Dark Adaptation during Systemic Hypoxia Induced by Chronic Respiratory Insufficiency

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PURPOSE. To investigate dark adaptation during hypoxia in patients with chronic respiratory failure.

METHODS. At three visits, dark adaptation was recorded by computerized dark adaptometry in 13 patients with chronic respiratory insufficiency treated by long-term oxygen therapy. At visits 1 and 3, the patients were administered their usual oxygen supplement. At visit 2, no oxygen was given. At each visit, an analysis of arterial blood gases measured pH, partial pressure of O2 (PaO2), partial pressure of CO2 (PaCO2), base excess (BE), standard bicarbonate (HCO3), and arterial oxygen saturation. Pulse oximetry (POX) was also recorded.

RESULTS. Significant differences were recorded between visits 1 and 2 and between visits 2 and 3 for PaO2, arterial oxygen saturation, and POX; no differences were found for pH, PaCO2, BE, or HCO3. No differences were seen between visits 1 and 3 for any of the laboratory parameters. All patients had normal and unchanged dark adaptation at the three visits.

CONCLUSIONS. Hypoxia in chronic respiratory insufficiency was associated with normal dark adaptation, in contrast to hypoxia in healthy persons at high altitudes, which is known to produce impaired dark adaptation. The result may partly reflect the influence of PaCO2 on the lumen of choroidal and retinal vessels. At high altitudes, with hypocapnic vasoconstriction the oxygen supply to the retina is further compromised, resulting in reduced dark adaptation. The authors hypothesize that respiratory insufficiency with hypercapnia or normocapnia will have larger choroidal and retinal vessel lumens, added to by further dilation of retinal vessels during hypoxia. The tentative net effect would be preserved dark adaptation. (Invest Ophthalmol Vis Sci. 2009;50:1317–13112) DOI:10.1167/iovs.08-2104

Dark vision is a demanding process for retinal photoreceptors that requires high metabolism. In darkness, photoreceptors are continuously depolarized, with high electrical activity and high transmitter exchange at the synapses. The metabolic demands on the retina thus increase significantly in darkness, and animal studies in cats, rats, and monkeys have shown that retinal oxygen consumption in light is between 36% and 68% that in darkness.1 Dark adaptation is a process consisting of the biochemical regeneration of bleached to unbleached rhodopsin, with synchronously increasing sensitivity to light during the course of approximately 30 minutes. This recovery of sensitivity in darkness can be recorded by measuring the brightness of light necessary for achieving the threshold of perception. The brightness of the flashing test light at threshold can be recorded as a function of time in the dark by dark adaptometry. Dark adaptation is a highly sensitive neural function affected by reduced arterial partial pressure of oxygen (PaO2) and by compromised circulation to the eyes and brain. The process has been shown to be defective in healthy subjects at altitudes as low as 1200 m during aviation11–12 and mountain climbing,7 when the influence is reversed by the inhalation of oxygen. Dark adaptation is also reduced in carotid artery disease,9 which is reversible after carotid endartertectomy10 and in polycythemia with improvement after venesection.11

The retina is supplied by two separate vascular systems with different properties. The inner retina is vascularized by the central retinal artery and its branches, and the outer retina is avascular and dependent on the choroidal circulation. Photoreceptors in the outer retina are supplied with oxygen mainly by diffusion from the choroidal circulation.1 Blood flow to the vascularized inner retina is known to be autoregulated by the arterial partial pressures of carbon dioxide (PaCO2) and oxygen (PaO2). Increased PaCO2 induces vasodilation with an increase of the blood flow11–14 whereas reduced PaCO2 has the opposite effect.14 Similarly, an increase in PaO2 leads to vasoconstriction and diminished blood flow,11,15–17 whereas a decrease in PaO2 results in vasodilation and increased blood flow.18 The choroidal circulation differs in that it has a very high blood flow, a low O2 extraction, and a high venous PO2.19 Regulation of the choroidal blood flow is not fully understood but may not be autoregulated by increased oxygen levels, whereas increasing PaO2 (by inhalation of carbogen) increases blood flow as it does in the retina.13,20,21

Healthy subjects with hypoxia at high altitudes have hypocapnia from hyperventilation. This is in contrast to patients with hypoxia and chronic respiratory failure who have normocapnia or, in many cases, hypercapnia. It can be expected that the hypocapnia of healthy subjects with hypoxia at high altitudes has a vasoconstrictive effect, at least in the inner retinal circulation.22 This would further diminish the oxygen supply to the retina and would explain the reduced dark adaptation. On the other hand, hypoxia in many patients with chronic respiratory insufficiency could theoretically be expected to have a vasodilatory effect on the retinal vessels because of hypercapnia. The effect of hypoxic hypercapnia or respiratory insufficiency on dark adaptation is unknown.

