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Hyperbaric Oxygen Therapy in Ophthalmic Practice: An Expert Opinion

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Abstract

Introduction: There has been a growing interest in hyperbaric oxygen therapy (HBOT) in recent years across multiple disciplines. In the field of ophthalmology, the implications of increased HBOT use may include expanded applications in treating ocular vascular pathologies as well as a greater incidence of HBOT-induced visual complications.

Areas covered: The authors review recent studies on HBOT usage in the treatment of ocular conditions. In addition to providing updates on the ophthalmic indications of HBOT, adverse visual effects of HBOT are also investigated.

Expert opinion: Further evidence substantiating HBOT as an effective treatment modality for ocular vascular pathologies, such as central retinal artery occlusion and diabetic retinopathy, have been published in recent years. With the identification of more prognostic factors, increased success in HBOT has been reported. However, studies also show that adverse ocular effects associated with hyperbaric oxygen exposure include myopia and cataracts. It is important to recognize the risks of iatrogenic changes in visual acuity when considering patients for HBOT.

Keywords: Hyperbaric oxygen, central retinal artery occlusion, diabetic retinopathy, myopia, cataracts, ocular complications

Article Highlights

- The authors review recent studies on hyperbaric oxygen therapy (HBOT) usage in the treatment of ocular conditions as well as the potential adverse visual effects of therapy.
- In the past few years, clinical studies have highlighted HBOT for ocular vascular pathologies, such as central retinal artery occlusion (CRAO) and diabetic retinopathy (DR).
- For CRAO, studies have reported more promising clinical outcomes, with many attributing HBOT success to predictive factors, such as time lag from symptom onset and the degree of pathologic retinal architecture.
- DR is emerging as an indication of HBOT with recent evidence indicating that hyperbaric oxygen exposure may reduce blood-retinal barrier breakdown.

- Complications of HBOT include the development of myopia and cataracts which are believed to be the result of the increased oxidative stress associated with treatment.
- The risk of adverse effects from HBOT may be related to factors such as duration, frequency, and route of administration.

1.0 Introduction

Ophthalmologists may have experience with hyperbaric oxygen therapy (HBOT) as both a treatment modality and a potential cause of ocular pathology. Characterized by the administration of 100% oxygen at pressures exceeding 1.0 atmosphere absolute (ATA), HBOT is used for various conditions ranging from scleral necrosis to diabetic ulcers [1]. The benefits of HBOT include correcting tissue hypoxia by increasing oxygen delivery [1], promoting healing by encouraging stem cell mobilization [1] and neovascularization [2], and exerting antimicrobial effects through the generation of reactive species [3]. In ophthalmology, these effects may be leveraged as therapy for vascular diseases, infections, and injuries [4]. Despite its therapeutic utility, hyperbaric oxygen has also been linked to several adverse visual changes including myopic shifts and cataract formation [5,6]. Although most complications resolve with the cessation of treatment, patients can suffer permanent unintended changes in vision as a result of HBOT. Herein, the authors review recent advancements in the understanding of HBOT both as a treatment for ocular pathologies and as a source of ocular complications.

2.0 Updates on Ophthalmic Indications of HBOT

Previously recommended applications of HBOT included a variety of ocular conditions ranging from infections such as rhino-orbital mucormycosis to conditions such as scleral necrosis [5]. Over a decade ago, several cases of scleral necrosis refractory to conventional care were successfully treated with daily 90 minute sessions of HBOT at 2.0 or 2.5 ATA [7,8]. Similarly, adjunctive HBOT with first-line treatment of surgical debridement and amphotericin B has been shown to improve outcomes in rhino-orbital mucormycosis when compared to standard therapies alone [9,10].

In recent years, clinical studies have fostered support for the use of HBOT in treating retinal vascular pathologies, such as central retinal artery occlusion (CRAO) and diabetic retinopathy (DR).

