Outcomes of hyperbaric oxygen treatment for central and branch retinal artery occlusion at a major Australian referral hospital

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Abstract
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Introduction: This study analysed the treatment outcomes of patients that received hyperbaric oxygen treatment (HBOT) for retinal artery occlusion (RAO) at the Royal Brisbane and Women's Hospital in Brisbane, Australia between 2015 and 2021.
Methods: Retrospective study from patient records including 22 eyes from 22 patients that received HBOT for either central RAO (17 patients) or branch RAO (five patients). Patients received the Royal Brisbane and Women's Hospital RAO protocol for their HBOT. Analysis included best corrected visual acuity pre- and post-treatment, subjective improvements, side effects and patient risk factors were also recorded.
Results: Improvement in best corrected visual acuity was LogMAR -0.2 for central RAO on average with 8/17 (47%) experiencing objective improvement, 5/17 (29%) experienced no change and 4/22 (24%) experienced a reduction in best corrected visual acuity. Subjective improvement (colour perception or visual fields) was reported in an additional 4/17 patients, resulting in 12/17 (71%) reporting improvement either in visual acuity or subjectively. There was no improvement in the best corrected visual acuity of any of the five patients suffering from branch RAO. Cardiovascular risk factors present in the cohort included hypertension, hypercholesterolaemia, previous cardiovascular events, cardiac disease and smoking. Limited side effects were experienced by this patient cohort with no recorded irreversible side effects.
Conclusions: Hyperbaric oxygen treatment appears a safe, beneficial treatment for central RAO. No benefit was demonstrated in branch RAO although numbers were small. Increased awareness of HBOT for RAO resulting in streamlined referrals and transfers and greater uptake of this intervention may further improve patient outcomes.

Introduction

The retina has an increased sensitivity to hypoxic states due to its high oxygen demand.[1,2] Central retinal artery occlusion (CRAO) or branch retinal artery occlusion (BRAO) can lead to profound and irreversible visual loss by hypoxic injury to the inner retina – usually within 4–6 hours.[3] In the acute phase, there are currently limited treatment options in both trying to resolve the occlusion and/or minimise the degree or duration of retinal hypoxia/ischaemia.

Hyperbaric oxygen treatment (HBOT) works by inhalation of 100% oxygen at pressures greater than atmospheric, which markedly increases dissolved oxygen tension in plasma. This mechanism is used to attempt to increase the oxygen delivered to the inner retina via the choroidal circulation while the central/branch retinal artery is compromised. The treatment may be required multiple times for an extended period, until the retinal artery or branch recanalises which is typically in the first 72 hours.[4]

This study reports on the outcomes of patients with acute CRAO and BRAO receiving HBOT at The Royal Brisbane and Women's Hospital (RBWH), a large tertiary referral centre in Queensland, Australia.

Methods

Ethics approval exemption was granted by the Human Research Ethics Committee of the Royal Brisbane and Women's Hospital. (Reference. EX/2022/QRBW/84263). The study was performed in line with the principles of the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

Figure 1

Pathway in the Royal Brisbane and Womens Hospital (RBWH) central retinal artery occlusion (CRAO) hyperbaric oxygen treatment (HBOT) protocol; BCVA – best corrected visual acuity; FiO_2 – fraction of inspired oxygen; VA – visual acuity

