Hyperbaric oxygen treatment of nonacute central retinal artery occlusion

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ABSTRACT

Four patients received hyperbaric oxygen therapy (HBOT): Three patients had nonarteritic central retinal artery occlusion (CRAO); a fourth patient had a CRAO in the right eye (OD) and a branch retinal artery occlusion (BRAO) with macular involvement in the left eye (OS) secondary to giant cell arteritis. The first two patients presented with a one-day history of CRAO, the third patient with a 10-day history of CRAO OD and the fourth patient with a three-week history of CRAO OD and a three-day history of BRAO OS.

The initial visual acuities ranged from light perception to counting fingers at 6 feet. The visual acuity and visual field improved in the first two patients with nonarteritic CRAO. Patients 3 and 4 did not improve. There were no complications. Hyperbaric oxygen treatment may be safe and effective in selected patients with nonacute, nonarteritic CRAO.

INTRODUCTION

Central retinal artery occlusion (CRAO) is an ophthalmologic emergency that frequently results in severe visual loss (1-3). Spontaneous improvement following visual loss is rare; this has led to the development of many proposed treatments including ocular massage, anterior chamber paracentesis, pharmacologic therapy, catheterization of the femoral artery with infusion of thrombolytic agents, etc. (2)

The many causes of this condition are reflected in the varying success of the various treatment modalities. The goal of these therapies is to remove the occlusion, thus increasing retinal oxygenation or maintaining retinal oxygenation until spontaneous recanalization occurs. Recanalization and reperfusion of the central retinal artery generally occur within 72 hours of thrombotic occlusion (2). Hyperoxia can restore retinal oxygenation after arterial occlusion, and favorable results using hyperbaric oxygen therapy (HBOT) for acute retinal artery occlusions have been reported (4-6).

Hayreh (7, 8, 9) has posited that there can be no effective treatment for nonacute CRAO cases with durations longer than 240 minutes based upon his study of old, atherosclerotic and hypertensive rhesus monkeys. Yet, Duker and Brown (10) reported spontaneous reperfusion and visual acuity improvement from light perception to 20/30 in a 70-year-old man with a 96-hour history of a combined CRAO and lateral posterior ciliary artery obstruction.

Hayreh’s acute clamping of the CRA in a rhesus monkey model may not be analogous to the human clinical situation. The human retina may be more resilient than previously thought. Duker and Brown (10) state that “the reversal of the arterial obstruction or increased retinal oxygenation through some other means during this period could theoretically lead to an improvement in vision in these specific cases.”

I have previously reported (11) treating three patients with CRAO of six-, seven- and eight-day durations with HBOT at 1.5 ATA. 1.5 ATA was empirically chosen for several reasons. The retina is a neural tissue and Holbach, et al. (12) reported that 1.5 ATA had a “favorable effect” on injured brain tissue as compared to 2.0 ATA. Animal and human studies have demonstrated that hyperoxia can restore retinal oxygenation (13,14). Visual improvement during treatment with supplemental normobaric oxygen also implies that mild hyperbaric pressure may be sufficient (14,15). Using a
lower ATA would also minimize the risk of complications and shorten the treatment time, making the HBOT more "palatable" to what is generally an elderly population, as well as to sometimes skeptical family members and referring physicians.

The pretreatment visual acuities were hand motion, hand motion and counting fingers (CF) at 3 feet, respectively. Post treatment, the visual acuities had improved to 20/200-1 after three HBOT treatments, 20/60+2 after five HBOT treatments and 20/50 post 10 HBOT treatments, respectively. There was no improvement in the visual field of any treated patient. As the retina in the macular area is thinner than the surrounding area (accounting for the cherry-red spot that represents the choroidal circulation seen through the transparent macula retina and highlighted by the surrounding edematous retina), the metabolic requirements are presumably less than the peripheral retina and more resilient to a decrease in perfusion.

A similar group of four patients with a one- to three-day duration of CRAO that refused HBOT treatment presented with visual acuities of no light perception (NLP), CF at 3 feet, CF at 6 feet and CF at 6 feet, respectively. The first patient's vision improved from NLP to hand motion. Patients 2 through 4 had no improvement in visual acuity or visual field.

HBOT treatment of an additional four patients with a one-day to three-week history of CRAO is now reported. The effectiveness of treatment is discussed in relation to the patient's medical condition.

Each patient underwent ophthalmic examination that included best corrected visual acuity, intraocular pressure, biomicroscopic and dilated fundus examinations, fundus photography, fluorescein angiography and other ancillary testing, as indicated. No adjunctive therapies – i.e., anterior chamber paracentesis, pharmaceuticals, etc. – were used. Patients were screened for the suitability of administering HBOT, and treatments were performed with 100% oxygen at 1.5 ATA for 1 hour.

