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Central retinal artery occlusion treated with oxygen: *A literature review and treatment algorithm*

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ABSTRACT

Central retinal artery occlusion (CRAO) is an uncommon eye disorder, but one that typically produces severe and irreversible vision loss in the affected eye. The retina has a dual blood supply, with the retinal circulation supplying the inner layers and the choroidal circulation supplying the outer layers. In CRAO, vision loss results from cell death in the inner retinal layers despite relative sparing of the outer layers.

If supplemental oxygen is provided, however, oxygen from the choroidal circulation may diffuse in adequate quantity to the inner layers of the retina to maintain retinal function and restore vision. In some patients this can be achieved with normobaric hyperoxia; in others, hyperbaric oxygen (HBO_2) may be required.

The challenge is to provide the supplemental oxygen early enough after the onset of vision loss to prevent irreversible damage to the retina. In experimental models of complete CRAO, the ischemic time window before permanent retinal damage occurs is just over 90 minutes; in the clinical setting where occlusion may be incomplete, return of vision may be achieved even after delays of eight to 24 hours.

In patients with a clinical picture of CRAO who present within 24 hours of vision loss, supplemental oxygen should be started immediately at the highest possible fraction of inspired oxygen (FiO_2). If vision is not quickly restored, emergent HBO_2 should be undertaken if feasible. If the patient responds to HBO_2, follow-up treatment with supplemental oxygen should be customized to maintain retinal viability until the obstructed retinal artery recanalizes, which typically occurs within the first 72 hours. This paper reviews the pertinent literature on CRAO and HBO_2 and provides a treatment algorithm.

BACKGROUND

Central retinal artery occlusion CRAO) is a relatively rare emergent condition of the eye resulting in sudden painless vision loss. This vision loss is usually dramatic and permanent, and the prognosis for visual recovery is poor. Patients particularly at risk include those with giant cell arteritis, atherosclerosis and thromboembolic disease. A wide variety of treatment modalities have been tried over the last one hundred years with little to no success, with the exception of hyperbaric oxygen (HBO_2) therapy.

RATIONALE FOR HYPERBARIC OXYGEN THERAPY IN THE MANAGEMENT OF CENTRAL RETINAL ARTERY OCCLUSION

The arterial blood supply to the eye is provided by the ophthalmic artery, one of the branches of cavernous portion of the internal carotid artery. Some of the branches of the ophthalmic artery (lacrimal, supraorbital, ethmoidals, medial palpebral, frontal, dorsal nasal) supply orbital structures, while others (central artery of the retina, short and long posterior ciliaries, anterior ciliaries) supply the tissues of the globe [1]. The central retinal

artery enters the globe within the substance of the optic nerve and serves the inner layers of the retina through its many branches. The long posterior ciliary arteries provide blood to the choroid and the outer layers of the retina. There are approximately 20 short posterior ciliary arteries and usually two long posterior ciliary arteries. The posterior ciliary vessels originate from the ophthalmic artery and supply the entire uveal tract, cilioretinal arteries, the sclera, the margin of the cornea and the adjacent conjunctiva. The anterior ciliary arteries also arise from the ophthalmic artery, supply the extraocular muscles, and anastamose with the posterior ciliary vessels to form the major arterial circle of the iris, which supplies the iris and ciliary body.

The visual signs and symptoms of vascular occlusive diseases of the retina are dependent on both the particular vessel occluded, the degree of occlusion, the location of the occlusion and the presence or absence of a cilioretinal artery. In approximately 15%-30% of individuals, a cilioretinal artery is present. This artery is part of the ciliary (not retinal) arterial supply but supplies the area of the retina around the macula (central vision area). If a cilioretinal artery is present, central vision may be preserved in central retinal artery occlusion. The outcome of these disorders also depends on the vessel occluded and the degree of occlusion, but also on the rapidity of instituting therapy, including supplemental normobaric or hyperbaric oxygen.

