

## Oxygen in the anterior chamber of the human eye \*

Horst Helbig, Jens-Peter Hinz, Ulrich Kellner, and Michael H. Foerster

Universitäts-Augenklinik, Klinikum Steglitz, Freie Universität Berlin, Hindenburgdamm 30, 1000 Berlin 45, Germany

Received: 1 December 1992/Accepted: 4 March 1993

**Abstract.** Oxygen partial pressure ( $pO_2$ ) was measured in the anterior chamber of the human eye during routine cataract surgery using a polarographic oxygen electrode. We found a reproducible spatial distribution of oxygen in the aqueous humor. The  $pO_2$  ( $n=8$ ) was  $44.9 \pm 9.1$  mmHg in the chamber angle,  $35.0 \pm 10.9$  mmHg above the pupillary margin, and  $13.5 \pm 8.0$  mmHg in front of the center of the pupil. Pretreatment of the eye with the alpha-adrenergic agonist phenylephrine (5%) resulted in a marked reduction in  $pO_2$  to  $19.8 \pm 5.8$  mmHg in the chamber angle,  $13.4 \pm 4.7$  mmHg above the pupillary margin, and  $7.4 \pm 3.3$  mmHg in front of the center of the pupil ( $n=8$ ). The  $pO_2$  in the anterior lens was very low ( $2.5 \pm 0.6$  mmHg,  $n=7$ ). We conclude that oxygen is supplied at the anterior iris surface to the aqueous humor. The lens is an extremely low oxygen compartment. Topical phenylephrine causes anterior-segment hypoxia, probably by the constriction of iris vessels.

**Zusammenfassung.** Im Rahmen von Kataraktoperationen wurde mit Hilfe von polarographischen Elektroden der Sauerstoffpartialdruck ( $pO_2$ ) in der Vorderkammer des menschlichen Auges gemessen. Wir fanden reproduzierbare  $pO_2$ -Gradienten im Kammerwasser. Die  $pO_2$ -Werte (in mmHg;  $n=8$ ) betragen  $44,9 \pm 9,1$  im Kammerwinkel,  $35,0 \pm 10,9$  über dem Pupillarsaum und  $13,5 \pm 8,0$  vor der Pupillenmitte. Lokale Gabe von Phenylephrin-Augentropfen (5%) führte zu einer deutlichen Verminderung des  $pO_2$  in der Vorderkammer ( $19,8 \pm 5,8$  im Kammerwinkel,  $13,4 \pm 4,7$  über dem Pupillarsaum und  $7,4 \pm 3,3$  mmHg vor der Pupillenmitte;  $n=8$ ). Der  $pO_2$  in der vorderen Linsenrinde war sehr niedrig ( $2,5 \pm 0,6$  mmHg;  $n=7$ ). Wir folgern, daß die Sättigung des Kammerwassers mit  $O_2$  in der Vorderkammer an der Irisvorderfläche erfolgt. In der Linse findet sich ausgesprochen wenig Sauerstoff. Phenylephrin-Augentropfen führen – wahrscheinlich durch Irisgefäßverengung – zur Hypoxie im Kammerwasser.

\* Presented at the 90th annual meeting of the Deutsche Ophthalmologische Gesellschaft, Mannheim, September 27–30, 1992

Offprint requests to: H. Helbig

### Introduction

Hypoxia is believed to play a role in the development of several important eye diseases such as diabetic retinopathy [17] and retinopathy of prematurity [5]. Hypoxia is a growth stimulus for ocular vascular cells [16] and probably triggers the development of ocular vasoproliferation, leading to rubeosis iridis in the anterior segment and retinal neovascularization in the posterior segment [17]. Thus, it is important to learn about the physiology and pathophysiology of oxygen supply in the eye.