The aim of the present study was to determine whether dark adaptation is reduced in chronic respiratory insufficiency. For this purpose, we used dark adaptometry as a functional test and sensitive marker of neural function to study a group of patients with chronic respiratory failure receiving long-term oxygen therapy (LTOT) with and without oxygen treatment. To our knowledge, dark adaptation in patients with chronic respiratory insufficiency has not been systematically examined.

METHODS

Subjects

Thirteen patients with chronic respiratory failure (six men, seven women; age range, 57–84 years; mean age, 68.7 years) were examined.

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All patients were nonsmokers or had quit smoking before the prescription of LTOT. Patients with neurologic disease or malignancy were excluded. To be included in the study, patients had to have a corrected visual acuity of at least 0.5 and an absence of ophthalmological disease such as amblyopia, glaucoma, and vascular occlusion.

The study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Regional Ethical Review Board at Lund University, Sweden. Written informed consent was obtained from each patient.

**Examination Schedule**

All patients were tested according to the same schedule and were examined on three separate days. The maximum duration between visits 1 and 3 was 27 days (mean, 16.7 days). All visits took place between 9:00 am and 3:00 pm. At visits 1 and 3, all patients received their normal oxygen dosage from an oxygenator (Oxygen Concentrator Zefir 5; Air Liquide Sante International, Paris Cedex, France). At visit 2, the patients had been without their oxygen therapy for at least 30 minutes and as long as 8 hours (mean, 4 hours). Visit 1 started with a general ophthalmologic examination. At each visit, each patient rested for 30 minutes, after which an arterial blood sample was taken and dark adaptometry was performed. Pulse oximetry (POX) was recorded immediately before and after dark adaptometry (Onyx 9500; Nonin Medical, Plymouth, MN).

**Dark Adaptometry**

Dark adaptometry records increases in retinal sensitivity in darkness over time. We used a computerized dark adaptometer (JUTA 1001), which was developed by two of the authors, for the examinations. The method has been previously described in detail.

The subject was placed in front of a white hemispheric bowl. Preadaptation with 5 minutes of exposure to white light was followed by 25 minutes in complete darkness, during which the subject was asked to press a button when a light was seen. A red fixation light was placed 6° above the test light. The random "light" or "no-light" testing sequence was presented. When three correct responses were given, the light intensity was decreased by one step. One incorrect response increased the light intensity by one step. The testing light remained lit until the subject noted detection, or for a maximum of 4.0 seconds. The computer did not allow three no-light events in a row so that subjects had to actively pass to the next test level. The intensity of light was decreased in 0.15 log unit steps until the subject could no longer reliably detect the light stimulus. As a measure of performance, we accepted the lowest step value obtained in which the subject delivered three correct answers consecutively and was not able to progress further down the scale. The lowest step (highest number) represented the lowest test light luminance level the subject could see (Fig. 1).

Two LCD shutters, one in front of each eye, controlled which eye was, or whether both eyes were, exposed to the test light. Each of these combinations was tested for 20 seconds in the sequence: right eye, left eye, both eyes. The sequence was then repeated. All examinations were performed with the pupil in its natural state.

**Laboratory Tests**

Arterial blood drawn from the radial artery was immediately analyzed for oxygen saturation, Pao2, Paco2, pH, base excess (BE), and standard bicarbonate (HCO3). Statistical Analysis

Data are expressed as mean ± SEM. Paired t-tests were used to compare the values for pH, Pao2, Paco2, BE, HCO3, oxygen saturation, and POX between visits 1 and 2, visits 2 and 3, and visits 1 and 3. Furthermore, POX before and after dark adaptometry was compared for each visit using paired t-tests. The lowest levels of dark adaptometry were also compared between visits 1 and 2, visits 2 and 3, and visits 1 and 3 for each eye and binocularly using paired t-tests.

Of the 13 subjects recruited for the study, two did not understand the instructions given for dark adaptometry at the first visit; their results from this visit were not included in the analysis. Therefore, results for 11 subjects were included in the analysis of visit 1, and results for 13 subjects were included in the analysis of visits 2 and 3.