**Case 1**

A 64-year-old woman with a history of diabetes, hypertension and glaucoma awoke with loss of vision OD. She was examined at 4 p.m. that same day, and the visual acuity was CF at 5 feet OD and 20/30 OS. Dilated fundus examination with fluorescein angiographic confirmation revealed a CRAO OD. Platelet emboli and a cherry-red spot were observed. (At a prior examination five month earlier, the visual acuity was 20/30 OD and 20/25 OS.)

She underwent one HBOT each day for four days, with the first treatment beginning the next morning. When she was next examined – four days later (Day 5 post CRAO) – the visual acuity had improved to 20/200. There was a decrease in the previously observed retinal edema, although the cherry-red spot was still visible. A marked improvement in the arteriolar filling time was observed by fluorescein angiography. The visual field showed no improvement.

The patient underwent six additional HBOT treatments, one per day. On Day 11 post CRAO, though there was no improvement in the central visual acuity, there was a mild improvement in the visual field. The examination remained stable two months later.

**Case 2**

A 91-year-old male with diabetes, cardiac disease and hypertension awoke with a loss of vision OD. He was examined at 11 a.m. the same day; the visual acuity was hand motions OD and 20/30 OS. Dilated fundus examination, confirmed by fluorescein angiography, revealed a CRAO OD. Platelet emboli were noted. The patient underwent one HBOT treatment that afternoon. He subsequently underwent two treatments on Day 2, two on Day 3 and one on Day 4. When he returned three days later (Day 4 post CRAO), the visual acuity OD had improved to 20/400 with eccentric fixation, and fluorescein angiography revealed an improvement in arteriolar filling.

He underwent six additional HBOT treatments over the next eight days. Twelve days later (Day 16 post CRAO), the visual acuity OD had further improved to 20/100, and a marked improvement in the visual field was observed. His medical work-up was positive for a 75% blockage of his right carotid artery, and he was scheduled for carotid endarterectomy.

Encouraged by the visual improvement, he elected to undergo six additional HBOT treatments, two treatments per day. Three days later,
19 days after the initial diagnosis, the visual acuity OD had improved to 20/30, with a concomitant improvement in the patient’s visual field.

Case 3
A 55-year-old male experienced a CRAO OD secondary to an embolic plaque from a right carotid occlusion. He underwent carotid endarterectomy four days afterward and was referred for consideration of HBOT six days later (Day 10 post CRAO).

The visual acuity was light perception (LP) OD and 20/400 secondary to amblyopia OS. A relative afferent pupillary defect was present OD. The anterior chamber was shallow, and gonioscopy revealed an occludable angle in each eye. Dilated fundus examination demonstrated a CRAO with retinal edema at the posterior pole and a cherry-red spot OD. There was a very significant delay in arteriolar filling time by fluorescein angiography (greater than 45 seconds). Subretinal fluid with a retinal thickness at the macula of 365 microns was noted by ocular coherence tomography (OCT).

The patient began HBOT at 1.5 ATA the next morning and underwent two treatments per day over the next four days. There was no significant change in the visual acuity on Day 14 after the CRAO. Less retinal edema was observed, and OCT showed there was a decrease in the subretinal fluid. The retinal thickness at the macula was 308 microns.

He underwent an additional seven HBOT treatments at 2.0 ATA, but due to sinus problems, the final two treatments were at 1.5 ATA. Twenty-one days after experiencing the CRAO, the visual acuity remained at LP OD; there was less retinal edema, an improvement in arteriolar filling time by fluorescein angiography was noted, and there was a further decrease in the subretinal fluid by OCT such that the retinal thickness at the macula was 269 microns.

Case 4
A 93-year-old woman with hypertension was referred with a three-week history of loss of vision OD and a three-day history of visual loss OS. The visual acuity was light perception OD and CF at 6 feet OS. Dilated fundus examination, confirmed with fluorescein angiography, demonstrated a CRAO OD and an inferior temporal branch retinal artery occlusion with macular involvement OS. Emboli were not observed in either eye. OCT did not demonstrate subretinal fluid.

An erythrocyte sedimentation rate (ESR) was normal for her age and although she denied systemic symptoms suggestive of giant cell arteritis (temporal arteritis), she underwent biopsy of the right and left temporal artery. Both specimens were diagnosed with severe temporal arteritis. The patient was placed on prednisone, 60 mg per day; she also began a course of six HBOT treatments, one per day, at 1.5 ATA for one hour. There was no change in the visual acuity or visual field of either eye following HBOT treatment.

DISCUSSION
In Hayreh’s model of elderly, atherosclerotic and hypertensive rhesus monkeys, a CRAO induced by clamping the artery for 240 minutes or longer resulted in massive and irreversible retinal damage (7, 8, 9). Unfortunately, the extrapolation of these facts to humans may have prevented research into treating longer-standing retinal artery occlusions.