In CRAO, the inner retinal layers (ganglion cell layer and inner nuclear layer), which are normally served by the retinal circulation, typically lose viability and this is responsible for the vision loss. These layers may, however, obtain enough oxygen via diffusion from the choroidal circulation to maintain viability if the individual is exposed to elevated partial pressures of oxygen. Animal models have shown that the choroidal vessels may supply sufficient oxygen to the inner layers of the retina to maintain ganglion cell viability even when the retinal vessels have been completely obliterated [2]. Normally, the choroidal circulation supplies the majority of the oxygen to the retina. Under normoxic conditions approximately 60% of the retina's oxygen comes from the choroidal circulation. Under hyperoxic conditions the choroid is capable of supplying 100% of the oxygen needed by the retina [3].

In considering the effect of treating CRAO with supplemental oxygen, there are four key factors:

1. therapy must be initiated before the retinal tissue is irreparably damaged;
2. the degree of occlusion of the blocked vessel may vary; this may account for why some patients respond to oxygen at lower partial pressures than others;
3. some patients may not respond to oxygen therapy, even if it is initiated promptly, if the level of occlusion is at the ophthalmic artery, because in this event, the blood supply to the posterior ciliary vessels is blocked as well, and there is no collateral circulation to provide oxygenation of the inner layers of the retina; and
4. an adequate partial pressure of oxygen must be maintained to keep the retinal viable until circulation is restored via natural recanalization, which usually occurs within 72 hours.

The etiology of the arterial occlusion (thrombosis, embolus, arteritis, vasospasm) has also been described as affecting outcome [4,5]. Careful classification of the factors involved in an individual case of CRAO is crucial to understanding the natural outcome and results of therapy. In the largest published series of CRAO patients, Hayreh describes the natural progression of this condition without hyperbaric oxygen therapy. He found that patients with transient CRAO (resolution of symptoms in minutes to hours) and those with cilioretinal arteries had much better outcomes than those who did not. In those patients without cilioretinal arteries or transient presentations, 80% or less had a final outcome of counting fingers, and only 1.5% of them obtained a final vision of 20/40 or better [5].

Recanalization occurs in retinal vessels after CRAO [6,7]. In relatively few cases, however, does this angiographic reperfusion lead to an improvement of vision [7]. The retina has the highest rate of oxygen consumption of any organ in the body at 13ml/100g/minute [8,9]. Therefore, it is very sensitive to ischemia. In order to be effective, the administration of supplemental oxygen must be continued until such time as flow through the retinal artery has resumed to a level sufficient to maintain inner retinal viability under normoxic conditions.

PATIENT SELECTION CRITERIA

The classic presentation of CRAO is sudden painless loss of vision in the range of light perception to counting fingers. In the case of vision loss to the level of no light perception, the patient may have an ophthalmic artery occlusion – and therefore no blood flowing to the choroidal vessels either. If central visual acuity is relatively spared in the presence of a fundus exam consistent with CRAO, the presence of a cilioretinal artery is likely.

On dilated fundoscopic exam, patients with CRAO will classically have a pale yellow/white-appearing retina due to ischemia or necrosis. A cherry-red spot may develop in the macula, but this finding may not always be present. Other physical exam findings may include: an afferent pupillary defect and boxcarring of arterioles.

Patients presenting within 24 hours of symptom onset should be considered for hyperbaric oxygen therapy. While there are a few case reports of patients presenting after this time interval having positive results when treated with hyperbaric oxygen therapy, the majority of cases do not respond when treated beyond this point [8,10,11,12,13,14].

While consideration of the pertinent physiology suggests that patients with branch retinal artery occlusions and central retinal vein occlusions may also benefit from hyperbaric oxygen therapy, there is insufficient data in the literature to support this as a routine recommendation [10,15,16].

