Measurement of PO₂ during vitrectomy for central retinal vein occlusion, a pilot study

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Abstract

Introduction. In this pilot study the effects of vitrectomy on PO₂ in the vitreous cavity in central retinal vein occlusion (CRVO) were investigated with a prospective, controlled, interventional study.

Methods. Six patients with CRVO in one eye and six with either macula hole or membrane undergoing vitrectomy were included as a control group. An oxygen probe was inserted before removal of the vitreous (pre-vitrectomy) and after removal of the vitreous (post-vitrectomy). Oxygenation recordings (PO₂) were taken in the mid-vitreous cavity and the preretinal vitreous.

Results. In both groups pre-vitrectomy the PO₂ adjacent to the retina was significantly ($p < 0.05$) less than mid-cavity: control, 15.0 ± 5.7 vs 33.7 ± 12.8 mmHg; CRVO, 8.1 ± 3.5 vs 19.8 ± 7.3 mmHg. Moreover the PO₂ was significantly less at each site in the CRVO group compared to control. Post-vitrectomy the PO₂ was significantly greater than pre-vitrectomy at both recording sites for the controls (75.8 ± 9.1 and 61.5 ± 13.9 mmHg, pre-retinal and mid cavity, respectively) and the CRVO group (59.8 ± 15.8 and 53.7 ± 17.9 , respectively). In addition the PO₂ gradient existing pre-vitrectomy from mid-cavity to pre-retina was abolished in both groups.

Conclusion. PO₂ is reduced in the vitreous cavity in eyes with CRVO. Vitrectomy is a method of increasing oxygen availability, at least in the short-term.

Introduction

Central retinal vein occlusion (CRVO) is second only to diabetic retinopathy as the most frequent vascular cause of visual loss ¹. The exact pathogenesis is not known ²; however, the central retinal vein appears to reduce in calibre as it passes through the lamina cribrosa ³. If the occlusion is minor, retinal ischaemia is limited, but more severe CRVO manifests as a more ischaemic type. Ischaemic retinal damage enhances production of vascular endothelial growth factor (VEGF) in the vitreous cavity ⁴, which in turn stimulates neovascularization of the posterior and anterior segment and is responsible for secondary complications such as neovascular glaucoma.

Several treatments have been proposed including injections of recombinant tissue plasminogen activator into the vitreous or direct injection into a cannulated central vein ⁵. The main surgical procedure over recent years has been radial optic neurotomy (RON) ^{6, 7}, thought to be effective by improving central retinal vein blood flow by relieving pressure on the vein as it exits the lamina cribrosa. In combination with pars plana vitrectomy, good anatomical and visual results in patients with non-ischaemic and ischaemic CRVO have been claimed with this approach. Vitrectomy may be useful by increasing oxygenation to the retina and thus reduce neovascularisation ⁸. We hypothesise that vitreous PO₂ measured in patients with CRVO is reduced, compared to control, and this hypoxia may be reversed post-vitrectomy by replacement of the vitreous humour with a physiological saline solution.

Methods

The study was undertaken with approval from the local Ethics Committee and with informed patient consent, in accordance with the Helsinki declaration. Six patients with CRVO in one eye, were recruited into the study. As controls, six patients for either macula hole or epiretinal membrane removal with vitrectomy were used. The affected eye was dilated using a mixture of phenylephrine 2.5% and Tropicamide 1%. Three sclerotomies were prepared; the infusion canula was inserted but not switched on.

Flexible Licox (polarographic) O₂ electrodes (Revoxode, Model CC1.SB, 0.8 mm tip diameter) were used in combination with a Licox CMP monitor (Integra Neurosciences). The O₂ electrodes were calibrated at source and the O₂ and temperature sensitivity stored on a card accompanying the probe. The card was inserted into the monitor prior to use so that absolute values of PO₂ were obtained. The temperature in the eye was assumed to be 37°C and this value was set on the monitor setting. The oxygen probe was inserted in to the eye and oxygenation recordings were taken in the mid-vitreous cavity and pre-retinal vitreous inferior to the disc and away from visible blood vessels. The direction of the probe was slightly tangential to the retina as the recording area is about 5 mm behind the probe tip. A reading in each position was taken when the monitor value had settled, about 3-4 minutes and in agreement with the manufactures details of a 90% response time of about 290 s *ex vivo*. Values of pulse, arterial blood pressure and arterial O₂ saturation were also taken when recordings were taken.

