

Oxygen Tension in the Aqueous Humor of Human Eyes under Different Oxygenation Conditions

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Purpose: To measure oxygen tension in the aqueous humor of human eyes under different oxygenation conditions.

Methods: This prospective comparative interventional case series consisted of two parts. In the first part, 120 consecutive patients scheduled for cataract surgery were randomized into group I (control group) in which surgery was performed under local anesthesia inhaling 21% oxygen; group II in whom general anesthesia using 50% oxygen was employed; and group III receiving general anesthesia with 100% oxygen. After aspirating 0.2 ml aqueous humor under sterile conditions, the aqueous sample and a simultaneously drawn arterial blood sample were immediately analyzed using a blood gas analyzer. In part II the same procedures were performed in 10 patients after fitting a contact lens and patching the eye for 20 minutes (group IV) and in 10 patients after transcorneal delivery of oxygen at a flow rate of 5 L/min (group V).

Results: Mean aqueous PO₂ in groups I, II and III was 112.3±6.2, 141.1±20.4, and 170.1±27 mmHg, respectively (P values <0.001) and mean arterial PO₂ was 85.7±7.9, 184.6±46, and 379.1±75.9 mmHg, respectively (P values <0.001). Aqueous PO₂ was 77.2±9.2 mmHg in group IV and 152.3±10.9 mmHg in group V (P values <0.001). There was a significant correlation between aqueous and blood PO₂ (r=0.537, P<0.001). The contribution of atmospheric oxygen to aqueous PO₂ was 23.7%.

Conclusion: Aqueous oxygen tension is mostly dependent on the systemic circulation and in part on the atmosphere. Increasing inspiratory oxygen and transcorneal oxygen delivery both increase aqueous PO₂ levels.

Keywords: Aqueous Humor; Oxygen Tension; Blood Gas Analyzer

J Ophthalmic Vis Res 2013; 8 (2): 119-125.

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Received: January 26, 2013

Accepted: March 17, 2013

INTRODUCTION

Oxygen delivery to the eye has been a matter of great interest and the subject of numerous studies. Oxygen and thereby aerobic glycolysis is the principle pathway of metabolism in the human eye, except for the lens.¹ Oxygen can

be supplied to the anterior segment of the eye from the atmosphere, the limbal circulation, the palpebral conjunctiva, and blood supply to the ciliary body and iris.²

There is considerable debate regarding the source of oxygen in the aqueous humor. Some authors have suggested that oxygen in

the aqueous humor is derived only from ciliary body and iris vasculature¹⁻⁴, while others have reported it to be derived from blood circulation as well as the atmosphere, especially behind the corneal endothelium.⁵⁻¹⁰

Based on mathematical modeling of oxygen movement, Fatt and Bieber calculated that all the oxygen needed for corneal metabolism in the open eye comes directly from the atmosphere, while palpebral conjunctival capillaries and the aqueous humor provide the necessary oxygen in the closed eye.¹¹

Most of the knowledge about oxygen kinetics in the anterior segment of the eye comes from measurements in the aqueous humor of animal models, with poor agreement between the results of similar studies.²⁻¹⁴ A few studies have measured oxygen tension in humans.¹⁵⁻¹⁷

This study measures oxygen tension in the aqueous humor of the human eye under different oxygenation conditions.

METHODS

This prospective comparative interventional case series was performed at Imam Khomeini Hospital, Ahvaz, Iran. The study was approved by the Institutional Review Board of Ahvaz Jundishapur University of Medical Sciences and adhered to the tenets of Declaration of Helsinki. Informed consent was obtained from all patients.