2.1 Central Retinal Artery Occlusion

Effective treatment of CRAO is of particular interest due to the acute onset of vision loss, significant functional morbidity, and relative intractability [11]. By enhancing oxygen delivery to ischemic retinal tissue, HBOT can serve as an acute therapy for CRAO aimed at minimizing vision loss prior to recanalization [12]. During HBOT, the increased partial pressure of oxygen has marked effects on ophthalmic vasculature, causing reversible vasoconstriction in both the arterioles and venules of the retina [13]. Despite this vascular response, the retina can remain adequately oxygenated due to the tremendous elevation of plasma oxygen within the choriocapillaris during treatment [5]. This is supported by the observation of bright red blood in the retinal veins and an increase in venous hemoglobin oxygen saturation [14-16]. As a result, the

hyperoxygenated choroidal vasculature can satisfy the entire retinal oxygen demand [5,17], with animal studies showing adequate oxygenation despite retinal artery occlusion [18] (Figure 1).

Early investigations of HBOT for CRAO reported varying results (Table 1A). In 2001, a retrospective study of 35 HBOT-treated patients and 37 matched controls demonstrated improvement of visual acuity in 82% of patients in the hyperbaric group compared to only 29.7% in the untreated group. The mean improvements as measured by Snellen chart were 0.1957 and 0.0457 respectively [19]. This is consistent with the findings of previous case studies showing enhancement of visual acuity in patients with CRAO post-HBOT [20,21]. However, a clinical trial in 2000 investigating HBOT in CRAO patients 1 day after symptom onset reported no significant difference in vision between the HBOT group and the control group receiving standard therapy of ocular massage, paracentesis, and intravenous acetazolamide [22]. Another failure of HBOT was reported in a case of CRAO in which there was complete occlusion of the retinal artery [23]. Still, recent studies have reported more promising clinical outcomes, with many indicating near or complete restoration of visual acuity post-HBOT [12,24-28].

The increase in the proportion of successful HBOT for CRAO usage in recent years likely results from identification of factors that contribute to patient prognosis. One such factor is the time between symptom onset and initiation of HBOT. Widespread recognition of CRAO as an emergent condition, often requiring prompt administration of multiple lines of treatment, has led to the reduction in HBOT referral time. Multiple recent case reports have attributed their success to the prompt delivery of HBOT from CRAO onset [25-27]. Given that irreversible damage begins

after 4 hours of retinal ischemia [29-31], the best outcomes have been documented when applying HBOT within 6-8 hours of symptom onset [32]. Various fundus findings, including the presence of a cherry-red spot, change in macular thickness, and degree of disorganization of retinal inner layers, are emerging as clinical markers that predict HBOT response. Hadanny et al. proposed that using a visible cherry-red spot as a physiologic indicator for reduced HBOT efficacy may be more predictive than the time lag from CRAO onset [33]. Other negative correlates of HBOT success are pathologic retinal architecture and macular thickening, which are both direct signs of ischemic severity and progression [28]. On the other hand, a positive physiologic indicator of HBOT success is the presence of cilioretinal collaterals, an anatomic variant seen in close to 20% of the population [34].

HBOT is a non-invasive and safe option for CRAO patients, especially in comparison to other means of treatment, such as paracentesis or intra-arterial fibrinolysis. The adverse effect rate of HBOT in the CRAO population was reported by a large-scale cohort study to be 5.5% with only minor and transient symptoms (e.g. middle ear/sinus barotraumas) experienced [33]. In contrast, the complications associated with thrombolytic therapy include hemorrhage, hypertensive crisis, and stroke [35]. Although promising, existing evidence is limited by small sample sizes and HBOT remains reserved for cases of refractory CRAO.

2.2 Diabetic Retinopathy

An emerging indication for HBOT, DR is one of the leading causes of vision impairment worldwide. The pathophysiology underlying hyperglycemia-induced visual decline is

