Hyperbaric oxygen treatment of retinal artery occlusion

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ABSTRACT

Five patients with a one- to 12-day history of symptoms secondary to retinal artery occlusion (RAO) were treated with hyperbaric oxygen therapy (HBO_2) for one hour at 1.5 ATA. Four patients had been diagnosed with branch retinal artery occlusion (BRAO) and one patient with a cilioretinal artery occlusion. The three patients with macular sparing occlusions had experienced a loss of visual field, and the remaining two patients with macular involvement had marked loss of central visual acuity. All patients improved following HBO_2 treatment. There were no complications. HBO_2 may be a safe and effective treatment for patients with RAO.

INTRODUCTION

Retinal artery occlusion (RAO) is a common retinal-vascular disorder frequently producing visual loss (1-3). The retinal arteries originate from the central retinal artery, and in approximately 33% of eyes, there is a cilioretinal artery that arises from the posterior ciliary artery.

There are three types of cilioretinal artery occlusions:

(1) non-arteritic;

(2) arteritic associated with giant cell arteritis; and

(3) associated with central retinal vein occlusion.

Central retinal artery occlusion (CRAO) accounts for approximately 57% of occlusions, branch retinal artery occlusion (BRAO) for approximately 38% of occlusions, and cilioretinal artery occlusion for 5% of occlusions (4).

62% of BRAOs are caused by embolic phenomena (5). Ulcerated atheromatous plaques of the carotid artery and cardiac valves may be a source of cholesterol and calcific emboli (6). These emboli are reflective in appearance and commonly lodge at the bifurcation of a retinal arteriole. Platelet emboli are grayish-white in appearance and may appear in "showers." Subacute bacterial endocarditis may produce a BRAO from septic emboli.

Other causes of BRAO include severe arteriosclerosis, diabetes mellitus, arteritis, dysproteinemias, collagen vascular diseases, malignant hypertension, atrial myxomas and vasospasm resulting from migraines.

The misconception that all retinal vascular disorders are the same has resulted in confusion regarding the efficacy of therapy (7). Recognizing the type of arteriolar occlusion as well as the type of embolus has diagnostic, treatment and prognostic value. Treatment of the underlying medical condition that caused the BRAO is beneficial.

Favorable results using hyperbaric oxygen therapy (HBO_2) for acute BRAO have been reported (8,9). It has been accepted generally that there are no successful treatments for cases of longer duration.

MATERIALS AND METHODS

Five patients with non-arteritic RAO underwent ophthalmic examination, which included best-corrected visual acuity, intraocular pressure, biomicroscopic and dilated fundus examinations, fundus photography, computerized visual field testing (automated perimetry), fluorescein angiography and other ancillary testing, as indicated. Following medical screening for HBO_2 and informed consent, each patient underwent

six to 10 treatments with 100% oxygen for one hour at 1.5 ATA in a monoplace chamber. No adjunctive therapies – *i.e.*, anterior chamber paracentesis or pharmaceuticals – were used.

Case 1 – This 49-year-old male diabetic smoker presented with a three-day history of loss of vision of the right eye (OD). The visual acuity was counting fingers at 6 feet OD and 20/20 in the left eye (OS). Dilated fundus examination revealed a superior temporal BRAO with retinal edema and a cherry-red spot at the macula OD. Emboli were not observed. Visual field testing demonstrated dense visual field loss temporally. Fluorescein angiography confirmed a significant delay in the filling of the superior temporal branch retinal arteriole.

The patient underwent six sessions of HBO_2 (1 hour, 1.5 ATA), and when he returned for follow-up evaluation seven days later the vision had improved to 20/70 OD and there was a significant decrease in the previously observed retinal edema. Visual field testing also demonstrated a significant decrease in the size of the pre-treatment visual field defect unassociated with eccentric fixation.