After the first readings, a standard three-port pars plana vitrectomy was performed in which the posterior hyaloid was detached and removed if required. A second set of oxygenation recordings

were taken post-vitrectomy, with balanced salt solution replacing the vitreous humour. RON was performed in a radial fashion to avoid transecting the nerve fibres into the nasal optic disc in patients with CRVO. A specifically-designed micro vitreoretinal (MVR) blade was inserted to a depth of 2.5 mm, as described previously ⁶. If bleeding was observed, the infusion bottle was raised to stop the haemorrhage. The eyes in control patients underwent standard epiretinal membrane removal or macula hole surgery. Phacoemulsification was performed before vitrectomy if required. Post-operative follow up was conducted at 2, 4, 8 and 16 weeks.

To check the zero-value reading after use, to ensure no drift in output had occurred during the experimental period, three O₂ electrodes were placed in 50 ml Hartmann's solution containing 10 mM Na bisulphite to absorb dissolved O₂ (PO₂, 0 mmHg) and the monitor temperature sensitivity setting changed to the ambient value of the operating theatre. In each case the monitor displayed values of 0 mmHg.

Data are quoted as mean $\pm$ standard deviation. Paired or unpaired Student's t-tests were used to examine differences between data sets. The null hypothesis was rejected at $p < 0.05$.

Results

Data were obtained from six control patients (5 males, 1 female) and six with CRVO (1 male, 5 females) and are shown in Table 1. In one patient from each group, measurements were made only in the middle of the vitreous humour cavity, whereas in the remainder additional measurements were made adjacent to the retina. The ages of the patients ranged from 46 to 82 years of age with a mean of 65 years with no difference in the mean age of the two groups. The time interval of CRVO diagnosis to treatment was 2 to 12 months, with a mean of 8 months. With all patients the post-operative follow-up period ranged from 3 to 12 months, with a mean of 7 months. The median preoperative best-corrected visual acuity (BCVA) was 6/60 for control eyes and counting fingers (CF) for study eyes. The median postoperative BCVA was 6/12 for control eyes and CF for study eyes. None of the eyes suffered retinal or iris neovascularisation within the follow up period.

Cardiovascular variables were monitored throughout the recording period to ensure that variation in O₂ saturation or haemodynamics could not affect PO₂ readings in the vitreous cavity. In all patients O₂ saturation was more than 98% throughout. There were no differences in mean arterial blood pressure (MAPD) or heart rate (HR) between controls and patients with CRVO either pre- or post-vitrectomy. In addition vitrectomy had no effect on PO₂ at either site in control and CRVO groups. Data are shown in Table 1.

In control eyes, pre-vitrectomy the mean PO₂ adjacent to the retina (pre-retina) was significantly less than in mid-cavity, Table 1. Figure 1A shows that in all five eyes in which paired results were obtained there was a PO₂ gradient in the same direction between the two sites: the mean difference was 18.0 ± 16.0 mm Hg, but this varied between a large gradient in some, and minor in two eyes.

This PO₂ gradient was also observed in the CRVO group with a mean value of 10.3 ± 7.8 mm Hg. Furthermore, at both recording sites the mean PO₂ was significantly less in eyes with CRVO, compared to control eyes; figure 1A, table 1. In three patients (one control, two CRVO), PO₂ measurements were also taken immediately behind the lens. The values were not different from those in the mid-cavity and were not recorded in subsequent experiments so as to minimise the duration of the experimental procedure.

Post-vitrectomy PO₂ values were significantly greater than pre-vitrectomy at both recording sites and in both control and CRVO eyes. Furthermore, the negative gradient of PO₂ between the mid-cavity and pre-retinal sites were abolished in both groups; in the control group there was even a small reversed PO₂ gradient (i.e. pre-retinal PO₂ > mid-cavity PO₂), whilst in the CRVO group there was no significant gradient. The results are also summarised in Table 1 and shown in figure 1B.

Figure 1. PO₂ values in the vitreous cavity. A: Values pre-vitrectomy in the mid-cavity (closed circles) or immediately adjacent to the retina (closed squares) in control and CRVO patients. Mean values are shown as horizontal bars in each dot-plot. * p<0.05 control compared to CRVO for the measurement sites. B shows the results after removal of the vitreous.