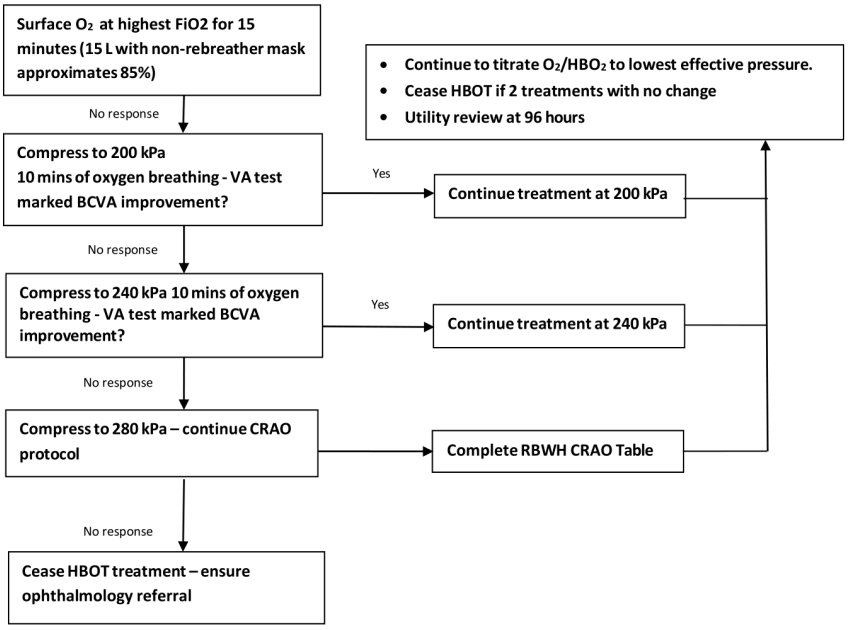
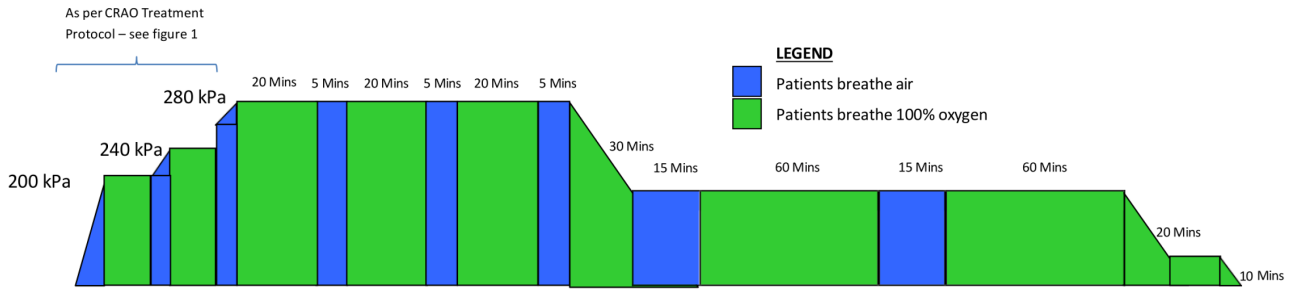


Figure 2

Hyperbaric oxygen treatment protocol for central retinal artery occlusion (CRAO) (see also Figure 1) designed to titrate the minimum treatment pressure to attain a 'marked improvement' in the patient's visual acuity



CLINICAL DATA COLLECTION

All patients presenting to the Royal Brisbane and Women's Hospital with CRAO and BRAO that received HBOT between 2015 and 2021 were included. Data points collected were patient risk factors (including age, sex, hypertension, smoking history, hyperlipidaemia, atrial fibrillation, and diabetes), best corrected visual acuity (BCVA) prior to treatment and after treatment, subjective improvement in visual acuity as reported by the patient, time to intervention from beginning of symptoms, maximum compression pressure, number of HBOT treatments and side effects of treatment. Visual acuity measured with Snellen charts was converted to the logarithm of the minimum angle of resolution (logMAR) using standard conversion charts for statistical analysis. Change in logMAR visual outcome was calculated by subtracting the initial logMAR BCVA from the final logMAR BCVA. Hyperbaric oxygen treatment was utilised as monotherapy in all included patients during the acute phase of their management.

HYPERBARIC OXYGEN TREATMENT AND MANAGEMENT

Ophthalmology registrars and consultants examine patients with suspected CRAO/BRAO in the emergency department and hyperbaric medicine consultants assess and instigate HBOT after the diagnosis is confirmed. Once confirmed, patients will then receive their first round of HBOT while still an emergency department patient where possible.

The HBOT given utilises the 'RBWH CRAO protocol' (Figure 1, pathway in the RBWH CRAO protocol and Figure 2, hyperbaric oxygen treatment protocol). This protocol is adapted from the Undersea and Hyperbaric Medical Society (UHMS) HBO_2 indications book

(14th edition).[5,6] As the aim of the therapy is to protect the retina from hypoxic injury while the retinal artery occlusion recannalises, the protocol utilises HBOT at the lowest pressure at which the patient has a marked improvement in their BCVA. Patients are maintained at lower pressures if marked improvement in BCVA is made prior to getting to the maximum 280 kPa absolute compression pressure specified in the RBWH CRAO protocol. The flow chart in Figure 1 demonstrates the HBOT pathway available to the hyperbaric medical team.