The study consisted of 2 parts. In part I, 120 consecutive patients with senile cataracts scheduled for cataract surgery were enrolled. Exclusion criteria included history of chronic cardiopulmonary disorders such as chronic obstructive pulmonary disease (COPD) that may interfere with normal oxygenation, uncontrolled diabetes, heavy smokers, the presence of any other ocular disease such as glaucoma, any degree of diabetic retinopathy and other ischemic disorders, uveitis and pseudoexfoliation syndrome, history of ocular surgery, topical glaucoma medication use and monocular status. The patients were randomized to cataract surgery under local anesthesia while breathing room air with fraction of inspiratory oxygen (FIO₂) of 21% (group I, which served as the control group), cataract surgery under

general anesthesia receiving oxygen with FIO₂ of 50% (group II), and cataract surgery under general anesthesia with FIO₂ of 100% (group III).

Part II consisted of 2 groups: in one group of 10 patients a soft contact lens [Soflens, Bausch and Lomb, London, UK; hydroxyethylmethacrylate soft lens with permeability of $8.4 \times 10^{-11}[\text{cm}^3 \text{O}_2 \times \text{cm}]/(\text{sec} \times \text{cm}^2 \times \text{mmHg})$] was placed on the cornea and the eye was patched for 20 minutes (group IV). In another group of 10 patients transcorneal oxygen was delivered at a flow rate of 5 L/min for 20 minutes using an eye shield (group V). To deliver transcorneal oxygen an eye shield was firmly taped over the eye and all holes were closed except two; through one hole, an oxygen tube was inserted in front of the eye while the second served for air exit to keep the conditions normobaric. This setting can also be achieved using swimming goggles.⁸

In the operating room, eyes assigned to groups I, IV and V were prepared and draped under local anesthesia such that the mouth remained uncovered. A speculum was inserted and the eye was irrigated. A small amount of heparin was drawn into a tuberculin syringe and then emptied to fill the dead space of the syringe and needle. Using a #27 gauge needle, 0.2 ml of aqueous humor was gently withdrawn to prevent inadvertent aspiration of air. In case of air aspiration the sample was discarded. Then after performing Allen's test to ensure patency of the ulnar artery, an arterial blood sample was obtained from the radial artery using another heparinized tuberculin syringe. Both samples were immediately sent to the laboratory on ice packs and PO₂, PCO₂ and PH were measured with a blood gas analyzer (AVL Compact 3 Blood Gas Analyzer, Roche, Austria). Cataract surgery was subsequently performed as planned in group I.

In groups II and III sampling was done 20 minutes after intubation and receiving 50% and 100% oxygen, respectively, to ensure equal distribution and diffusion of oxygen in different tissues including the eye.

Statistical Analysis

Statistical analysis was performed employing the

SPSS software version 17.0 (SPSS Inc. Chicago, IL, USA). To describe data we used mean ± standard deviations (SDs) and 95% confidence intervals (95% CIs). Analysis of variance (One Way ANOVA) was performed to determine differences among mean values of the study groups. Whenever a significant difference existed, the Tukey and Mann-Whitney tests were used for two by two post-hoc comparisons. Pearson's correlation was used to investigate the correlation between aqueous PO₂ and arterial blood PO₂ (PaO₂). P values less than 0.05 were considered as statistically significant.

RESULTS

Overall 140 eyes from 140 patients including 69 men and 71 women were included. The study groups were matched in terms of age (P=0.940) and sex (P=0.929). Table 1 summarizes the results of aqueous humor and arterial blood gas analyses in all study groups.

After systemic administration of oxygen, mean aqueous PO₂ and PaO₂ in groups II and III was higher as compared to group I (both P values <0.001, Table 1). A significant correlation was found between PaO₂ and aqueous PO₂ in

groups I, II, and III (r=0.537, P<0.001, Fig. 1).

Multiple comparisons of mean values for aqueous PCO₂ revealed a significant difference only between groups I and III (P<0.001). Mean arterial blood PCO₂ in groups I, II and III were comparable (P=0.113, ANOVA).