CLINICAL MANAGEMENT

Patients who present with sudden painless loss of vision due to CRAO should be triaged as "emergent" because of the need for immediate oxygen therapy. Visual acuity should be documented as soon as possible. If decreased vision (less than 20/200) is confirmed without improvement with pinhole, the emergency physician should immediately perform a fundoscopic exam, using dilation if feasible and not contraindicated. The presence of flashes or floaters preceding the vision loss, pain, history of recent trauma/ocular surgery, or age younger than 40 suggests an alternate diagnosis (*e.g.*, retinal detachment/vitreous hemorrhage). An ophthalmologist should be consulted emergently, but treatment with supplemental oxygen should not be delayed awaiting the arrival. Intraocular pressure should be measured and treated if elevated. Ocular message has been anecdotally reported to dislodge clot on occasion [17].

Diagnostic work up to screen for conditions that may predispose to CRAO should include: CBC (to screen for platelet disorders or infectious causes), ESR (for arteritic causes), hypercoagulable panel (fibrinogen, PT/PTT, antiphospholipid antibody), lipid panel, EKG, carotid ultrasound, and echocardiography. HBO_2 should not be delayed to accomplish any of these diagnostic measures. In cases of suspected arteritic CRAO, treatment with IV corticosteroids should be initiated emergently, but HBO_2 therapy should still be undertaken.

Fundoscopic findings of CRAO should trigger management as below if symptom onset is within 24 hours or less. Oxygen delivery should be titrated to patient response as follows:

1. Deliver oxygen immediately at one atmosphere absolute (atm abs) at the highest possible FiO_2.
2. If vision improves significantly with normobaric oxygen within 15 minutes, the patient should be admitted to the hospital and given intermittent normobaric oxygen for 15 minutes every hour alternating with 45 minutes of breathing room air. Visual acuity should be checked at the end of each air-breathing period. This regimen should be continued until angiogram shows patency, the patient's vision remains stable on room air for two hours or a maximum of 96 hours.
3. Refer for hyperbaric oxygen therapy if no response within the first 15 minutes.
4. Compress to 2 atm abs on 100% oxygen.
5. Other adjunctive therapies to lower intraocular pressure and/or cause retinal vasodilatation may be performed as well, but should not delay compression. If vision improves significantly at 2 atm abs, remain at this depth for 90 minutes (air-breathing periods at this depth may not be necessary since the incidence of oxygen toxicity seizures is four times lower at 2.0 than at 2.4 atm abs [18]), then proceed as outlined in Section 8 below.
6. If vision fails to improve significantly at 2 atm abs by the first air breathing period (or 30 minutes), compress to 2.4 atm abs. If vision improves significantly at this depth, conduct a U.S. Navy Treatment Table 9 and then proceed as outlined in Section 8 below.
7. If vision does not improve significantly at 2.4 atm abs, compress to 2.8 atm abs and conduct a USN Treatment Table 6. If vision improves significantly, proceed as outlined in Section 8 below. If there is no response to the initial Table 6, options are to discontinue treatment, continue with normobaric oxygen as in Section 2 or give two additional treatments for 90 minutes at 2.8 atm abs with air-breathing periods on a twice-daily schedule.
8. If the patient has return of vision during hyperbaric treatment, inpatient monitoring and intermittent supplemental oxygen should be considered. Monitoring by a retina specialist should continue. Recovery of vision during the initial treatment of CRAO with HBO2 indicates retinal viability and the potential for return of vision despite the ischemic period suffered prior to treatment. Patients with such a recovery should have their visual status

monitored frequently after completion of HBO_2. Patients should be monitored at the chamber for two hours post-treatment. If vision remains normal, they can be discharged home with instruction to monitor vision every hour. Should vision loss recur, aggressive use of intermittent normobaric oxygen as described in Section 2 or customized hyperbaric oxygen is indicated to preserve retinal function until CRA recanalization occurs. Twice- or three-times-daily hyperbaric treatments may be necessary until the angiogram normalizes or the patient has no further improvement for three treatments.