characterized by a loss of pericytes and basement membrane thickening [36]. These changes often lead to vascular endothelial growth factor (VEGF)-initiated blood-retinal barrier (BRB) breakdown and, consequently, formation of macular edema or uncontrolled neovascularization resulting in blindness [37]. Since hyperoxia decreases expression of VEGF in the adult retina [38], HBOT may ameliorate diabetic BRB breakdown. This is consistent with the finding that long-term HBOT significantly lowers vascular permeability in a murine model of DR [39]. Treatment with HBOT in a case of diabetic macular edema resulted in bilateral improvement in vision from 20/125 to 20/63 in the right eye and 20/320 to 20/160 in the left eye after 14 sessions over the course of 1 month [40]. Although macular edema reoccurred in the succeeding months, HBOT controlled visual decline each time [40]. The reported success in long-term management of DR with HBOT suggests a potential delay in disease progression (Table 1B). Similarly, two clinical trials of patients with macular edema both reported improvements in visual acuity after chronic HBOT [41,42]. One showed improvement by 2 lines or more in 68% of eyes whereas the other reported a mean increase of 3.5 lines [41,42]. Recently, one prospective cohort study found that HBOT has a thinning effect on the macula in diabetic eyes [43], further supporting the hypothesized mechanism of hyperbaric oxygen on BRB breakdown. These early results are encouraging and indicate that HBOT may be used to treat ocular complications of diabetes mellitus.

3.0 Adverse Ocular Effects of HBOT

Although HBOT has shown promise in the treatment of various conditions, it has also been associated with adverse ocular effects in patients with otherwise healthy eyes. The rise in arterial oxygen tension leads to the production of reactive oxygen species (ROS), which can incur

oxidative stress on the crystalline proteins of the lens [6,44]. Consequently, ocular complications such as myopia or cataract formation have been observed (Figure 2).

3.1 Hyperoxic Myopia

Progressive myopia is a well-known and commonly reported complication of HBOT that occurs at a rate of approximately 0.25 diopters per week (Table 2A) [45-48]. It is estimated that 60% of patients undergoing HBOT will develop at least a 1-line change on Snellen eye chart [49]. In 1978, Lyne documented a myopic shift ranging from 0.5 to 5.5 diopters in a series of patients receiving HBOT at 2.5 ATA. The myopia progressed in severity throughout treatment and gradually reversed upon completion [50]. A recent longitudinal study reported similar findings, with an average myopic shift of 0.95 diopters after 30 sessions at 2.4 ATA [51]. Interestingly, the investigators observed a transient reversal of the myopia during treatment, initially occurring after 5 sessions and then again after every 10 sessions. The repeated shift towards hypermetropia was short-lived and small compared to the overall trend towards myopia [51]. Nonetheless, these findings could help explain limited reports of hypermetropia after HBOT [52-54]. Although treatment pressures typically range from 2.0 to 3.0 ATA, hyperoxic myopia has even been reported in pressures as low as 1.3 ATA [55]. The myopic shift generally reverses within 3 to 6 weeks after discontinuing HBOT but can persist for as long as 6 to 12 months [5]. While there are concerns of permanent visual acuity changes in patients receiving hundreds of treatments [45], this level of exposure is exceedingly rare under current practices.

Hyperoxic myopia and short-term hypermetropia are thought to be related to oxidative changes that alter the refractive index of the crystalline lens [51]. Lenticular involvement is further supported by the absence of myopic shifts in pseudophakic eyes [56], and previous studies have excluded other factors such as changes in retinal thickness due to vasoconstriction [47], axial length and anterior chamber depth [46,50,57], corneal shape [46,48,50,57], and lens thickness [46,57]. It is thought that HBOT affects the refractive index of the nucleus and the deeper layers of the lens cortex [51]. Since the refractive index gradient of the lens is determined by its composition of structural proteins and water [58], hyperoxia may modify protein concentrations and local water distribution, leading to a reduction in backscattered light and optical density [54].

It may be possible to reduce the risk of refractive change by decreasing the pressure of oxygen in direct contact with the eyes [44,59]. In studies of patients given HBOT either by hood or oronasal mask, the myopic shift was markedly lower in the latter group where the eyes were kept from direct contact with hyperbaric oxygen. Patients receiving oxygen by mask also demonstrated a lower incidence of myopia and shorter recovery times for visual acuity. This suggests that lenticular oxygen toxicity may stem from both local and systemic effects of hyperoxia [59]. It has also been reported that the risk of oxygen toxicity can be reduced by providing 5 minutes of room air for every 20 to 25 minutes of HBOT [6], and there is evidence to suggest that decreasing treatment pressure reduces the likelihood of myopic change [49,60]. This may even be applicable to conditions of acute ischemia (e.g. CRAO) given that the proposed benefits of HBOT are attributed to the elevation of oxygen within the choroidal vasculature as opposed to the oxygen in direct contact with the retina [17,18]. Taking these steps to minimize lenticular oxygen toxicity

may prevent the development or limit the severity of hyperoxic myopia, preserving quality of life for patients undergoing treatment.