The difference among mean aqueous PH in groups I, II and III was statistically significant

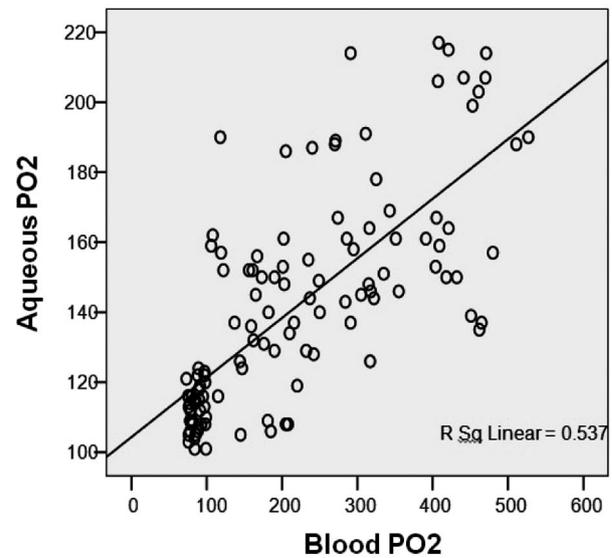


Figure 1. Correlation between aqueous and arterial blood PO₂. (Pearson correlation, r=0.537, P<0.001).

Table 1. Results of aqueous and blood gasometry in the study groups[†]

Group	Number of patients	Age (year) M±SD	Sex (M) (%)	Aqueous PO ₂ (mmHg) M±SD	Aqueous PCO ₂ (mmHg) M±SD	Aqueous PH M±SD	PaO ₂ (mmHg) M±SD	PaCO ₂ (mmHg) M±SD	Blood PH M±SD
I	40	59.9±12.9	19 (47.5)	112.3±6.2	38.9±8.3	7.24±0.08	85.7±7.9	38±5.9	7.34±0.06
II	40	57.8±10.3	21 (52.5)	141.1±20.4	34.6±11.8	7.28±0.015	184.6±46	35.2±7.9	7.38±0.07
P*		0.940**	0.929**	< 0.001	0.118	0.192	<0.001	0.113**	0.06
95% CI				-39.29 to -18.21			-126.21 to -71.59		
III	40	57.2±13.3	18 (45)	170.1±27	30.3±8.4	7.30±0.092	379.1±75.9	35.4±5.5	7.39±0.059
P*		0.940**	0.929**	< 0.001	<0.001	0.036	<0.001	0.113**	0.007
95% CI				-68.29 to -47.21	3.49 to 13.71	-0.11 to -0.003	-320.71 to -266.09		-0.08 to -0.01
IV	10	60.6±5.8	5 (50)	77.2±9.2	48.1±5.2	7.16±0.03	83.6±5.4	39.2±4.2	7.38±0.02
P*		0.940**	0.929**	P<0.001 [‡]	0.001 [‡]	0.005 [‡]	0.519	0.715**	0.074
95% CI				30.25 to 40	-14.79 to -3.71	0.06 to 0.13			
V	10	58.6±6.3	6 (60)	152.3±10.9	34±5.8	7.30±0.08	86.7±6.2	38±2.7	7.36±0.04
P*		0.940**	0.929**	<0.001 [‡]	0.065 [‡]	0.040 [‡]	0.576	0.386**	0.845
95% CI				-47.91 to -32.04		-0.13 to -0.004			

[†]Group I included patients with fraction of inspiratory oxygen (FIO₂) of 21%; group II, patients with FIO₂ of 50%; group III, patients with FIO₂ of 100%; group IV, patients with contact lens and eye patch; group V, patients with trans-corneal oxygen at a flow rate of 5 L/min

*compared with group I based on Tukey test

**based on ANOVA

[‡]based on Mann-Whitney test

PO₂, oxygen pressure; PCO₂, carbon dioxide pressure; PaO₂, arterial blood oxygen pressure; PaCO₂, arterial blood carbon dioxide pressure; 95% CI, 95% confidence interval of the difference with group I; P, p-value; M, mean; SD, standard deviation

only between groups I and III ($P=0.036$). A significant difference was also observed in mean arterial blood PH between groups I and III ($P=0.007$).