**RESULTS**

All 13 patients had chronic respiratory failure and had been receiving LTOT for at least 4 months and for as long as 12 years. The underlying causes of chronic respiratory failure varied; 10 patients had obstructive pulmonary disorders and 3 had restrictive pulmonary disorders. Forced expiratory volume in 1 second (FEV1) ranged between 15% and 96% of predicted value (mean, 41.9%). Forced vital capacity (FVC) ranged between 30% and 105% of predicted value (mean, 62.6%). FEV1/FVC ranged between 22% and 92% (mean, 52.3%). All patients were treated by domiciliary oxygen for 16 hours or more per day at a flow of 1.0 to 4.5 L/min (mean 2.0, L/min).

Best-corrected visual acuity was 0.6 to 1.0 (mean, 0.82) in the right eyes and 0.6 to 1.0 (mean, 0.78) in the left eyes. Refractions were between −1.75 and +3.25. The degree of astigmatism was between 0 and −3.5. Intraocular pressure was 12 to 20 mm Hg (mean, 16.5 mm Hg) in the right eyes and 12 to 19 mm Hg (mean 16.4 mm Hg) in the left eyes. Pupillary reactions and undilated fundus examination results were normal in all patients. Eight patients had heterophoria (eight when tested at near distance, two at far distance). Three patients had undergone surgery for cataracts and intraocular lens implantation in both eyes. Four patients had minor cataract in either eye.

Laboratory test results are presented in Table 1. There were significant differences between visits 1 and 2 for Paco2 (mean difference, Δ2.15 kPa; P < 0.001), arterial oxygen saturation (mean, Δ6.3%; P < 0.005), and POX (before dark adaptation: mean, Δ4.9%; P < 0.001; after dark adaptation: mean, Δ4.7%; P < 0.01), though no significant differences were found for Pao2, BE, HCO3, or pH. Virtually the same statistical results were obtained when visit 2 was compared with visit 3 for Paco2 (mean, Δ2.08 kPa; P < 0.001), arterial oxygen saturation (mean, Δ5.8%; P < 0.005), and POX (before dark adaptation: mean, Δ6.0%; P < 0.001; after dark adaptation: mean, Δ5.5%; P < 0.001). When comparing visit 1 with visit 3, both of which included oxygen supplementation during testing, no significant differences were found for any of the parameters. There were also no significant differences in POX before or after dark adaptometry for any of the visits.

Results from dark adaptometry are summarized in Table 2. No significant differences were observed between the three visits for the right eye, the left eye, or both eyes. The perceived luminance level was lower when both eyes were used compared with monocular testing of the right or left eye. The three pseudophakic patients showed a tendency to perceive lower luminance levels than the phakic patients, but this finding was not significant.

**DISCUSSION**

The present study investigated whether there are any differences in dark adaptation dependent on oxygen supplementation in patients with chronic respiratory failure treated by LTOT. To our knowledge, this category of patients has not been previously evaluated by dark adaptometry. Our main findings were that dark adaptation was normal for their age and
unchanged in all patients and that oxygen treatment made no
difference, despite a significant difference of at least 5.8% in
arterial blood oxygen saturation. It is well known that there is a normal age-related deterio-
ration of dark vision.27–29 When we originally developed the
computerized dark adaptometer (JUTA 1001), we examined 18

FIGURE 1. Dark adaptometry curves of an 84-year-old woman with respiratory insufficiency for the right eye, left eye, and both eyes obtained simultaneously from the same test session. The example shown is from visit 1, which included an oxygen supplement. The step number on the y-axis represents the perceived test light luminance level. One step corresponds to 0.15 log unit. Increasing step numbers further down the scale indicate that test light luminance levels were lower. Dark adaptation of this patient was normal for her age.
healthy persons (mean age, 34.4 years). In the present study of 13 patients with respiratory insufficiency, the mean age was 68.7 years; the span between the mean age of the two groups is 34.3 years. Robertson and Yudkin examined the age-related deterioration in 758 persons between 14 and 71 and found increases for every 10 years in age; the reduction in dark adaptation ranged from approximately 0.10 log units between the ages of 20 and 30 years to approximately 0.15 log units between the ages of 50 and 60. Based on these numbers, 34.3 years corresponds to 0.792 log units. The difference between the two age groups in dark adaptation (final luminance threshold) was 4.3 steps, corresponding to 0.645 log units. Consequently, we feel it is justified to say that our patients had normal dark vision for their age.