After initial HBOT treatment, patients are then admitted under a medical team with hourly checks of their BCVA. Whilst patients are on the medical ward, they receive 15 minutes of oxygen at15 $L \cdot min^{-1}$ via a nonrebreather mask every hour and breathe room air for 45 minutes in the hour. If any loss of BCVA is detected during the hourly observations or detected after any changes noted by the patient, further HBOT is considered immediately. In the absence of deterioration, the same protocol is then followed for further HBOT treatment the following day. Once no further improvement is realised, HBOT is ceased, the total number of cycles that were used was then recorded. The medical team also assesses the patients for cerebrovascular risk factors, investigates and where appropriate commences secondary prevention of cerebrovascular disease.

STATISTICAL ANALYSIS

Summary statistics were presented as mean and standard deviation for continuous variables and as number and percentage for categorical variables. Multiple linear regression was used to investigate the effect, on the dependent variable of change in logMAR BCVA, of the independent variables of age, delay to initiation of HBOT, number of HBOT cycles and maximum compression pressure reached. Stata IC version 16.1 for Mac was used for regression analysis and to generate figures.

Results

Twenty-two eyes of 22 patients were included in the study. Patients comprised 15 males and seven females with a mean age of 64 years. Seventeen of the 22 patients had CRAO and five of the 22 patients had BRAO. Baseline characteristics are summarised in Table 1.

CRAO PATIENTS

Pre-HBOT BCVA of CRAO patients ranged from perception of light only to 6/60 (LogMAR 2.7 – LogMAR 1.0). After treatment there was an average improvement of LogMAR -0.2 ranging from a final BCVA of no perception of light to 6/12 (LogMar 3.0 – LogMAR 0.3).

Of the 17 patients with CRAO, 8/17 (47%) had an objective improvement in their BCVA, 5/17 (29%) had no change and 4/17 (24%) had a reduction in their BCVA. Four of the five patients that did not have an objective improvement in their BCVA, did report subjective improvement in their vision such as brighter colours, or subjective reduction in visual field defect.

Table 1
Baseline and hyperbaric oxygen treatment (HBOT) characteristics of central (CRAO) and branched retinal artery occlusion (BRAO) patients; SD – standard deviation

Retinal artery occlusion type	CRAO (*n* = 17)	BRAO (*n* = 5)
Age, years mean (SD)	67.4 (14.6)	51.0 (21.9)
Sex, *n* (%)		
Male	11 (65)	4 (80)
Female	6 (35)	1 (20)
Risk factors, *n* (%)		
Hypertension	11 (65)	3 (60)
Hyperlipidaemia	8 (47)	1 (20)
Former smoker	5 (29)	1 (20)
Current smoker	3 (18)	0 (0)
Atrial fibrillation	1 (6)	1 (20)
Diabetes	1 (6)	0 (0)
HBOT factors, mean (SD)		
Delay to HBOT, hours	12.4 (4.9)	15.5 (6.4)
Number of cycles	6.5 (5.1)	4.0 (3.7)

Mean delay to treatment time in CRAO patients was 12 hours, range 3–24 hours. Maximum compression pressures were 280 kPa for 16 out of 17 patients and 1 patient received treatment to a maximum of 240 kPa. Patients received on average 6.5 compression cycles, range of 1–18 (Table 1).

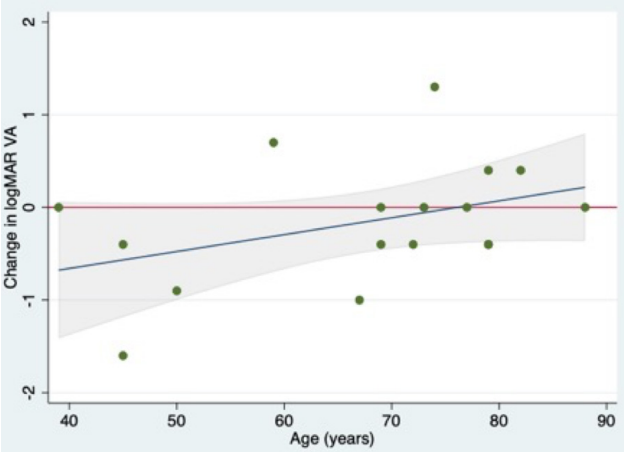
For CRAO patients, multiple linear regression analysis failed to predict the dependent variable of change in logMAR visual acuity with the independent variables of age, delay to HBOT or number of HBOT cycles, $F(3,12) = 1.46$, $P = 0.28$, adjusted $R^2 = 0.08$. Table 2 breaks down the results of regression analysis for each variable. Maximum HBOT pressure could not be used in the linear regression analysis due to collinearity as all values for CRAO patients, except one, were 280 kPa.