2.2 Cataracts

Another potential, but lesser seen complication of HBOT is the formation and progression of nuclear and cortical cataracts (Table 2B) [45,61,62]. Palmquist et al. reported the occurrence of cataracts in patients undergoing extensive HBOT regimens involving at least 150 exposures at 2.0 to 2.5 ATA. In this study of 15 patients with clear lenses, 7 developed nuclear cataracts over the course of treatment. The authors noted that despite the discontinuation of treatment, the changes in lens opacities were not completely reversible [45]. Current HBOT regimens seldom exceed 75 sessions [44], and there is evidence to suggest that many indicated chronic conditions can be appropriately treated with as few as 30 sessions [63]. Although cataracts are less likely to form under these durations, there have been reported cases in patients receiving as few as 46 treatments at 2.5 ATA [61,62]. A prospective study conducted by Riedl et al. also found a significant increase in nuclear color and opalescence, two characteristics of nuclear cataract, following 40 sessions of HBOT. The change in lens transparency appeared be linearly related to exposure and persisted on examination 12 weeks after treatment [64]. On the other hand, a previous study conducted by Evanger et al. found no such changes in nuclear color or opalescence in patients undergoing 21 sessions of HBOT [59]. Nonetheless, the formation or progression of cataracts represents a permanent change to the lens that may necessitate lens replacement surgery.

Although the mechanism is not fully understood, it is believed that cataracts form due to oxidative stress to the crystalline lens [61]. It has been suggested that the nucleus of the lens is particularly susceptible to oxygen toxicity as opposed to the cortex or the epithelium [64]. The nucleus contains lower amounts of important antioxidants such as glutathione [65-67], which is essential in maintaining the transparency of crystalline proteins in the lens [67,68]. Animal studies have shown that lenticular glutathione decreases significantly after in vitro exposure to HBOT [66], with damage to the lens progressing from the periphery to the center [69]. Furthermore, the lenticular damage accumulates throughout treatment, with greater exposure causing greater damage [69]. As a result, treating guinea pigs with hyperbaric oxygen produces protein aggregates and peptides suspected to be involved in cataractogenesis [70-73].

Cataracts are more common with increasing age and more prevalent in older patients receiving HBOT [45,74]. Though myopia has been associated with an increased risk for nuclear, cortical or posterior subcapsular cataracts [75-79], the development of myopia does not necessarily precede cataract formation since the latter can cause refractive changes towards myopia before detection [80]. Consequently, finding a myopic shift could be an early sign of cataract development [54,64]. Given that cataract formation is an irreversible complication of HBOT, it is important to adequately counsel patients on this possibility and its long-term implications prior to initiating treatment.

3.0 Conclusion

HBOT has long been recognized for its potential in treating ocular conditions such as rhino-orbital mucormycosis and scleral necrosis. Recent literature indicates that HBOT can also be an effective treatment modality for certain ophthalmic vascular diseases. Concerns regarding its efficacy in CRAO have been moderated by the identification of new prognostic factors, such as HBOT referral time and physiological indicators of ischemia severity. In DR, preliminary evidence supports HBOT as a method of mitigating BRB breakdown and would be especially recommended for diabetic patients with macular edema.

Although HBOT is an effective treatment modality for various hypoxia-related conditions, it also presents a distinct set of ocular risks. While hyperoxic myopia is a common but transient side effect of treatment, cataract formation is an infrequent but irreversible complication only correctable through surgery. While the treatment of acute conditions is unlikely to incur adverse ocular effects, treatment for chronic conditions may warrant further consideration for ocular implications. Despite the possibility of unintended visual acuity changes during HBOT, the risks are manageable with adequate counseling prior to therapy and careful monitoring throughout care.