Within the eye we face a unique situation. Intraocular tissues such as cornea, lens, and chamber-angle structures are not vascularized and depend on other mechanisms for the supply of nutrients and oxygen. It is assumed that the aqueous humor delivers nutrients and provides gas exchange for these tissues. The saturation of the aqueous humor with nutrients is believed to occur mainly at the ciliary epithelium, the site of aqueous humor formation [15]. However, aqueous humor is produced at a rate of only about  $2 \mu\text{l}/\text{min}$ , and the oxygen and nutrient content of  $2 \mu\text{l}$  aqueous is too low to fulfill for 1 min the metabolic demands of the lens [9] and the other nonvascularized tissues facing the anterior chamber. Therefore, other mechanisms should contribute to the delivery of oxygen and nutrients to the aqueous humor. Recently Hoper et al. [10] have concluded from their animal experiments that the anterior iris surface may provide oxygen for the aqueous humor in the anterior chamber. In the present study we tested this hypothesis by measuring the spatial distribution of oxygen in the anterior chamber of the human eye.

The second part of the study was designed to test the effect of adrenergic drugs on the oxygen tension in the anterior chamber. Adrenergic drugs in very high concentrations are widely used in ophthalmology. Epinephrine is used in glaucoma therapy to lower intraocular pressure. Phenylephrine is a common diagnostic mydriatic. Adrenergica are very potent drugs with a wide spectrum of action. Serious systemic as well as local side effects of phenylephrine eye drops have been reported [6]. Many

side effects are due to the vasoconstrictive action of adrenergic drugs. The effect of adrenergic stimulation on the uveal blood flow is well known [2], and it was postulated that adrenergic stimulation might cause or exacerbate anterior-segment hypoxia. Therefore, we tested whether topical phenylephrine would cause anterior-segment hypoxia.

### Patients and methods

We measured oxygen partial pressure ( $pO_2$ ) using the  $O_2$ -Histograph (Eppendorf, Berlin, Germany). The polarographic electrode used was a 100- $\mu$ m platinum wire coated with polyurethane and placed in a cannula measuring 320  $\mu$ m in diameter and 3.5 cm in length. The electrode was sterilized in ethylene oxide gas. Calibration was performed before each measurement in a sterile saline solution equilibrated with sterile pure nitrogen and room air at room temperature. Since calibration was performed in a protein-free solution, the higher protein content in the tissue may induce a small error in the measurements made in a protein-rich environment. The actual measurements were corrected digitally for a tissue temperature of 34 °C. The electrode was connected with a 50-cm shielded cable to a preamplifier. A polarometric voltage of 700 mV was applied. The  $pO_2$  values were displayed digitally and printed on a plotter.

Oxygen measurements in the anterior chamber were performed during routine cataract surgery. Patients with serious general diseases or other eye pathology were excluded. Patients were informed about the nature of the surgery and the  $pO_2$  measurements. The experimental character of the measurements was stressed. Written and oral consent was obtained. Patients received different premedications, but we did not find any difference between these groups.

Cataract surgery was performed using local anesthesia with the patients breathing room air. At the beginning of the operation an incision was made at the limbus with a 0.45-mm cannula. Care was taken to avoid loss of aqueous humor or injection of saline. The electrode was inserted through the corneal incision into the anterior chamber and was moved parallel to the anterior iris surface to various locations in the anterior chamber. The distance between the electrode and the iris or lens surface, respectively, was about 300  $\mu$ m (one electrode diameter). The entrance of the inserted electrode was essentially watertight. If leakage of aqueous humor occurred, the measurement was discarded.

Patients were randomly assigned to one of two different regimens to achieve preoperative mydriasis of the pupil. Patients from group I received a drop of 0.5% scopolamine and 0.5% tropicamide in the morning at about 2 h before surgery. At about 60 min and 30 min before surgery, they received another drop of 0.5% tropicamide. Patients in group II were treated similarly but additionally received a 5% phenylephrine eye drop at about 2 h as well as 60 and 30 min before surgery. Statistical analysis was performed using student's paired and unpaired *t*-test. *P* values of  $>0.05$  were considered to be statistically non significant.

### Results

In each of the two groups there were eight patients, including six women and two men. The age of the patients in group I (no phenylephrine) ranged from 68 to 88 years (mean  $79 \pm 6$  years). The age of the patients in group II (with phenylephrine) ranged from 62 to 90 years (mean  $77 \pm 9$  years). The pupil diameter was larger in eyes that had received phenylephrine (group II,  $7.2 \pm 0.7$  mm) than in those that had not (group I,  $6.3 \pm 0.8$  mm).