- **NOTE:** the retina may not tolerate periods of ischemia that persist longer than 90 minutes. Cases of relapse of loss of vision and resultant blindness after discharge home have been reported [7,12,19,20], and patients should be instructed to return immediately for supplemental oxygen therapy if vision loss recurs after discharge.
- **NOTE:** one exception to the above regimen is CRAO that results from arterial gas embolism. In this event, the treatment regimen on the UHMS web site for AGE should be followed. Patients with history of DCI, recent hemodialysis or general anesthesia should always be treated with HBO_2.
- **NOTE:** also that all patients who have lost vision in one eye should be directed to present immediately to a hospital or to their ophthalmologist if vision loss occurs in the fellow eye.

EVIDENCE-BASED REVIEW – HBO_2 AND CRAO

Possible causes of retinal arterial occlusive disease include atherosclerosis-related thrombus, embolism, vasospasm and giant cell arteritis. A CRAO with significant visual loss is an ophthalmic emergency. Treatment should be aimed at promptly supplying oxygen to the ischemic retina at a partial pressure sufficient to maintain viability while medically assisted or spontaneous restoration of central retinal artery blood flow occurs. Animal models of retinal injury have shown a reduction in apoptosis from 58% cell loss to 30% in animals treated with HBO_2 after experimental CRAO [21].

Traditional therapeutic regimens for CRAO have been aimed at promoting a downstream movement of the embolus by lowering intraocular pressure and producing vasodilatation. These measures include ocular massage, anterior chamber paracentesis, intraocular pressure-lowering medications, vasodilators and oral diuretics [7,8,19]. These treatment modalities have been relatively unsuccessful [7,19,22]. Acute obstruction of the central retinal artery, even when treated promptly, typically results in severe, permanent visual loss [5,7]. Hayreh stated that no currently used therapy is efficacious for CRAO [5,23], but he did not consider the use of HBO_2.

More recent treatment modalities include thrombolytic agents [24,25,26] and surgical removal of the embolus or thrombus [27,28]. One study reporting the limited success with thrombolytics used in conjunction with intraocular pressure-lowering medications, anterior chamber paracentesis and methylprednisolone included only patients seen within 48 hours of onset of symptoms and noted that all eight patients in whom visual acuity improved had symptoms for less than 12 hours [25].

Supplemental oxygen therapy has been used in conjunction with the above regimens. When retinal arterial flow is interrupted, the retinal tissue undergoes a period of ischemia. Blood flow is usually re-established via recanalization, but if ischemia and hypoxia have resulted in cell death and necrosis in the inner layers of the retina, supplied by the retinal artery, vision may not return when blood flow is re-established [29]. The tissue that is ischemic, yet capable of recovery within a certain time frame, is called the ischemic penumbra [29].

Supplemental oxygen need not always be provided at hyperbaric pressures to successfully reverse retinal ischemia in CRAO. One patient suffered a CRAO in his only seeing eye and presented within approximately one hour of vision loss to the emergency department, where he was found to have vision of 20/400 and fundus findings typical of a CRAO. He was treated with oxygen supplied by a non-rebreathing mask at one atmosphere in the ED, and his vision quickly improved to the 20/25 level. After a period of approximately five minutes, the supplemental oxygen was removed, whereupon vision equally quickly returned to 20/400. This process was repeated several times to confirm the efficacy of the supplemental oxygen, with the same results. The patient was then hospitalized, anticoagulated and maintained on supplemental oxygen for approximately 18 hours, after which his central retinal artery presumably recanalized, since removal of the supplemental oxygen at that point no longer caused a drop in vision. He was discharged with a visual acuity of 20/25 in his only seeing eye [30].

Patz reported improvement in two CRAO patients given oxygen at 1 atm abs. One patient received oxygen after a four-hour delay to therapy, and improvement was maintained after oxygen was discontinued

four hours later. The second patient improved significantly after a delay to treatment of 90 minutes and maintained this improvement when oxygen was discontinued three hours later. In both patients, early discontinuation of oxygen was followed by deterioration of vision within minutes and visual recovery when oxygen breathing was resumed shortly thereafter. This phenomenon was observed several times in both patients [2].