Expert Opinion

HBOT may play an important role in the treatment algorithm of ocular conditions either as a primary or adjunct therapy. In the field of ophthalmology, recent evidence supports its usage especially for vascular pathologies, such as CRAO and DR. Increased utilization of HBOT may salvage sight in otherwise refractory cases of CRAO and may be an effective treatment option in

DR. However, several challenges can deter its widespread integration into the current standard of practice. First, the current level of evidence supporting HBOT efficacy remains low. Although recent literature has reported positive results, the majority of studies are observational in nature and limited by small sample sizes. Second, there are concerns regarding the potential adverse effects of HBOT. Studies suggest that long-term hyperbaric oxygen exposure may result in the development of myopia and cataracts. Although the number of sessions typically used in the treatment of most ophthalmic conditions is relatively low, there remains a risk of iatrogenic changes in visual acuity. Fortunately, the likelihood of complications is rare as reported by two recent randomized controlled trials [81].Third, there is limited accessibility to hyperbaric facilities and the expenses associated with maintaining and providing HBOT may be prohibitive to some institutions and patients. In the United States, the cost of a 90-minute treatment session is approximately $200 to $500 [82]. However, treatment is often more affordable than the alternatives for debilitating conditions such as central retinal artery occlusion (i.e. fibrinolytics), and largely justified when considering the potential for increased efficacy as well as the consequences of failed treatment.

It should also be noted that with the evolving trends in HBOT use across multiple disciplines, more cases of HBOT-related ocular complications may be encountered in ophthalmic practice. As some investigators have hypothesized, the nucleus of the lens lacks an effective defense to hyperoxia because oxygen cannot readily diffuse under normal conditions [64]. Consequently, the increased production of ROS during HBOT may cause ocular damage through oxidative stress to lenticular proteins [6,44]. It is now generally understood that oxygen toxicity plays a central role in

the development of myopia and cataracts, however, further studies are needed to elucidate the precise mechanisms of ocular involvement.

To minimize the adverse effects of HBOT, it may be appropriate to conduct eye examinations prior to treatment to detect pre-existing conditions and follow changes in visual acuity, refraction, and lens status should they occur. Furthermore, to mitigate changes in visual acuity, it may be advisable to administer HBOT using an oronasal mask instead of by hood or chamber.

Future research involving controlled trials with more participants will help clarify best practices regarding HBOT usage. These studies should aim to elucidate the role of HBOT in ocular treatment and determine the optimal regimens of care. Further clarification of the prognostic factors will aid in the identification of specific patient subgroups that would benefit most from treatment. As we continue to enhance our understanding of the physiologic response to hyperoxia, we will be able to better identify therapeutic applications and limit adverse effects.

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Declaration of Interests

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Table 1A. Summary of included primary literature investigating HBOT for central retinal artery occlusion.

Reference	Study Type	Sample Size	Pressure	Duration	Sessions	Follow-Up Time	Key Findings
Masters et al. (2019)[24]	Retrospective Cohort	39	2.4 ATA	90 min.	10	Immediately after last session	Mean improvement in VA of 5.05 lines on modified Snellen
Johnson et al. (2019)[27]	Case Series	4	2.5 – 2.8 ATA	90 min.	2.5 – 5	Immediately after last session	65 – 70% improvement in VA
Weymouth et al. (2019)[26]	Case Report	1	1.0 – 1.82 ATA	60 min.	2	Immediately after last session	VA improved from light perception to 20/50 after 1 day of HBOT
Yilmaz et al. (2019)[28]	Retrospective Cohort Study	28	-	90 min.	Mean of 14	Mean of 11 months	Mean improvement in logMAR BVCA of 0.85 ± 0.97 Disorganization of retinal inner layers and change in MT highly correlated with post-HBOT BCVA
Bagli et al. (2018)[25]	Prospective Cohort Study	10	2.4 ATA	120 min.	20	Immediately after last session	Improvement from mean VA of logMAR 3 to 1.8
Kim et al. (2018)[12]	Case Report	1	2.8 ATA	140 min.	3	1 month	Improvement from hand motion VA to 0.4 for far vision and 0.5 for near vision on decimal scale
Hadanny et al. (2016)[33]	Retrospective Cohort Study	128	2.0 – 2.4 ATA	90 min.	Mean of 4	Immediately after last session	Mean improvement in BCVA of logMAR 0.526 ± 0.688 Macula cherry-red spot associated with worse outcomes