Given the low sample size ($n = 17$) and the relatively low P-value for age ($P = 0.08$), graphical analysis and simple linear regression were performed with only age as the independent variable and change in logMAR VA as the dependent variable to investigate this relationship in more detail. Figure 3 shows the results of this regression analysis. This model, again, did not statistically significantly predict the change in logMAR visual acuity, $F(1,15) = 2.79$, $P = 0.12$, adjusted $R^2 = 0.10$, with a slightly smaller effect

Table 2
Multiple linear regression for change in logarithm of the minimum angle of resolution (logMAR) visual acuity for central retinal artery occlusion patients; SE – standard error

Variable	Coefficient	SE	*t*	*P*-value	95% confidence interval
Age	0.0207	0.0110	1.88	0.08	-0.0033 to 0.0447
Delay	-0.0343	0.0387	-0.88	0.39	-0.1187 to 0.0502
Number of cycles	-0.0444	0.0371	-1.20	0.25	-0.1252 to 0.03636
Intercept	-0.8011	0.8854	-0.90	0.38	-2.7302 to 1.1281

Figure 3
Dependent variable change in logarithm of the minimum angle of resolution (logMAR) visual acuity by age for patients with CRAO



size for age (coefficient = 0.0182, SE = 0.0109, t = 1.67, P = 0.12).

Simple linear regression analysis was performed and is illustrated in Figure 3: dependent variable change in logMAR VA by age for patients with CRAO. The blue line represents the multiple least squares regression line. Grey shading represents the 95% confidence interval for the regression line. The red line is at y = 0, representing no change in VA.

Recorded side effects in the CRAO patients were limited to haemotympanum (three patients) and anxiety (two patients).

BRAO PATIENTS

Pre-HBOT BCVA ranged from no perception of light to 6/5 (with central scotoma) (LogMar 3.0 – LogMar -0.1). After treatment the post-HBOT BCVA ranged from no perception of light to 6/5 (with central scotoma) (LogMar 3.0 – LogMar -0.1). One patient described a decreased scotoma subjectively. However, of the five BRAO patients, none had any change in their BCVA.

Mean delay to treatment time in BRAO patients was 16 hours. Maximum compression pressures were 280 kPa for four patients and 240 kPa for one patient. Patients received on average four compression cycles, with a range of 1–10 (Table 1).

For BRAO patients, multiple linear regression could not be used as all patients had no change in logMAR BCVA, making all variables multicollinear. Side effects in the BRAO patients were limited to one of the five patients who needed frequent stops for anxiety associated with the apparatus.

A patient summary including occlusion type (branch or central), presenting BCVA, intraocular pressure, and BCVA post treatment is presented in Table 3.

Discussion

This study reviews the experience at the RBWH with hyperbaric oxygen therapy for the treatment of CRAO and BRAO. The use of HBOT for retinal artery occlusion is controversial among ophthalmologists as its potential benefit is variable and this is shown in our results where any visual acuity recovery was variable.

As previously reported, the rate of objective improvement in BCVA in CRAO patients receiving HBOT varies widely. Previous studies have shown objective improvement in BCVA in 29–59% of patients, with a mean logMAR improvement ranging from -0.05 to -0.53.[7–9] Conversely, a recent meta-analysis concluded that there was no significant change in BCVA post HBOT.[10] The authors did however suggest that subgroups of patients receiving early HBOT did show improvement in several of the studies.[10]

One major contributor to this variability may be the average time to initial HBOT treatment from onset of symptoms. In previous reports with early HBOT initiation this delay has ranged from 5.3 to 8.4 hours. Although other studies have shown a potential benefit of early HBOT,[11,12] only four of the 17 CRAO patients in our study received HBOT within eight hours of the onset of symptoms and of these patients only one showed improvement in BCVA. Our analysis confirmed that

Table 3
Presenting best corrected visual acuity (BCVA), intraocular pressure (IOP) (measured with either iCare IC100 or iCare IC200 handheld tonometer) and final BCVA; CF –count fingers; F – female; HM – hand movements; M – male; NPL – no perception of light; PL – perception of light