Stone *et al.* reported two patients with CRAO of greater than six hours' duration treated with intermittent carbogen (95% oxygen and 5% CO_2), retrobulbar anesthesia and anterior chamber paracentesis. The first patient had vision loss of six hours' duration. His vision improved from hand motion to 20/20 on the above therapy, with carbogen being administered for 10 minutes every hour. The second patient presented eight hours after onset of visual loss and had improvement from finger counting to 20/25. Carbogen was administered 10 minutes every hour for 48 hours [19].

Of note is that carbon dioxide was added to the oxygen to help prevent retinal vasoconstriction in the cases above. Elevated partial pressures of oxygen cause retinal artery vasoconstriction [31,32,33]. Carbon dioxide is added to the gas mix in carbogen to counter this effect through its vasodilatation of retinal vessels. If the mechanism of improved oxygenation to the retina is diffusion from the choroidal circulation, however, then the addition of carbon dioxide should be of little benefit, since unlike retinal blood flow, choroidal blood flow is not significantly affected by changes in oxygen tension [3,33]. The hyper-oxygenation of the choriocapillaris was noted to more than offset the reduced retinal blood flow as observed by the appearance of arterialized bright-red blood in the retinal veins during HBO_2 [31]. Note that carbogen should never be used during HBO_2 because elevated partial pressures of CO_2 potentiate the development of central nervous system oxygen toxicity.

The study published by Augsberger and Magargal in 1980 was notable in that it demonstrated the criticality of the time to oxygen treatment in successful outcome. They used paracentesis, ocular massage, carbogen, acetazolamide and aspirin to treat 34 consecutive cases of CRAO. Twelve of the 34 patients were successfully treated, with seven of the 12 having been treated within 24 hours of onset of symptoms. The longest delay to treatment in which treatment was considered successful was 72 hours. The average delay to therapy in the patients with successful outcomes was 21.1 hours, compared to 58.6 hours in those who did not improve. Carbogen inhalation was conducted for 10 minutes every hour during waking hours and 10 minutes every four hours at night and continued for 48-72 hours in these patients [12].

One remarkable case report described a patient with angiographically documented obstruction of both the central retinal artery and his temporal posterior ciliary artery [7]. He presented after five hours of visual loss with minimal light perception vision. In addition to ocular massage, anterior chamber paracentesis, timolol and acetazolamide, he was given carbogen for 10 minutes every hour around the clock. His vision did not improve significantly during his three days of hospitalization, but improved spontaneously approximately 96 hours after onset of vision loss. His vision in the affected eye was documented to be 20/30 one week after discharge. Although the authors of this case report do not necessarily ascribe his recovery to any one of the treatments used [7], the role of supplemental oxygen in maintaining retinal viability must be considered. Patients with CRAO rarely improve spontaneously [7].

If hyperoxia at one atmosphere is not effective in reversing vision loss in CRAO, emergent compression and 100% oxygen breathing should be undertaken. Phillips *et al.* reported a 71-year-old white female patient with CRAO in whom surface oxygen was ineffective in restoring "total" vision loss of approximately two hours' duration [34]. Initial treatment with supplemental oxygen at one atmosphere did not reverse this vision loss. Light perception returned as she was compressed on 100% oxygen to 1.45 atm abs (15 fsw), and at the end of the first air breathing period at 2.8 atm abs, she had return of full vision. She was discharged with a visual acuity of 20/30 in her only seeing eye and the 2+ afferent papillary defect noted prior to treatment had resolved after treatment.

The timing of HBO_2 therapy is critical in CRAO. There is a threshold of time beyond which ischemic tissue can no longer recover from a hypoxic event, even if reperfusion occurs [3]. Hayreh *et al*. reported a study in which the ophthalmic artery of rhesus monkeys was completely occluded for varying periods of time. Retinas exposed to greater than 105 minutes without blood flow showed permanent damage. If the duration of occlusion was kept to less than 97 minutes, the retinas returned to normal, as evaluated by multiple types of diagnostic testing [35].