The  $pO_2$  value was determined at different locations within the anterior chamber of the human eye. There

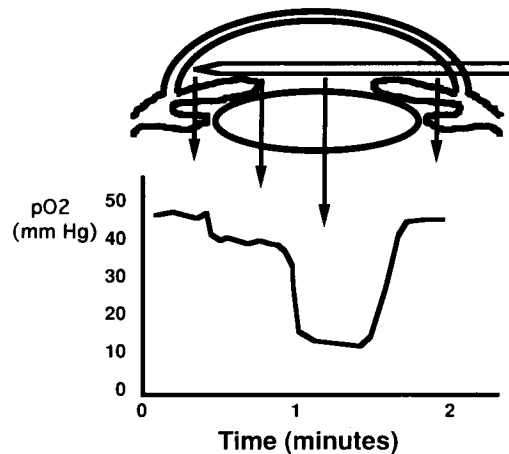


Fig. 1. Original recording of  $pO_2$  in the anterior chamber of a patient from group I. The electrode was moved from the chamber angle to the pupillary margin, the center of the pupil, and the contralateral chamber angle as indicated by the arrows. The electrode was left in each position until a stable recording was obtained

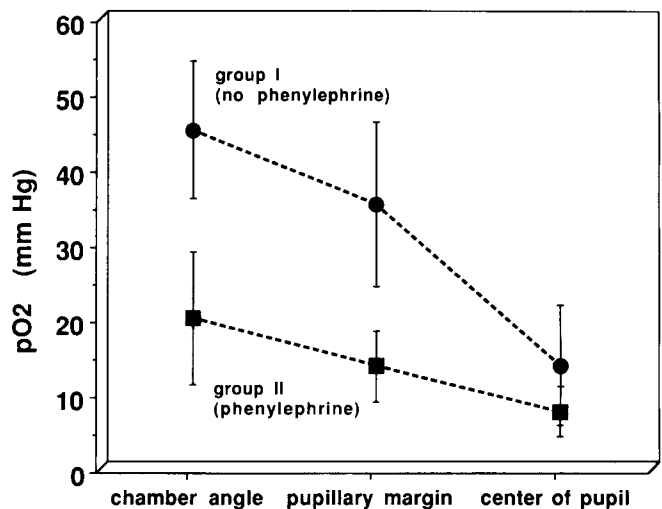


Fig. 2. Mean  $pO_2$  values ( $\pm$ SD) obtained at 3 different locations in the anterior chamber of eyes pretreated with and without phenylephrine. Differences between group I and group II (Student's unpaired *t*-test): chamber angle,  $P < 0.001$ ; pupillary margin,  $P < 0.001$ ; center of pupil; nonsignificant

were marked differences between the different locations, and we found the same pattern of spatial distribution of oxygen in the aqueous humor of all patients. The highest  $pO_2$  values were found near the chamber angle; slightly lower values were measured above the pupillary margin, and the lowest levels were detected above the center of the pupil (Fig. 1). This pattern was similar in both groups of patients. However,  $pO_2$  values were nearly twice as high in group I as compared with group II (Fig. 2).

We found no correlation between age, sex, and  $pO_2$ . Patients in group II had a slightly larger pupil size and a lower  $pO_2$  value as compared with those in group I, but within the groups there was no correlation between pupil size and  $pO_2$ .

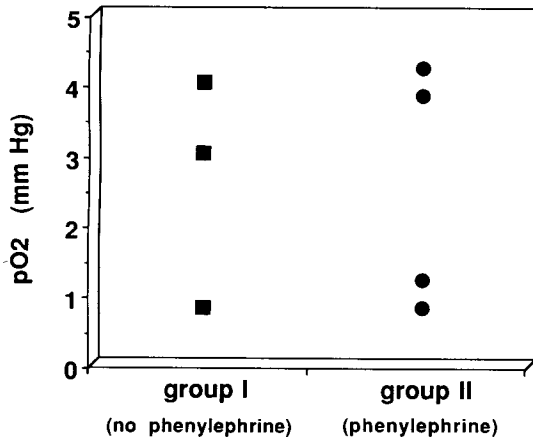


Fig. 3. The pO<sub>2</sub> values obtained in the anterior lens cortex of eyes pretreated with and without phenylephrine