Patient ID	Age	Sex	*n* HBOT	CRAO/ BRAO	Initial IOP (mmHg)	Initial BCVA	Final VA	Subjective improvement noted (if applicable)
1353	74	M	8	CRAO	22	6/60	HM	Visual field
1719	79	M	3	CRAO	23	HM	CF	Visual field
1757	67		12	CRAO	11	CF	6/48	Visual field
1818	79	F	18	CRAO	21	CF	HM	Visual field
1859	77	F	3	CRAO	13	PL	PL	Colour perception, brighter light
1871	73	M	3	CRAO	12	HM	HM	Visual field, luminance
1946	79	F	8	CRAO	14	PL	HM	Visual field, brightness
1991	51	F	5	BRAO	14	6/6, inferior quadrantanopia	6/6, inferior quadrantanopia	
2153	18	M	1	BRAO	14	6/5, central scotoma	6/5, central scotoma	
2171	45	M	16	CRAO	14	CF	6/12	Visual field
2230	50	F	3	CRAO	13	CF	6/60	Luminance
2247	57	M	3	BRAO	20	6/7.5, scotoma	6/7.5, scotoma	Visual field
2251	69	M	1	CRAO	10	HM	HM	
2260	50	M	1	BRAO	23	6/6, temporal quadrantanopia	6/6, temporal quadrantanopia	
2280	72	M	11	CRAO	16	HM	CF	
2333	82	M	8	CRAO	12	HM	PL	
2365	69	F	8	CRAO	16	PL	HM	Visual field
2397	45	M	6	CRAO	18	HM	CF	
2414	39	F	1	CRAO	12	HM	HM	
2441	88	M	2	CRAO	13	HM	HM	
2457	59	M	1	CRAO	9	HM	NPL	
2573	79	M	10	BRAO	10	NPL	NPL	

there was no statistically significant relationship between shorter delay to initial HBOT and improvement in logMAR BCVA in our cohort.

Among all our CRAO patients, the average time to initial HBOT treatment was longer at 13 hours with a range of 3–24 hours. This can be partly explained by the large geographical catchment area of the RBWH and the increased time it can take patients to present to hospital. Despite this delay, in patients with CRAO who received HBOT, 47% of patients had an objective improvement in their BCVA and 24% reported subjective improvement including decrease in visual field defects, brighter perception of light or greater perception of colours. In terms of trying to identify those patients who may improve, unfortunately our CRAO results also could not identify a factor that was a significant predictor of BCVA improvement after HBOT e.g., age or pre-HBOT BCVA. A post-hoc power analysis showed that the regression analysis investigating the relationship between age and change in logMAR BCVA was underpowered at around 0.09, therefore, despite a visible graphical relationship and close *P*-value for the relationship between age and outcome, this analysis could not detect a correlation beyond chance. We suspect this may not be the case with a larger sample.

Although other studies have shown significant BCVA improvement in 75% of patients post-HBOT,[2] our patients did not show any change in BCVA after treatment albeit in a small five patient group.

In terms of side effects of HBOT, these were limited to five patients in the cohort, three experienced haemotympanum and another two patients had several breaks during treatment due to anxiety. The rare side effects discussed in the literature such as severe barotrauma or generalised seizures were not seen.[10]

Future studies may benefit from utilising a protocolised diagnostic workup for patients presenting with CRAO. Consistent recording of the presence or absence of a cherry red spot which has been shown to be an important prognosticator and may be used to guide therapy is warranted.[7] Fundus fluorescein angiography also provides important diagnostic and prognostic information, for CRAO allowing further classification into subtypes including non-arteritic CRAO (NA-CRAO), NA-CRAO cilioretinal artery sparing, transient NA-CRAO and Arteritic CRAO as described by others.[13] Visual field testing at time of diagnosis and after treatment would also allow the clinician to separate true improvement in BCVA from eccentric fixation that may confound changes in BCVA after treatment.[13]

Conclusions

In summary, objective logMAR BCVA improvement was seen in 47% of CRAO patients but no improvement was seen in any BRAO patient in our cohort. No patient factor was identified which might predict an improvement in BCVA with HBOT. Although our cohort had minimal side effects from HBOT, it is clear from the current limited evidence that larger randomised studies are required to better understand the efficacy and safety of HBOT in treatment of RAO.

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