In the clinical setting of CRAO, however, some residual retinal blood flow has been detected by fluorescein angiogram [6,12]. This may help explain the great variability in visual outcome with different time delays until treatment. Ideally, the shorter the time delay

until treatment, including HBO_2, the better the likelihood of recovering ischemic retina that is threatened but viable (penumbra) [3,12,36]. Ophthalmology literature includes cases in which humans with a CRAO have regained significant vision even when treatment was delayed for periods of up to two weeks [37], with the strongest evidence for symptomatic improvement in cases with less than 12 hours' delay [3,8,14,38]. See Table 1 *(below and facing page)* for a summary of the cases treated with HBO_2. It is difficult for the clinician to predict which patients will respond to HBO_2 beyond the recognition that minimizing the retinal ischemic time maximizes the potential for visual recovery [39].

Hertzog *et al.* reported a series of 17 patients with CRAO treated with HBO_2. They retrospectively divided patients into fout treatment groups based on the time to onset of treatment and noted that HBO_2 seemed useful

Table 1. Treatment of retinal artery occlusions: Literature summary

Report	CRAO/ BRAO	Therapy	Delay to Tx	Initial VA	Final VA	Total patients (*n*)	Cases Improved (*n*)
Gool & Jong 1965 (41)	BRAO CRAO CRAO BRAO	HBO_2: 3 atm, anticoagulants, Complamin	5 days 2 days Unkn (<24hr) 10 days	1.5% nil 125% 1.6%	100% nil 125% imp VF 1.6%	4	2
Haddad & Leopold, 1965 (32)	CRAO	HBO_2	Unknown	NLP CF	NLP CF	2	0
Anderson *et al.* 1965 (11)	BRAO CRAO BRAO	HBO_2, retrobulbar lidocaine, ocular massage, nicotinic acid	"several hrs" 40+ hrs 6+ days	CF 2-3 ft 20/25 20/200	20/20 20/25 imp VF Unkown	3	2
Takahashi *et al.* 1977 (42)		HBO_2: 2.5 atm, ocular massage, paracentesis, vasodilator	1-6 days	Graph	Graph	9	0
Pallota *et al.* 1978 (43)	CRAO	HBO_2: 2.8 atm		NLP	10-10	1	1
Sasaki *et al.* 1978 (44)	CRAO	HBO_2, stellate ganglion block				10	7
Szuki *et al.* 1980 (45)	CRAO	HBO_2				6	6
Krasnov *et al.* 1981 (46)	CRAO	HBO_2				39	22
Zhang & Cao 1986 (36)	CRAO	HBO_2				80	49
Desola 1987 (47)	CRAO	HBO_2				20	11
Miyake *et al.* 1987 (13)	CRAO (53) BRAO (19)	HBO_2: 2 atm or 3 atm, varied vasodilators, stellate ganglion block, 2% carbocaine	18 hours to 15 days, all but 3 within 12 days	Graph	Graph	72	32
Kindwall & Goldmann 1988 (48)	CRAO	HBO_2				14	7
Hirayama *et al.* 1990 (49)	CRAO	HBO_2; mixtures of urokinase, steroid, bifemelane HCL	<1 month	Graph	Graph	11	15

Table 1. Treatment of retinal artery occlusions: Literature summary – *continued*