Mori et al. (2007)[23]	Case Report	1	-	-	-	1 month	No visual improvement with documented involvement of the ophthalmic artery
Beiran et al. (2001)[19]	Retrospective Cohort Study	72	2.8 ATA	90 min.	≥ 9	Immediately after last session	Significant mean VA improvement in HBOT-treated group of 0.1957 on Snellen
Takeuchi et al. (2001)[20]	Case Study	1	3.1 ATA	120 min.	19	54 days	Adequate vision to drive a car was restored
Aisenbrey et al. (2000)[22]	Prospective Cohort Study	8	2.4 ATA	90 min.	≥ 11	3 months	No significant difference in VA change between HBOT and control groups
Beiran et al. (1993)[21]	Case Series	4	2.5 ATA	90 min.	Case 1: 15	2 years	VA improved from 6/6 to 6/20
					Case 2: 12	1 year	VA improved from hand motion to 6/6
					Case 3: 10	Immediately after last session	VA improved from finger counting to 6/9
					Case 4: 11	2 years	VA improved from hand motion to finger counting

Abbreviations: ATA = atmospheres absolute, BCVA = best correct visual acuity, HBOT = hyperbaric oxygen therapy, MT = macular thickness, Min. = minutes, VA = visual acuity.

Table 1B. Summary of included primary literature investigating HBOT for diabetic retinopathy.

Study	Design	Sample Size	Pressure	Number of Treatments	Sessions per Treatment	Session Duration	Follow-Up Time	Key Findings
Maalej et al. (2020)[43]	Prospective Cohort Study	50	2.5 ATA	1	30	90 min.	Immediately after last session	Significant decrease in mean central MT
Averous et al. (2006)[40]	Case Report	1	-	3	14	-	3 years	VA improved from 20/125 to 20/63 in right eye and 20/320 to 20/160 in left eye Reoccurrences of macular edema treated with repeat HBOT resulted in successful reduction of MT
Krott et al. (2000)[42]	Case Series	5	2.4 ATA	1 – 2*	Median of 15	90 min.	15 months	Mean increase in VA of 3.5 lines on logMAR
Ogura et al. (1988)[41]	Case Series	11	2.0 ATA	1	35 sessions	60 min.	1 – 13 months	VA improved by 2 lines in 68% of eyes

*3 patients received 2 treatment courses, 2 patients received 1 treatment course.

Abbreviations: ATA = atmospheres absolute, HBOT = hyperbaric oxygen therapy, MT = macular thickness, Min. = minutes, VA = visual acuity.

Table 2A. Summary of included primary literature on myopic shift after HBOT.

Reference	Study Type	Sample Size	Depth	Duration	Sessions	Key Findings
Bennett et al. (2019)[83]	Randomized Controlled Trial	120	2.43 ATA	90 min.	30	Myopic shift was greater after both 20 sessions and 30 sessions in patients using the hood than in patients using a mask
Riedl et al. (2019)[64]	Prospective Cohort	29	-	-	40	Median myopic change of 0.75 D (left eye) and 0.66 D (right eye) seen in almost 90% of participants
Evanger et al. (2018)[51]	Prospective Cohort	23	2.4 ATA	90 min.	30	Myopic shift of -0.95 ± 0.54 D in the right eye and -0.95 ± 0.53 D in the left eye developed during 6 weeks of treatment
Churchill et al. (2016)[49]	Retrospective Cohort	85	2.0 ATA	90 min. (monoplace) 100 min. (multiplace)	10 – 79	Nearly 30% of patients had at least a 2-line change in visual acuity by Snellen test
Evanger et al. (2015)[54]	Prospective Cohort	20	2.4 ATA	90 min.	20	Reduction in optical density in the lens nucleus and backward scattered light with a mean myopic shift of 0.58 D
Evanger et al. (2014)[47]	Prospective Cohort	15	2.4 ATA	90 min.	20	Mean myopic shift of 0.62 D while the axial length of the eye remained unchanged
Churchill et al. (2013)[60]	Prospective Cohort	22	1.5 ATA	60 min.	60	Myopic change of 2-3 lines were reported by 3 out of 22 patients