Retinal perfusion has many variables, including the varying degrees and acuteness of the reduction in flow and the range, depending upon the patient, of differing perfusion pressures required to avoid retinal damage in different areas of the retina. There are multiple factors affecting the transit time of fluorescein dye: the size and distance of the vessel chosen for injection; the patient’s pulse rate, blood pressure and blood flow to the eye; and the fact that the test is performed on a patient when they are sitting (especially in the elderly) may not be truly representative of the arteriolar transit time to the eye of a supine patient undergoing HBOT.

The CRA may not be totally occluded but partially occluded or obstructed, and there are many variables that would determine the perfusion distal to the obstructed area.

It is reasonable to assume that, depending on the type and degree of obstruction, there will still be flow around the obstruction.

This differs from the acute and complete occlusion
in Hayreh’s monkey experiments. Delayed arteriolar filling of fluorescein dye in patients with CRAO is frequently seen, which Hayreh feels is artifactual, a point disputed by others (16). It is also reasonable to assume that the slow obstruction of a vessel may enlist compensatory mechanisms not present in Hayreh’s rhesus monkey model of an acute clamping of the central retinal artery.

There are other factors to consider. HBOT has been shown to reduce intraocular pressure, presumably from a decrease in episcleral venous pressure or a reduction in aqueous formation (17). The luminal size and shape of human cerebral bifurcations change with distending pressure (18). Changes in shape will vary the cross-sectional area, which would lead to a change in acceleration of the flow to the eye.

It is unknown whether the viscoelastic properties of the carotid bifurcation attenuate the variations in flow between systole and diastole. In addition, tethering of the anatomic structures may also act to constrain luminal shape changes.

These variables have not been addressed in the natural history studies that have previously been published, and it is unknown what role they play. As the HBOT treatments were all performed with the patient supine, the perfusion pressure to the eye (in this group of patients with vasculopathy) may be greater than if the patient were sitting. HBOT may not only provide increased oxygenation, but the reduction in intraocular pressure and an increase in perfusion pressure may help to move an embolus or thrombus to a more distal site and allow the “ischemic penumbra” to sufficiently reperfuse and to become functional.

These factors may all help to explain the temporary visual improvements described in patients while breathing supplemental, normobaric oxygen, as compared to the more long-standing visual improvement of those patients undergoing hyperbaric oxygen therapy.

The presence of subretinal fluid by OCT (Patient 3) may have contributed to the poor visual results. Whether pharmaceutical intervention, i.e., acetazolamide, which may reduce subretinal fluid, would have been beneficial in this instance is unknown. Future studies should include OCT assessment to determine whether the presence of subretinal fluid holds therapeutic implications.

Giant cell arteritis (temporal arteritis) is an important clinical entity whose mechanism of visual loss – and consequently its therapy – should not be grouped with nonarteritic CRAO. Unlike CRAO, temporal arteritis may produce a CRAO and also involve the posterior ciliary artery, the occlusion of which causes an anterior ischemic optic neuropathy and massive visual loss, sometimes in both eyes, as in Case 4. It is imperative that when suspected, the diagnosis and treatment of this condition should be promptly instituted.

Likewise, prompt investigation for the source of embolic phenomena is important to prevent a cerebral stroke from occurring. Treating the CRAO with HBOT should begin after the conditions that may result in serious morbidity and mortality have been excluded.

CRAO occurs in only 0.85 per 100,000 persons per year (2), which has made standardizing treatments difficult in a large trial. Yet, in Europe, the first randomized controlled prospective study comparing two treatment strategies for CRAO is ongoing (19). The EAGLE study was begun in June 2002, and the calculated sample size is 100 patients per subtrial (200 patients total). As of April 2005, 47 patients had been enrolled at 16 centers. The study seeks to compare “conservative therapy,” which they define as isovolemic hemodilution, ocular massage, one eyedrop of timolol 0.5% (a beta-blocker) and anticoagulation therapy for at least six months versus intra-arterial fibrinolysis. Inclusion criteria include CRAO not older than 20 hours.

Hayreh’s criticisms of the study (20) includes the 20-hour duration (which he feels is too long), the lack of a control group, the absence of specific information regarding patients with giant cell arteritis and, most importantly, that only 15.5% of emboli are platelet-fibrin in nature. The majority of emboli, 84.5%, are composed of cholesterol or calcium and are unlikely to be affected by fibrinolytic therapy (20).

This procedure is not without risk, including death (21), requires the continuous presence of specialized personnel and is expensive.

HBOT may address many of these concerns. The treatment is relatively safe, easily administered, low-cost (by comparison) and may potentially result
in better visual results, as it restores oxygen to the retina, irrespective of the type of embolus producing the occlusion (though this may affect long-term success). It seems apparent that in the above cases of nonarteritic retinal arterial occlusion, the retina may retain functional ability for a longer period of time than previously thought.

References