Report	CRAO/ BRAO	Therapy	Delay to treatment	Initial VA	Final VA	Total patients (*n*)	Cases Improved (*n*)
Hertzog *et al.* 1992 (8)	CRAO	HBO_2: 1.5-2.0 atm; mixtures of Timolol maleate 0.5%, acetazolamide, paracentesis, arbogen, vasodilator, steroids, ocular massage, retrobulbar anesthesia	<8 hrs >8, >/=24hrs >24hrs All patients	Graph	Graph	19	14
Beiran *et al.* 1993 (38)	CRAO	HBO_2: 2.5 atm, ccular massage, SL nifedipine, oral glycerol	2: <100min 1: occluding 1: 6 hrs	LP HM CF 2m HM	6/20 6/6 6/9 CF 60cm	4	4
Yotsukura *et al.* 1993 (14)	CRAO	HBO_2, ocular massage, IV urokinase, & 2/15 with IV prostaglandin	3 hrs to 6 days	Graph	Graph	15	8
Li *et al.* 1996 (3)	BRAO OS BRAO OD (15mo later)	HBO_2: 2.32 atm HBO_2: 2.82 atm	<24 hours <24 hours	20/200 CF 2ft	20/25 20/25	2	2
Phillips *et al.* 1999 (34)	CRAO	100% surface O_2, HBO_2: 2.4 atm	<2 hrs	NLP	20/30	1	1
Aisenbrey *et al.* 2000 (50)	CRAO (8) BRAO (10)	HBO_2: 240kPa, ocular massage, paracentesis, IV acetazolamide		Graph	Graph	18	12
Matsuo, 2001 (37)	BRAO (OU)	HBO_2, IV rostaglandin, Urokinase	4 days	20/30 20/600	20/15 20/400	2	2
Beiran *et al.* 2001 (40)	CRAO (29) BRAO (6)	HBO_2: 2.8 atm; mixt. of ocular massage, retrobulbar block, timolol, acetazolamide, paracentesis	<8 hours	Graph	Graph	35	29
Weinberger *et al.* 2002 (51)	CRAO	HBO_2, ocular massage, antiglaucoma eyedrops	4-12 hours	Graph	Graph	21	13
Murphy-Lavoie *et al.* 2004 (10)	CRAO BRAO	HBO_2: 2.0 atm	6 hrs-4 days	Graph	Graph	16	12
Imai *et al.* 2004 (52)	BRAO	HBO_2, stellate ganglion block	2 days	CF	0.08	1	1
Weiss, 2009 (53)	CRAO (4) BRAO (1)	HBO_2: 1.5 atm, prednisone for the one patient with biopsy-proven arteritis	1-21 days	CF 5ft HM LP LP/CF	20/200 20/30 LP LP/CF	4	2
Weiss, 2010 (54)	BRAO	HBO_2: 1.5 atm	1-12 days	CF CF 6ft visual field def	20/70 20/50	5	5
Cope *et al.* 2011 (55)	RAO	HBO_2: 2.4 atm	5-144 hours	Graph	Graph	11	8
Menzel *et al.* 2012 (56)	CRAO	HBO_2: 2.4 atm, hemodilution	<12 hours	Graph	Graph	51	30
TOTAL % IMPROVED						476	306 65%

Note: see full graphs of patient results in original papers

in preserving visual function when applied within the first eight hours from the onset of visual impairment. The patients in this study were treated for 105 minutes of oxygen at 2.0 atm abs three times a day until they ceased to show improvement in visual acuity or for three to four days if no improvement occurred, receiving a mean of 29.3 hours of HBO_2 over five to six days early in the data collection period and 34.6 hours over five to six days later in the data collection period. The authors modified their treatment protocol to a 1.5 atm abs prolonged exposure midway through the data collection period accounting for the differences in treatment times. The authors point out that the colloquialism "time is muscle," used in management of myocardial infarctions can be changed to "time is vision" in CRAO [8].

Another paper demonstrated success in treating three cases of CRAO in which the patients presented shortly after the onset of symptoms. One patient treated 90 minutes after onset of visual loss had vision improve from light perception to counting fingers after the first 10 minutes of HBO_2, with subsequent improvement to 20/70 following five days of two 90-minute HBO_2 treatments at 2.5 atm abs daily for 5 days. Another patient presented 40 minutes after visual loss and improved from hand motion to 20/20 after 12 treatments at 2.5 atm abs in nine days. A third patient presented four hours after the onset of symptoms with finger-counting vision. He received 10 90-minute HBO_2 treatments at 2.5 atm abs, with gradual improvement of visual acuity to the 20/30 level. A last patient who was treated with HBO_2 six hours after symptom onset showed no significant improvement in vision [38].