Case 2 – This 74-year-old woman with a history of BRAO OS presented with a one-day history of a paracentral scotoma OD. The visual acuity was 20/20 in each eye (OU). Dilated fundus examination revealed retinal edema secondary to a superior temporal BRAO not involving the macula. The diagnosis was confirmed by fluorescein angiography. No emboli were seen.

The patient underwent six HBO_2 sessions (1 hour, 1.5 ATA), and when she returned five days later, there was a decrease in retinal edema, an improvement in the arteriolar filling time by fluorescein angiography and a significant improvement in the visual field.

Case 3 – This 78-year-old diabetic male with a history of carotid artery obstruction reported a one-week history of seeing a "shadow" in the right eye. The visual acuity was unchanged from prior examinations at 20/60 OU consistent with the patient's cataracts. Dilated fundus examination revealed an inferior temporal BRAO with visible platelet emboli. The diagnosis was confirmed by fluorescein angiography and visual field testing confirmed the loss of the superior visual field. He underwent four HBO_2 treatments (1 hour, 1.5 ATA), and four days later there was no change in the ophthalmic examination or in the visual field. When the patient returned another four days later, after undergoing an additional six HBO_2 treatments, he reported a decrease in the size of the "shadow." There was a significant decrease in the retinal edema and a mild improvement in the visual field. Two weeks later, he underwent right carotid endarterectomy.

The patient subsequently underwent cataract surgery OU, and the visual acuity improved to 20/25 OD and 20/30 OS.

Case 4 – This 87-year-old male with diabetes and cardiac disease reported a one-week history of seeing a "shadow" in the vision of the left eye. He was diagnosed with a macular sparing cilioretinal artery occlusion. No emboli were observed. The patient underwent six HBO_2 treatments (1 hour, 1.5 ATA), and five days later he reported a decrease in the size of the previously observed "shadow" OS, which was confirmed by visual field testing. There was a complete resolution of the retinal edema.

Case 5 – An 81-year-old woman with significant mitral valve disease (on Coumadin®) was found to have 20/25 vision OD and 20/40 vision OS. She returned 12 days later complaining of a one-week history of decreased vision OS. The visual acuity OS was now counting fingers at 6 feet. Dilated fundus examination revealed an inferior temporal BRAO with retinal edema and a macular cherry-red spot. A Hollenhorst plaque (cholesterol plaque) was visible in the corresponding arteriole at the optic disc.

The patient underwent four HBO_2 sessions (1 hour, 1.5 ATA), and when she returned on the third day after treatment the visual acuity was unchanged. Four additional HBOT treatments were performed, and 12 days later the visual acuity OS had improved to 20/50 + 2, where it remained three months later. A resolution of the retinal edema and an improvement in the visual field was also noted.

TABLE 1

Patient	Symptom duration (days)	Vision pre-Rx	Visual acuity post-Rx	Visual field (VF) post-Rx	No. of HBO_2 Rxs	F/U (days)
1	3	CF 6 ft OD[1] VF loss	20/70 OD	IMPROV	6	7
2	1	20/20 OU[2] VF loss	20/20 OU	IMPROV	6	5
3	7	20/60 OU cataract OU VF loss	20/60 OU post-cataract surg. 20/25 OD 20/30 OS	IMPROV	10	8
4	7	20/20 OU VF loss	20/20 OU	IMPROV	6	5
5	12	CF 6 ft OS[3] VF loss	20/50+2 OS	IMPROV	8	12

[1]OD = Right eye [2]OU = Both eyes [3]OS = Left eye

RESULTS

Four patients diagnosed with BRAO and one patient with a cilioretinal artery occlusion underwent HBO_2 treatment without complications. The three patients with macular sparing occlusions demonstrated improvements in the visual field, and the two patients with macular involvement demonstrated improvements in visual acuity and visual field (*Table 1*, above).