After a contact lens had been placed on the cornea, aqueous PO_2 decreased significantly as compared to group I ($P<0.001$), aqueous PCO_2 increased significantly ($P=0.002$) and aqueous PH decreased significantly ($P<0.001$). Blood gasometry was not different between groups I and IV (Table 1).

After transcorneal oxygen delivery, aqueous PO_2 was 152.3 ± 10.9 ($P<0.001$ as compared to group I; $P=0.101$ compared to group II; and $P=0.003$ compared to group III); aqueous PCO_2 decreased ($P=0.087$); and aqueous PH increased as compared to group I ($P=0.038$).

The contribution of atmospheric oxygen to aqueous PO_2 was calculated to be 23.7% by the following equation:

$$\frac{\text{Aqueous } PO_2 \text{ in group I} - PaO_2 \text{ in group I}}{\text{Aqueous } PO_2 \text{ in group I}} \times 100$$

DISCUSSION

A variety of techniques have been used to measure aqueous humor oxygen tension including employing polarographic electrodes in the eye,^{2,4,5,10,13,15,16} and on the bare corneal stroma,¹⁴ paracentesis and use of a blood gas analyzer,⁸ ocular scanning fluorometry¹² and the use of optical oxygen sensors (optodes).^{9,17,18}

Table 2 summarizes aqueous PO_2 levels reported in different studies. Even in studies using the same instrument and in the same species, there is poor agreement among the reports.

Jampol et al used a blood gas analyzer similar to our study and measured aqueous PO_2 of 63.5 ± 12.3 mmHg.⁸ They concluded that under normal conditions most of the oxygen in the aqueous humor is derived from vascular supply to the iris and ciliary body.⁸ Using 100% oxygen at the corneal surface or hyperbaric inspiratory O_2 (21%), they observed an increase in aqueous PO_2 .⁸

Kleinsteinst et al estimated aqueous PO_2 without penetrating the globe, (i.e. with removal

of the corneal epithelium and using oxygen electrodes on bare stromal surface).¹⁴ Aqueous PO_2 was measured at 13 mmHg and increased to 150 mmHg using 100% inspiratory oxygen.¹⁴

Shui et al used a fiberoptic oxygen sensor (optode) to measure PO_2 in different regions of the rabbit eye.⁹ They observed that oxygen levels in the ocular fluids change markedly under hypoxic or hyperoxic conditions.⁹ Oxygen levels were highest near the retinal vasculature, iris vasculature, and the inner surface of the central cornea; and lowest near the anterior chamber angle and close to the lens.⁹ They suggested that intraocular oxygen is mostly derived from retinal and iris vasculature and by diffusion across the cornea.⁹

Helbig et al measured aqueous PO_2 during routine cataract surgery in 8 eyes using a polarographic oxygen electrode.¹⁵ In contrast to the study by Shui et al⁹, aqueous PO_2 was reported to be highest in the chamber angle and lowest at the center of the pupil; the authors concluded that oxygen is supplied to the aqueous humor at the anterior iris surface.¹⁵

In another study by Siegfried et al¹⁷ aqueous oxygen tension was measured in different parts of the anterior segment of human eyes. They observed an increase in angle PO_2 after vitrectomy and cataract surgery compared to eyes that had not previously undergone surgery.¹⁷ Surgery was considered to have a potential role in damaging the trabecular meshwork and inducing glaucoma.¹⁷

Hypoxia during anesthesia is defined as $PaO_2<60$ mmHg. The corresponding value for tissues is considered to be 40 mmHg.¹⁹ Keeping these in mind and considering the wide range of measured aqueous PO_2 using polarographic oxygen electrodes in different studies (13-72 mmHg) which is sometimes unexpectedly low, we assumed that this method is not ideal for measurements. Additionally, it has been suggested that polarographic electrodes may consume oxygen and thereby underestimate aqueous PO_2 .¹⁸