Evanger et al. (2011)[56]	Prospective Cohort	22	2.4 ATA	90 min.	20	Myopic shift ≥0.50 D seen only in phakic eyes with no change in pseudophakic eyes
Gesell & Trott (2007)[61]	Case Report	1	2.5 ATA	90 min.	48	Myopic change from -1.00 D in the right eye and -0.75 D in the left eye to -2.50 D in both eyes, eventually progressing to -4.25 D with no signs of reversal
Evanger et al. (2006)[52]	Case Report	1	2.4 ATA	90 min.	31	Myopia followed by hypermetropia that returned to pre-treatment values after 1.5 years
Evanger et al. (2004)[59]	Prospective Cohort	32	2.4 ATA	90 min.	21	Larger myopic shift with longer return to baseline when HBOT delivered by hood as opposed to oronasal mask
Fledelius & Jansen (2004)[53]	Case Report	1	2.4 ATA	90 min.	30	Hypermetropic shift of 2 D in both eyes beginning 10 days after completing HBOT
Fledelius, Jansen, & Thorn (2002)[46]	Prospective Cohort	17	2.5 ATA	95 min.	30	Myopic change ranged from 0 to 1.5 D with average of 0.58 D
Ross et al. (1996)[57]	Case Series	8	2.0 ATA	120 min.	20	Myopic change seen in 2 of 8 participants
Palmquist et al. (1984)[45]	Case Series	25	2.0-2.5 ATA	60 min.	150 – 850	Mean myopic change of 3.0 D with maximal change between 100 and 300 hours of HBOT

Anderson & Farmer (1978)[48]	Case Series	10	2.0 ATA	120 min.	40	Mean myopic change of 1.6 D at an average rate of 0.25 D per week
Lyne (1978)[50]	Case Series	26	2.5 ATA	120 min.	28 – 364	Myopic change ranging from 0.5 to 5.5 D

Abbreviations: ATA = atmospheres absolute, D = diopters, HBOT = hyperbaric oxygen therapy, Min. = minutes.

Reference	Study Type	Sample Size	Depth	Duration	Sessions	Key Findings
Hagan et al. (2019)[62]	Case Report	1	2.5 ATA	90 min.	46	Bilateral nuclear and cortical cataracts developed after 46 treatments
Riedl et al. (2019)[64]	Prospective Cohort	29	-	-	40	Increase in nuclear color and opalescence that persisted 12 weeks after treatment
Gesell & Trott (2007)[61]	Case Report	1	2.5 ATA	90 min.	48	De novo cataract formation in both eyes after standard HBOT regimen
Palmquist et al. (1984)[45]	Case Series	25	2.0 – 2.5 ATA	60 min.	150 – 850	Evidence of cataract development in subset of patients after minimum of 150 dives

Table 2B. Summary of included primary literature on cataract formation after HBOT.

Abbreviations: ATA = atmospheres absolute, HBOT = hyperbaric oxygen therapy, Min. = minutes.

