with a 5° red target was not affected more by hypoxia than rod function measured at 45° eccentricity tested with a 5° white target (compare data from Table I with that from Table III). The difference in results may be due to the different sizes of targets used and the different eccentricities tested.

The first four minutes of our rod and cone dark-adaptation curves were not affected by hypoxia, even though later segments were elevated. Other investigators also showed that the early portion of dark adaptation is unaffected by hypoxia. McFarland and Evans reported that the early cone segment of the dark-adaptation curve was little affected by hypoxia. The foveal cone curve shown in another publication (Fig. 3, A of reference 19) was unaffected in its first few minutes by hypoxia. The early minutes of the rod dark adaptation curve reported by Bunge in his Fig. 6 is similarly unaffected by hypoxia. A possible explanation for these findings is that early and latter stages of dark adaptation depend on different mechanisms. Recent electrophysiographic studies both in the rat and cat implicate the existence of an early neural stage of dark adaptation in contrast to the later photochemical stages. Possibly the early neural changes of dark adaptation are more resistant to hypoxia.

It is of interest to consider the relation-
ship between hypoxia produced by dilution of oxygen and that produced by rarification of the atmosphere. Both situations result in a decrease in the partial pressure of oxygen in the inspired air. At an altitude of 18,000 feet above sea level the barometric pressure is decreased by approximately one half and the partial pressure of oxygen \( (pO_2) \) in the air has also been reduced by one half. Actually, because the partial pressure of water vapor within the alveoli is constant, the alveolar \( pO_2 \) at 18,000 feet is less than one half what it is at sea level. A question that has not been resolved is whether there is an independent effect of barometric pressure on threshold. Therefore, visual data obtained under the two different conditions should not be compared.

The increase in amplitude of the ascending and descending threshold excursions (pursuance) was characteristic of all the hypoxia measurements. McFarland,\textsuperscript{23} employing a test requiring discrimination and choice, also demonstrated an impairment in function with hypoxia. Thus, we believe that the difficulties the subjects manifested in their pursuance tasks were due to hypoxic effects on the central nervous system rather than on retinal changes.

REFERENCES