The blood gas analyzer is the gold standard for measuring arterial blood gases.²⁰ We measured aqueous PO_2 , PCO_2 and PH exactly in the same way as that performed for

Table 2. Summary of studies measuring oxygen tension in the aqueous humor

Study	Year	Method	Animal	Aqueous PO ₂ (mmHg)	Aqueous PO ₂ (mmHg) (Special conditions)
Heald et al ⁵	1956	Polarographic analysis	Rabbit	53.5	
Fatt et al ¹¹	1968	Needle-type Clark oxygen electrode	Rabbit	55	
Kwan et al ²	1972	Oxygen ultramicroelectrode	Rabbit	72±5	
Kleinstein et al ¹⁴	1981	Polarographic electrode on bare stroma	Rabbit	13	150 (after 100% inspiratory O ₂)
Stefansson et al ¹³	1987	Polarographic oxygen electrode	Rabbit	23± 2	16±4 (CL)
Jampol et al ⁸	1988	Blood gas analyzer	Rabbit	63.5±12.3	139.5±32.4 (transcorneal O ₂)
Sobecki ⁴	1993	Polarographic oxygen electrode	Rabbit	64.4	
Helbig et al ¹⁵	1993	Polarographic oxygen electrode	Human	44.9±9.1 (angle) 35±10.9 (pupil) 13.5±8.0 (in front of the center of the pupil)	19.8±5.8 (angle) 13.4±4.7 (pupil) 7.4±3.3 (in front of the pupil center) [topical phenylephrine]
Helbig et al ¹⁶	1994	Polarographic oxygen electrode	Human (PEX)	19±6 (angle) 16±4 (pupil)	
Mc Laren et al ¹²	1998	Ocular scanning fluorometer	Rabbit	23± 2	4±2 (20 min CL) 10±3 (lid closure)
Fitch et al ¹⁰	2000	Polarographic oxygen electrode	Rat	63±9	279±45 (transcorneal and inspiratory O ₂)
Shui et al ⁹	2006	Fiberoptic oxygen sensor (optode)	Rabbit	27±3 (angle) 43±2 (inner surface of the cornea)	31±2 (preretinal)
Siegfried et al ¹⁷	2010	Optode	Human	12.9 (angle) 24.2 (inner surface of the cornea)	24.7 (angle) 26.7 (inner surface of the cornea) [after vitrectomy and cataract surgery]
Sharifipour et al	2013	Blood gas analyzer	Human	112.3±6.2	77.2±9.2 (20 min CL) 152.3±10.9 (transcorneal O ₂)

PO₂, oxygen pressure; CL, contact lens; PEX, pseudoexfoliation

blood samples. An advantage of this method is simultaneous measurement of PO₂, PCO₂ and PH with precision to a thousandth of a fraction. However, a major shortcoming of this technique is that the measurements represent mean aqueous PO₂.

In this study aqueous PO₂ was 112.3±6.2 mmHg which is higher than simultaneous PaO₂ of 85.7±7.9 mmHg. After placing a contact lens

with low oxygen permeability on the cornea and patching the eye (thereby eliminating the contribution of atmospheric oxygen to the aqueous), aqueous PO₂ decreased to 77.20±9.2 mmHg; a value lower than PaO₂. This finding demonstrates diffusion of atmospheric oxygen across the cornea into the anterior chamber. This observation concurs with previous studies showing a contribution of atmospheric oxygen

to the aqueous.^{5-10,17} Although we measured aqueous PO₂ to be higher than previous reports (Table 2), values obtained in group IV supports the accuracy of our technique. It has been reported that methods similar to the ones in the current study are subject to air contamination during sampling.¹² However, to decrease measurement errors, we discarded air contaminated samples and used the same method for all study groups, so sampling technique would probably not have affected our observations.