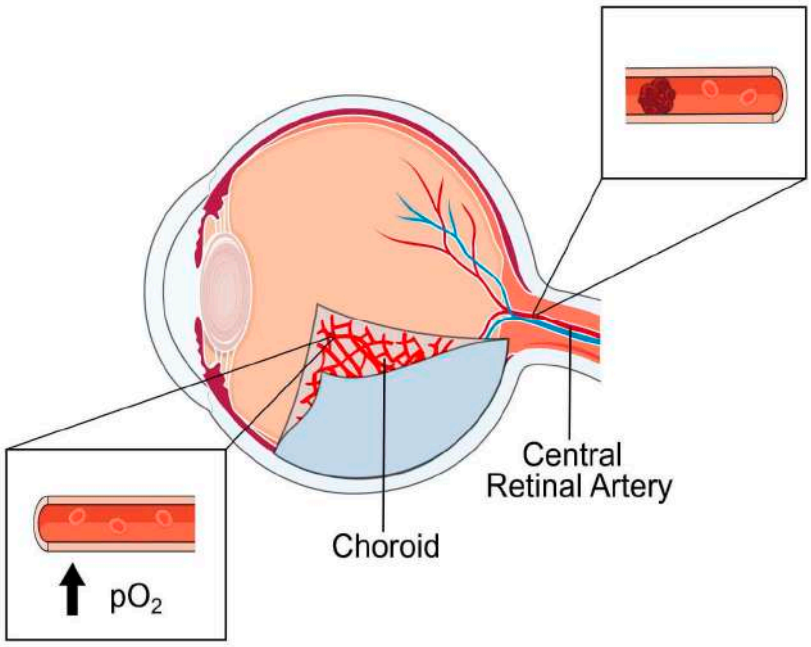

Figure 1. Effects of HBOT-induced choroidal hyperoxygenation during CRAO. Figure modified from Servier Medical Art (https://smart.servier.com/) licensed under a Creative Commons Attribution 3.0 Unported License

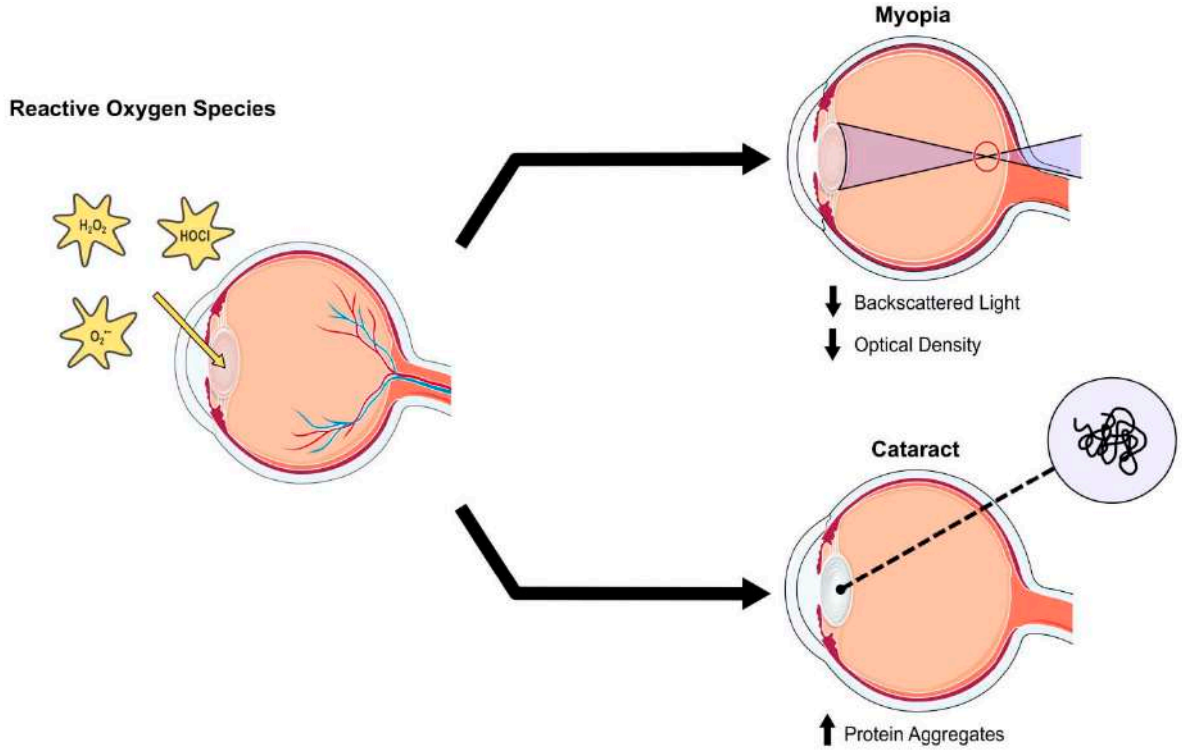

Figure 2. Adverse effects of ROS production in the lens resulting from HBOT. Figure modified from Servier Medical Art (https://smart.servier.com/) licensed under a Creative Commons Attribution 3.0 Unported License