Since the early days of aviation, it has been known that a reduction in atmospheric oxygen leads to impaired retinal function, which can be measured by reduced dark adaptation. At high altitudes, the subject is exposed to low atmospheric oxygen, producing both hypoxia and the necessity to hyperventilate to keep arterial oxygen levels as high as possible. The subject experiences low PaO2 and, because of hyperventilation, low PaCO2. Impaired dark adaptation has been recorded at altitudes as low as 1200 m. If dark adaptation is reduced at low altitudes in healthy persons with a reasonably limited exposure, it was concluded that the cerebral circulation is less sensitive to hypoxia than to hypocapnia. Consequently, our hypothesis is that in a state of choroidal and retinal vasodilation in patients with chronic respiratory insufficiency, regardless of whether oxygen is given; we believe that a basic explanation lies in the obvious difference between the two groups in the arterial levels of carbon dioxide.

Photoreceptors in the outer retina are dependent on the choroidal circulation for their oxygen supply, as has been shown with the use of microelectrodes in animal studies examining oxygen distribution across the retina. In a study on cats, Linsenmeier et al found that, in light, the choroid supplied 100% of the oxygen to the photoreceptors. In darkness, when the photoreceptors need approximately twice as much oxygen, the choroid supplied approximately 91% of the oxygen, and the retinal circulation contributed the rest. Evidence that the outer retina is very sensitive to hypoxia has been shown in cats by electroretinography (ERG), which was altered at a PaO2 at which the blood was nearly saturated. However, in human ERG studies during systemic hypoxia, the a-wave was intact whereas the b-wave was decreased in amplitude, suggesting that the inner retina was more affected. Similar results were presented by Feigl et al in light-adapted retina using multifocal ERG showing the inner retina to be more susceptible to hypoxia. Conversely, Marmor et al studying the hypoxia-hyperoxia effect with electrocoagulography under dark-adapted conditions, found results suggesting that the retinal pigment epithelium and the photoreceptors are sensitive to hypoxia. One possible explanation for these differences might be that the investigations are performed under different conditions of light, in which the dark-adapted retina has a much higher metabolism. In addition, there is evidence that cones are more resistant to hypoxia than rods, which may also influence the results, depending on which area in the retinal fundus is examined.

The retinal circulation autoregulates in response to Pao2 and Paco2 and the choroidal circulation likely autoregulates only in response to Paco2. High altitude with hypoxia and hypocapnia implies reduced oxygenation of choroidal blood without increased flow. Simultaneously, reduced oxygenation of the retinal circulation occurs, along with decreased retinal blood flow caused by the vasoconstriction induced by hypocapnia. Consequently, our hypothesis is that photoreceptors receive an inadequate oxygen supply from the choroid and the retina. With the use of transcranial Doppler, Poulin et al found that subjects with hyperoxia had a 6% decrease in cerebral blood flow during hypocapnia compared with normocapnia. Norcliffe et al reported similar results. It was concluded that the cerebral circulation is less sensitive to hypoxia than to hypocapnia. Whether this can be applied to retinal blood flow regulation is unknown, but it seems probable that it is regulated in the same way as cerebral blood flow. These conditions may explain the fact that reduced dark adaptation has been seen at altitudes as low as 1200 m. If at this altitude, it can be expected that hypoxia is limited but is extensive enough to induce compensatory hyperventilation resulting in reduced Paco2.

Our patients had normal and unchanged dark adaptation at all three visits, despite a significant decrease in arterial oxygen saturation at the second visit. They also had unchanged hypercapnia or normocapnia at all three visits, implying a tentative state of choroidal and retinal vasodilation in patients with hypercapnia and larger vessel lumens in patients with normocapnia than could be expected in those with hypocapnia. At

### Table 1. Arterial Blood and Pulse Oximetry Laboratory Results in 13 Patients with Chronic Respiratory Insufficiency at Three Visits for Dark Adaptometry

<table>
<thead>
<tr>
<th></th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Reference Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen saturation</td>
<td>93.9 ± 0.90</td>
<td>87.6 ± 1.43</td>
<td>93.4 ± 1.10</td>
<td>93%–99%</td>
</tr>
<tr>
<td>Pulse oximetry</td>
<td></td>
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<tr>
<td>Before DA</td>
<td>92.7 ± 0.99</td>
<td>87.8 ± 1.45</td>
<td>93.8 ± 0.75</td>
<td>95%–99%</td>
</tr>
<tr>
<td>After DA</td>
<td>93.3 ± 0.75</td>
<td>88.6 ± 1.63</td>
<td>94.1 ± 0.85</td>
<td>95%–99%</td>
</tr>
<tr>
<td>PaO2</td>
<td>9.30 ± 0.49</td>
<td>7.15 ± 0.31</td>
<td>9.23 ± 0.47</td>
<td>10–13 kPa</td>
</tr>
<tr>
<td>PaCO2</td>
<td>5.52 ± 0.41</td>
<td>5.72 ± 0.34</td>
<td>6.00 ± 0.41</td>
<td>4.7–6.0 kPa</td>
</tr>
<tr>
<td>pH</td>
<td>7.48 ± 0.01</td>
<td>7.44 ± 0.01</td>
<td>7.42 ± 0.01</td>
<td>7.35–7.45</td>
</tr>
<tr>
<td>BE</td>
<td>2.50 ± 0.98</td>
<td>4.25 ± 1.19</td>
<td>5.54 ± 0.84</td>
<td>~3.0–~3.6 mmol/L</td>
</tr>
<tr>
<td>HCO3</td>
<td>26.8 ± 0.90</td>
<td>28.0 ± 1.14</td>
<td>27.5 ± 0.82</td>
<td>21–25 mmol/L</td>
</tr>
</tbody>
</table>