DISCUSSION

I have previously reported using HBO_2 at 1.5 ATA in the treatment of non-acute central retinal artery occlusion (10). Though 2.0 ATA was the recommendation in the UHMS HBO_2 Committee Report (11), 1.5 ATA was chosen for several reasons.

1. Hyperoxia in animal and human studies has been shown to restore retinal oxygenation (11,12).
2. Supplemental normobaric oxygen has resulted in visual improvement in some cases of retinal artery occlusion (11,13).
3. The retina is a neural tissue, and Holbach, *et al.*(14) reported that 1.5 ATA demonstrated a "favorable effect" on injured brain tissue as compared to 2.0 ATA.
4. A lower ATA would minimize the risk of complications, especially important in the elderly population that is most frequently affected by RAO.

The one-hour HBO_2 treatment was empirically chosen, and it is possible that longer-duration or additional treatments administered at the same or another pressure or even at various pressure levels may have resulted in a further improvement in visual acuity and/or the visual field.

After an RAO, the inner neuronal cells, supplied by the retinal arterioles, becomes edematous. The foveal retina has no inner layers and is supplied from the choriocapillaris. If the RAO includes the fovea, no edema or necrosis in the fovea occurs, and a cherry-red spot (due to the visualization of the choroidal vasculature through the transparent retina) is observed. These facts may impart a protective effect to the fovea and may

help to explain the visual improvement in the more long-standing cases. The two patients with observed emboli were both diagnosed with surgically correctable conditions. One patient underwent carotid endarterectomy; unfortunately, the second patient was not in sufficient health to undergo cardiac valve replacement.

Retinal artery obstruction may be a more accurate diagnosis than "occlusion," as most commonly a delay, not a complete absence in arteriolar filling is noted, implying a degree of blood flow. The label RAO does not differentiate between the varying degrees of obstruction, or the acuteness of the obstruction that is sufficient to restrict the perfusion and produce the clinical findings. A gradual onset of obstruction and the degree of obstruction may enlist compensatory mechanisms, as compared to an acute and complete occlusion, which may have a different prognosis. An understanding of the complexities of fluid dynamics (15,16) places the studies of vascular occlusion in proper perspective (17,18).

At low velocity (as in the eye), blood flow is non-turbulent and laminar. Dye infused in a vessel, such as fluorescein, flows along smooth lines called streamlines; there is little mixing across the fluid layers, as would occur in turbulent flow (although high-speed cinematography demonstrates that the red blood cells often collide with other red blood cells and with the vessel wall). Blood in motion displays a shear force called viscosity. The blood viscosity depends on many factors, including the hematocrit and the diameter of the blood vessel. In small vessels like retinal arterioles, that are less than 200 microns in diameter, the viscosity actually decreases with the blood vessel diameter. The red blood cells are approximately the same diameter as the capillary, and a parabolic velocity profile, as seen in larger vessels, does not occur. When blood flows from a blood vessel of large diameter into one of smaller diameter, the velocity profile changes with the distance along the smaller blood vessel. It can be assumed that there would be an abrupt change in velocity at the leading edge of an obstruction, and as the distance past the obstruction increases, a parabolic velocity profile would be obtained. The Poiseuille equation is typically used to describe the features of blood vessel flow.

$$i = \pi R^4 / 8\eta \ \ \Delta p / \Delta x$$

i = flux of viscous fluid
π = mathematical constant
R = radius of the blood vessel
$\Delta p / \Delta x$ = pressure gradient along the blood vessel
η = viscosity

However, the Poiseuille equation ignores the forces required to accelerate the blood, as would occur as the cross-section of the blood vessel changes and the pressure change required to accelerate the fluid between the two points (before and after a partial occlusion or obstruction) as in the acceleration of blood that occurs during systole.

Other deviations from Poiseuille flow are caused by the:

1. elasticity of blood vessel walls;
2. variations in viscosity caused by vessel size and hematocrit;
3. turbulence; and
4. a non-parabolic velocity profile, as occurs in capillaries and through a partial occlusion or obstruction.