In 2001, Beiran published a retrospective controlled trial of 35 patients treated with hyperbaric oxygen therapy compared to 37 matched controls from another facility where hyperbaric oxygen was not available [40]. All patients were treated within eight hours of symptom onset, and none of the patients included in the study had a cilioretinal artery. The patients in the hyperbaric group received 2.8 atm abs for 90 minutes BID for the first three days and then once daily until no further improvement for three consecutive days. In the hyperbaric group, 82% of the patients improved, compared to only 29.7% of patients in the control group. Improvement was defined as reading at least three lines better on the Snellen chart compared to admission. The mean visual acuity for the hyperbaric group at discharge was 6/20 in metric, or about 20/70 in feet.

As with oxygen administration at one atm abs, hyperbaric oxygen must be started within the time interval that retinal tissue can still recover [7]. Reports that describe failure of HBO_2, sometimes fail to provide any information concerning the delay to therapy [32], and HBO_2 therapy in these cases may have been started after the time window for successful treatment had passed. Miyake reported on 53 patients with CRAO and 19 with branch retinal artery occlusions treated with HBO_2 over a 13-year period. He found no significant difference between time to treatment and response to HBO_2; however, only three of these patients received HBO_2 within 24 hours of symptom onset, so most of these individuals were outside the window where HBO_2 would have had a chance for success. 44% of the patients in this study showed improvement of at least two levels on the visual acuity scale after treatment with HBO_2 despite this delay to treatment. Unfortunately, no distinction was made between patients with cilioretinal arteries and transient occlusions and those without [13].

See Table 1 for a summary in the literature of the cases treated with HBO_2. Overall 65% of cases have shown improvement when treated with HBO_2. These cases make it apparent that some patients with CRAO can be treated successfully with hyperoxia, either at 1 atm abs or with HBO_2. Patients with sudden painless loss of vision should report to the nearest medical facility as soon as possible. Triage nurses should be aware that sudden painless loss of vision of less than 24 hours' duration is an emergency that should be triaged for immediate examination by the emergency physician. If the patient is found to have exam findings consistent with CRAO, the patient should immediately be started on the highest possible fraction of inspired oxygen [2,7,12,19,39]. Visual recovery should occur within minutes if surface oxygen is to be sufficient. If vision is not restored, there should be consideration (ideally in consultation with ophthalmology) of emergent referral to the nearest recompression facility, and the patient should be maintained on supplemental oxygen at the highest possible FiO_2 until arrival.

Based on the American Heart Association classification of evidence, treatment of CRAO with hyperbaric oxygen therapy is Level IIb [60]. There is fair to good evidence to support its use with retrospective case series but no prospective randomized controlled trials. It is acceptable, safe, considered efficacious but lacks confirmation of efficacy by Level 1 studies. There is no evidence of harm, and consistently positive results, when HBO_2 is started

shortly after onset on vision loss. In addition, there are no alternative therapies with similar outcomes [22,23], that would present ethical considerations for a proposed randomized trial. The relatively rare incidence of this condition does not lend itself to randomized controlled trials, as evidenced by the paucity of trials for other therapies in treating this condition. As of 2012, a Medline search revealed only four small randomized controlled trials for all of the proposed therapies, none of which revealed clinically positive results. The hopeless and recalcitrant nature of this condition when left untreated mandates we utilize all potentially helpful treatments, including hyperbaric oxygen therapy.

UTILIZATION REVIEW

The optimum number of treatments will vary, depending on the severity and duration of the patient's symptoms and the degree of response to treatment. The majority of patients will stabilize within a few days after symptom onset. Utilization review is recommended for patients treated for more than three days after clinical plateau and no further improvement.

ECONOMIC IMPACT

There are no formal cost analyses for this condition in the literature; however, the treatment cost for a hyperbaric oxygen therapy is between $200 and $500 per 90-minute treatment in the clinic/outpatient setting. If each CRAO patient received 10 treatments, the cost would be between $2,000 and $5,000 per patient. This is a reasonable price to pay to restore a patient's vision.

DISCLAIMER

The opinions expressed in this paper are those of the authors and do not necessarily reflect those of the Department of the Defense or the Department of the Navy

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