Measurements at each visit are shown as mean ± SEM. At visits 1 and 3, patients received oxygen treatment. At visit 2, no oxygen treatment was given. DA, dark adaptometry.

### Table 2. Dark Adaptation Levels in 13 Patients with Chronic Respiratory Insufficiency at Three Visits

<table>
<thead>
<tr>
<th></th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right eye</td>
<td>19.5 ± 0.86</td>
<td>19.2 ± 1.08</td>
<td>19.2 ± 0.79</td>
</tr>
<tr>
<td>Left eye</td>
<td>18.4 ± 1.31</td>
<td>19.6 ± 0.76</td>
<td>19.5 ± 0.97</td>
</tr>
<tr>
<td>Both eyes</td>
<td>20.9 ± 0.68</td>
<td>20.4 ± 0.85</td>
<td>20.8 ± 0.76</td>
</tr>
</tbody>
</table>

Measurements at each visit are shown as mean ± SEM. At visits 1 and 3, patients received oxygen treatment. At visit 2, no oxygen treatment was given.

Values for visit 1 were excluded for two patients with obvious learning problems.
the second visit, when they were not receiving oxygen therapy, all patients had hypoxia, which obviously would have induced vasodilation in the retinal circulation but probably would not have affected choroidal circulation. The net effect compared with that in healthy persons with hypoxia or hypoxia should be increased choroidal and retinal blood flow. Tentatively, this blood flow would be sufficient to compensate for the reduction in arterial oxygen saturation. Thus, the metabolic needs of the photoreceptors were met, even during dark adaptation, which consequently remained normal.

The retina has a high glycolytic capacity that increases under hypoxic conditions. It is likely that, during darkness, this partly compensates for an oxygen deficit in the photoreceptors. However, given that reduced retinal function is evident during even mild hypoxia through decreased dark adaptation and the effects on the electric signals from the outer retina, glycolysis obviously lacks the capacity to fully compensate for an oxygen deficit. Furthermore, glycolytic metabolism was expected to be the same in healthy persons and in our patients and, therefore, could not explain the difference in dark adaptation.

Our patients had significant decreases in arterial PO2, but how did this compare with previous reports on the effects of high altitudes? Glenfield measured O2 saturation through POX at altitudes between 1200 and 8235 m. At the lowest altitudes, POX ranged from 98% to 99%; at 4000 m, it was approximately 87%. Therefore, all our measurements correspond to conditions of high altitude in terms of O2 saturation, which have been shown to decrease retinal sensitivity.

As discussed, O2 and CO2 affect the lumen diameter of blood vessels and, thus, the blood flow in the retina and the central nervous system. The change in lumen diameter affects blood flow in accordance with Poiseuille’s law, which states that the flow in a vessel is proportional to the fourth power of the vessel lumen radius. This means that even small differences in lumen size will have an impact on flow. Previous studies have shown a significant improvement in dark adaptation after carotid endarterectomy and after venesection in patients with polycythemia. Both interventions primarily affect blood flow, which would be improved in the central nervous system and the eye, affecting both choroidal and retinal circulation. These studies demonstrate that blood flow itself has an effect on retinal function.

In a further clinical context, there is strong evidence that CO2 affects the circulation and function of the retina. Several studies have examined the retinal circulation in subjects inhaling 100% O2 compared to the addition of 2.5% to 8% CO2. The change in PO2 in choroidal and retinal vessels than would be the case with hypoxia. At the same time, hypothetically, hypoxia-induced retinal vasodilatation occurred. Our theory is that these conditions resulted in a higher blood flow in the choroidal and the retinal circulation that was sufficient to counteract the reduced arterial oxygen saturation, and the net effect was unchanged dark adaptation.

## References