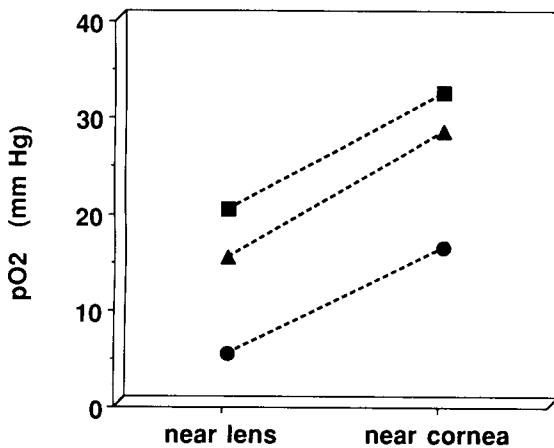


Fig. 4. The pO<sub>2</sub> values obtained in 3 eyes from group I in which the electrode was elevated from a position near the lens toward the corneal endothelium in the center of the pupil ( $P < 0.05$ , Student's paired *t*-test)

In seven patients (three from group I and four from group II), we punctured the lens capsule with the oxygen electrode and measured the pO<sub>2</sub> within the anterior lens cortex. We observed an immediate drop in pO<sub>2</sub> to values between 0.8 and 4 mmHg. No difference was found between eyes treated with (pO<sub>2</sub> = 2.6 ± 1.0 mmHg) and without (pO<sub>2</sub> = 2.5 ± 0.6 mmHg) phenylephrine (Fig. 3).

In only three cases was it possible to compare the pO<sub>2</sub> value obtained close to the lens and with that measured close to the corneal endothelium in front of the middle of the pupil. In most attempts, leakage of aqueous humor occurred during this maneuver. In all three patients we found higher values when the electrode was elevated from the lens to the cornea (Fig. 4). However, in all three cases the pO<sub>2</sub> value measured in the chamber angle was higher than that obtained close to the corneal endothelium in front of the middle of the pupil.

## Discussion

In the present study we found the oxygen tension in front of the anterior iris surface to be considerably higher than that in front of the lens. Until recently it was believed that

oxygen and nutrients in the aqueous humor are derived from the ciliary processes, and passed with the aqueous humor into the anterior chamber. The data from our study indicate that oxygen is delivered to the aqueous humor in the anterior chamber by the iris blood vessels. The total number of iridal capillaries is much higher than would be expected from the nutritive needs of the iris stroma. They lie mostly beneath the anterior surface and are in close contact to the aqueous humor [10]. The iris capillaries are of the nonfenestrated type and are impermeable to high-molecular-weight molecules, but they do not present a barrier for oxygen. Moreover, the iris crypts provide a magnified surface. This is obviously the morphological basis for gas exchange at the anterior iris surface.

Oxygen tension in the anterior chamber has been studied in several animal species. Most studies have been done in the rabbit [3, 10, 11, 13, 19, 21], where values between 23 [19] and 72 mmHg [13] have been reported. Similar values have been obtained in the anterior chamber of cat [14, 18], dog [7], and monkey eyes [10]. One study has measured pO<sub>2</sub> in the anterior chamber of the human eye [12]. The authors found a mean value of 53 mmHg (range, 37–67 mmHg) by analyzing aqueous humor microprobes. Using this technique, however, the authors could not pay attention to the spatial distribution of O<sub>2</sub> in the anterior chamber. Only one study has focused on the relationship between electrode position and pO<sub>2</sub> [10]. This study in rabbits and monkeys found the same oxygen profile noted in the present investigation in human eyes.

The measurements in our study were performed on patients lying in the supine position. In upright patients there will be a thermic circulation with an upward flow in front of the iris and a downward flow behind the cornea. The thermic circulation will certainly affect the oxygen profile obtained in the anterior chamber of the upright patient. The fluid movement caused by the thermic circulation is much stronger than the flow caused by the formation of aqueous humor in the ciliary processes, which is only about 2 μl/min. Thus, in the upright patient the combination of saturation of the aqueous humor with oxygen (and possibly other nutrients) and thermic aqueous circulation may provide an effective supply of oxygen to the non-vascularized ocular tissues lining the anterior chamber.