There are many risk factors and causes of thrombosis which have been implicated in the development of non-uniform hemodynamics leading to blood vessel narrowing and occlusion. Atherosclerotic lesions tend to develop where there are significant disturbances in flow. The flow pattern is related to the geometry of the blood vessel and the input and waveform of the input flow.

A multitude of theories have been devised to predict the development of thrombotic lesions within the artery. One theory, high-wall shear stress, postulates that damage to the endothelial cells causes platelet aggregation. A contradictory theory, low-wall shear stress, states that there are recirculation zones where the velocity and shear stress are lower than normal flow conditions. Because there are longer particle resident times in these areas, the platelets become trapped, which leads to thrombosis.

The intravascular environment is complex, and in the absence of accurate mathematical

modeling and quantitative blood flow measurements, discussions regarding arteriolar occlusion will be observational. It is likely that the subjective and qualitative nature of treatment effectiveness will continue to result in controversy.

In order to fairly evaluate a new therapy, it is important to know what is being treated. RAO caused by a thrombus, may produce a greater obstruction to blood flow than a cholesterol crystal, which may allow flow around its edges. Consequently, the effectiveness of the treatment may be related to the cause of occlusion, and thus mixing the various types of RAO may not be appropriate.

Hayreh's model of elderly, atherosclerotic and hypertensive rhesus monkeys (19), in which a CRAO induced by clamping the artery for 240 minutes or longer resulted in massive and irreversible retinal damage, may not be applicable to the human situation. In the clinical setting, there are 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. It seems apparent that in the above cases of non-arteritic RAO, the retina, or at least a portion of the retina, may retain functional ability for a longer period of time than previously thought.

There is autoregulation of the retinal but not the choroidal blood supply, and oxygen diffuses into tissue by simple diffusion, not just saturation. Retinal oxygenation can be restored after arterial occlusion by hyperoxia (11,12). The administration of 70% oxygen one day after experimental retinal detachment in cats was found to be highly effective in preserving photoreceptors and in reducing proliferation (20). Hyperbaric oxygen may also prove valuable in the preoperative treatment of retinal detachment patients to improve the postoperative visual acuity (especially in macular-off retinal detachments) and possibly to reduce the development of proliferative vitreoretinopathy, a significant cause of the failure of retinal detachment repair. While it is assumed that hyperoxia accounts for the treatment successes, there may also be other biochemical benefits of HBO_2. In order to assess the effectiveness of treatment, comparisons must be made to the natural history of the condition. In the Mason, *et al.,* study (5), 10 of 14 patients (71%) with BRAO who presented with a visual acuity of 20/200 or less, did not improve. If the presenting visual acuity was 20/40 or better, 89% maintained good visual acuity.

Hayreh, *et al.*, reported (1) that abnormal central visual field defects improved in 47% of those patients seen within seven days of onset and 6% worsened. Abnormal peripheral visual field defects improved in 52% and worsened in 3% of eyes seen within seven days of onset. Treatments for RAO, such as laser embolysis (4) and surgical embolus removal (21) carry significant risk and, according to Hayreh (1), have results no different from that expected from the natural history of RAO.

While a randomized controlled trial (RCT) is considered the "gold standard" to determine the benefits of a therapy, Hawkins, *et al.* (22) have called into question whether sham treatments are necessary when visual acuity is the outcome of interest. Data from the control arms of five completed randomized trials of treatments for age-related macular degeneration were analyzed, and no important differences were noted in the two-year visual acuity outcomes. This information may be used to construct a lower-cost RCT free from the expenses of developing and administering the placebo used to evaluate the effectiveness of HBO_2 in the treatment of RAO.

HBO_2 is a relatively safe, inexpensive and easily administered treatment that may produce an improvement in vision in an otherwise visually devastating condition. Further study is required to determine the value of this therapy in the treatment of retinal artery occlusions.

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