Discussion

Intravitreal oxygen has not been measured previously in patients with CRVO, and in this pilot study it was reduced in eyes with CRVO compared to controls. The vitreous is in contact with the retina, ciliary body, lens and aqueous, all of which may provide diffusion of O₂ molecules into the vitreous. If the source of O₂ is from the retina this is consistent with a reduced retinal blood supply in these patients, as detected on fluorescein angiography and Doppler studies ⁹. Other conditions displaying retinal ischaemia, namely diabetic retinopathy, are also associated with low vitreal PO₂ ¹⁰⁻¹⁵. However, it is of note that only 2-3% of total ocular blood flow is directed to the retina ¹⁶, so that other sources of vitreal O₂ are likely.

With animal models, the PO₂ in the mid-vitreous is similar to that reported here in control human eyes ^{17,18}. In these studies a vitreal PO₂ gradient between the retinal and the anterior region near the lens was either absent, or very shallow - increasing towards the retina. However, close to the lens (<1 mm) PO₂ increased significantly. With this study in human eyes a PO₂ gradient was observed in control and CRVO eyes, but decreasing towards the retina. A similar, small gradient, has also been measured between anterior and mid-vitreous spaces in human eyes ¹⁹. Therefore, we hypothesise that in human eyes other fractions of ocular blood flow do indeed contribute significantly to vitreal O₂ content, and furthermore that the vitreous may actually be an O₂ source to the retina, especially during ischaemia. This study could not confirm the presence of submillimetre PO₂ gradients near to the retina: the polarographic O₂ probes used in this study measure the average value within about 1 mm of the probe surface (sampling volume about 45 nl); and for ethical reasons we avoided placing the electrodes within about 1 mm of the retina.

After removal of the vitreous and replacement with salt solution, vitreal PO₂ increased preoperatively, most likely due to prior bubbling the infusion bottle with air. We do not know how long these higher PO₂ levels persisted postoperatively, however in animal studies raised PO₂ levels persisted for up to eight weeks ¹⁸ and in a human study PO₂ levels were higher in patients re-investigated after previous vitrectomy ¹⁹. Vitrectomy may therefore be useful as a therapy for ischaemic eye conditions, particularly in the retina, e.g. as a potential mechanism for the improved prognosis for diabetic retinopathy ²⁰. The lack of similar PO₂ gradients post-vitrectomy suggests that O₂ diffusion into the vitreal chamber is facilitated by replacement of the vitreal gel with saline solution. This may indicate that O₂ can diffuse into the chamber more readily from different sources such as the ciliary body, the choroid or from the anterior segment of the eye through the cornea ²¹.

Visual recovery is improved in patients with CRVO after radial optic neurotomy ^{6,7}. However that may be due to the accompanying vitrectomy on oxygenation rather than decompression of the central retinal vein by RON ⁸. Indeed RON *per se* causes swelling of the optic nerve head in an animal model, which might increase pressure on the vein in the short term ²², and this may also occur in humans ³.

There were too few patients in this study to analyze the relationship between intravitreal PO₂ and other surrogate measures of retinal ischaemia such as fluorescein angiography. However, because PO₂ is reduced in CRVO patients, the need to find ways to improve their oxygenation is reinforced and several techniques are available. Hyperbaric oxygen breathing increases retinal and vitreal PO₂ in animals ²³ and has been tried in retinal vein occlusion ²⁴. This could be used overnight when

dark adaptation increases oxygen consumption ²³. Perfusion of the vitreous cavity with O₂-rich fluids either balanced salt solution or perfluorocarbon liquids may protect the retina from ischaemia ^{25,26}. Relative barriers to O₂ diffusion, such as silicone oil, should be avoided ²⁷.

The objective to increase oxygenation of the vitreous chamber should be offset by the caveat that increased PO₂ is implicated in the generation of nuclear sclerotic cataracts ^{10,28}. Therefore, a balance between maintaining sufficient oxygenation to support the viability of surrounding tissues but preventing the development of unwanted side-effects needs to be established. However, this pilot study has demonstrated reduced PO₂ measurements in the vitreous cavity of patients with CRVO. We propose that vitrectomy may be useful in increasing vitreous PO₂ thereby potentially improving oxygenation to the retina.

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