The pO<sub>2</sub> value measured in the anterior lens was as low as 2.5 mmHg. It has been postulated that low intralental oxygen levels may be necessary to keep the lens clear and that mechanisms exist to keep intralental oxygen low [4], since light-induced oxygen radicals may cause irreversible damage to the lens [20]. Hyperbaric oxygen treatment can indeed produce cataract in experimental animals [20]. Kwan et al. [13] have also measured a much lower pO<sub>2</sub> value in the rabbit lens as compared with the aqueous humor, but their absolute pO<sub>2</sub> values of 21 mmHg in the lens were several times higher than the 2.5 mmHg that we found in the human lens. However, there are some differences between our measurements and those at Kwan et al. [13] report. Our measurements were made in old patients with cataractous lenses, where-

as Kwan et al.'s young rabbits had clear lenses. Moreover, in the rabbit experiments the electrode penetrated at right angles to the lens capsule. We penetrated the lens capsule at flat angles, which might have resulted in a better sealing of the hole in the lens capsule and led to more reliable values. However, at present we cannot explain this difference.

In some experiments we found oxygen tension to be significantly higher when the electrode was elevated in the center of the pupil from the lens toward the corneal endothelium. This elevation could be explained by a diffusion of oxygen from the room air through the cornea into the aqueous humor. However, the precorneal air is not a source for aqueous humor oxygenation [13]. The inner cornea has a lower  $pO_2$  than the aqueous humor, and oxygen for the corneal endothelium is provided by the aqueous humor [13]. Thus the higher  $pO_2$  value obtained near the cornea may be explained by an oxygen diffusion gradient from the aqueous toward the lens, which is known to consume oxygen [9].

Topical phenylephrine led to a marked decrease in anterior-chamber  $pO_2$ . A similar dramatic effect of phenylephrine and epinephrine has been described in cats [14–18]. This reduction in oxygen tension could be explained by a reduced blood flow in the tissues facing the aqueous humor, by a reduction in aqueous humor formation, by mydriasis, or by an increase in oxygen consumption.

Oxygen consumption is likely to be increased by the phenylephrine-induced contraction of the iris dilator muscle. This mechanism might contribute to a minor extent to the phenylephrine-induced anterior-chamber hypoxia. Dilatation of the pupil did not seem to be responsible for the difference observed in phenylephrine-treated eyes. Pupils in our study were only slightly larger after the application of phenylephrine as compared with tropicamide alone. In addition, we did not find a correlation between pupil size and  $pO_2$  within the two groups. Other investigators have found no effect of atropine-induced dilation of the pupil on aqueous humor  $pO_2$  in experimental animals [14, 18]. Decreased aqueous humor formation could cause a reduced aqueous humor oxygen concentration if the oxygen consumption of the surrounding tissues remains unchanged. However, our data indicate that oxygenation of the aqueous humor in the anterior chamber occurs at the iris and that oxygenation of the forming aqueous humor at the ciliary epithelium plays a minor role for the anterior chamber.

Reduced iridal blood flow is the most likely explanation for the observed phenylephrine-induced anterior-chamber hypoxia. The blood flow in the iris and ciliary body has been shown to be decreased after topical application of epinephrine [1] and sympathetic nerve stimulation [2]. The finding that sympathomimetic drugs can cause anterior-segment hypoxia by vasoconstriction in the anterior uvea may have clinical relevance for a variety of ocular disorders. On the basis of this assumption, sympathomimetic drugs should be avoided in conditions such as diabetes and neovascular glaucoma, where it could exacerbate the hypoxia that is felt to be a stimulus for ocular neovascularization [17]. In aphakic patients these

drugs could penetrate more posteriorly and cause a similar hypoxic effect in the retina and the optic nerve.

In conclusion, our measurements indicate that oxygenation of the aqueous humor in the anterior chamber of the human eye occurs at the anterior iris surface. Oxygen tension in the cataractous lens is extremely low. Topical phenylephrine causes anterior-segment hypoxia.

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