In this study, higher levels of inspiratory oxygen increased aqueous PO₂. This was previously reported in several animal studies.^{8,10,14} A significant correlation was found between aqueous and blood PO₂. By increasing FIO₂ and thus PaO₂ in groups II and III, aqueous PO₂ increased, but to a level lower than PaO₂. This may be explained by the fact that under normobaric conditions, atmospheric PO₂ is about 150 mmHg (at the sea level, 21% oxygen x 760 mmHg =159.6 mmHg). In groups II and III, aqueous PO₂ was 141.1±20.4 mmHg, and 170.1±27 mmHg, respectively, while atmospheric PO₂ remained about 150 mmHg. We postulate that these levels of aqueous PO₂ may decrease or eliminate the gradient for atmospheric oxygen to diffuse across the cornea into the aqueous, although our observations do not support or disprove these explanations. Thus it seems that atmospheric oxygen may play a major role under normal conditions but not under hyperoxic states. Transcorneal oxygen at a flow rate of 5 L/min increased aqueous PO₂ by increasing diffusion of oxygen across the cornea. This was also previously observed in some animal studies^{8,10}, and was shown to be beneficial in special clinical conditions.²¹ After transcorneal oxygen delivery at the above-mentioned flow rate, aqueous PO₂ was 152.3±10.9 mmHg which was comparable to aqueous PO₂ in group II (systemic oxygen with FIO₂ 50%, P=0.101), while significantly higher than the control group (group I with FIO₂ 21%, P<0.001) and lower than group III (systemic oxygen with FIO₂ 100%, P=0.003). This shows that transcorneal oxygen may be considered as an alternative to systemic oxygen therapy in certain anterior segment diseases.

To the best of our knowledge, this is the first report of aqueous PCO₂ and PH measurement in humans under physiologic and different oxygenation conditions. By increasing inspiratory oxygen, PaO₂ and aqueous PO₂ increased, simultaneously blood and aqueous PCO₂ decreased. However, this was only significant for aqueous PCO₂ between groups I and III (P<0.001). Alternately, aqueous and blood PH increased (became more alkaline) in parallel to a decrease in PCO₂, again this was only significant between groups I and III (P=0.036 and 0.007, respectively). Insignificant or mild changes in both blood and aqueous PCO₂ and PH can be explained by the fact that both blood and aqueous have buffer systems, mainly bicarbonate, to prevent significant changes in PCO₂ and PH. In group IV, after placing a contact lens on the cornea and patching the eye, aqueous PCO₂ increased to 48.1±5.2 (P=0.002 compared to group I) and aqueous PH decreased (i.e. became more acidic) to 7.16±0.03 (P<0.001). This observation supports the current belief that CO₂ leaves the aqueous mainly via diffusion across the cornea to the atmosphere and not through the iris vasculature.¹ Thus by interfering with the escape of CO₂ from the eye by a contact lens in group IV, CO₂ accumulated in the aqueous, the buffer system was overwhelmed, and PH became acidic. After transcorneal oxygen delivery, aqueous PCO₂ was decreased as compared to the control group but failed to reach a statistically significant level.

In summary, this study provides information regarding gasometry and PH of the aqueous humor in normal physiologic state as well as under different oxygenation conditions, and compares them with corresponding arterial blood values. According to our findings, most of the oxygen in the aqueous is provided by the systemic circulation which can be increased by increasing FIO₂. A proportion of aqueous oxygen is provided by the atmosphere under normal conditions and can be increased by transcorneal oxygen delivery. The contribution of atmospheric oxygen to aqueous PO₂ becomes less significant and negligible under hyperoxic states such as systemic oxygen therapy. By increasing blood or transcorneal oxygen, aqueous oxygen increases,

which may play a role in anterior segment disorders associated with ischemia.

Conflicts of Interest

None.

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