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CASE REPORT

Early Onset of Ocular Neovascularization After Hyperbaric Oxygen Therapy in a Patient With Central Retinal Artery Occlusion

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ABSTRACT

Central retinal artery occlusion (CRAO) is an infarction to the retina that results in acute, frequently severe vision loss. Long-term complications such as ocular neovascularization (ONV) can occur and result in neovascular glaucoma and vitreous hemorrhage. Recent studies have explored acute hyperbaric oxygen (HBO) therapy as a promising treatment for CRAO to improve long-term vision potential; however, its effects on CRAO complications have not been well characterized. This study was conducted to better characterize the effects of HBO therapy on complications from CRAO. We present a unique case of ONV in an eye within 1 month after successfully completing acute HBO therapy for a CRAO, highlighting the importance of routine monitoring in this unique population.

Keywords: Central retinal artery occlusion; Glaucoma; Hyperbaric oxygen; Neovascular glaucoma

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INTRODUCTION

Occlusion of the central retinal artery can cause retinal ischemia, infarction, and acute vision loss [1]. Similar to ischemic cerebrovascular accidents, an embolic etiology is commonly from either a carotid artery or cardiac plaque, the latter often from atrial fibrillation [1, 2]. Recent studies have shown that the most meaningful risk factor for central retinal artery occlusion (CRAO) is an ipsilateral carotid artery stenosis; thus early imaging of the greater neck vessels is essential for management [3]. Ocular neovascularization (ONV) has been reported to occur in up to 19% of cases [4–7]. This can involve neovascularization of the iris, the optic

disc, or the surrounding retina. ONV onset following CRAO has been described anywhere from 2 weeks to 2 years after the original event, although the majority occur between 8 and 12 weeks afterward [6, 8]. ONV can further decrease vision and cause pain if neovascular glaucoma develops. Currently, there is a paucity of proven clinical treatments for CRAO. Treating CRAO with hyperbaric oxygen therapy (HBO) has been reported in animal studies and small series; however, we lack large controlled human studies [9–14]. Its impact on downstream complications such as ONV is currently not well understood; thus, there is great interest in further investigation within this unique patient population.

CASE REPORT

A 70-year-old African male reported to the emergency department with decreased vision in the right eye (RE) and headache. His past medical history included hypertension, hyperlipidemia, diabetes mellitus, long-term poor vision in the left eye (LE) from previous ocular trauma, and pseudophakia of the RE. He described intermittent darkening of RE vision for the past 4 days along with a mild headache; however, he was able to read small print until 24 h prior to admission, when his RE vision decreased abruptly. He denied recent weight loss, fever, myalgia, or jaw claudication. He had an erythrocyte sedimentation rate of 32 mm/h (normal: 0–10 mm/h), C-reactive protein of 1.6 mg/L (normal < 5.00 mg/L), and platelet count of 286 k/cmm. His best-corrected visual acuity (BCVA) was 2/200 in the RE with eccentric fixation and light perception in the LE. Intraocular pressure (IOP) was 15 mmHg in the RE. Anterior segment examination revealed a normal-appearing RE with a deep anterior chamber depth and no rubeosis or cell, while the LE had the appearance of phthisis bulbi. Gonioscopy showed that the RE angle was open to trabecular meshwork without neovascularization of the angle. Fundus examination showed a normal-appearing optic nerve in the RE, patchy retinal edema and whitening throughout the macula, and a cherry red spot, and normal-appearing peripheral vasculature (Fig. 1). His clinical presentation was most consistent with intermittent episodes of amaurosis fugax beginning 4 days prior with onset of CRAO 1 day prior to presentation.

The patient was admitted for stroke evaluation as well as acute HBO therapy. The patient was initiated on daily clopidogrel therapy for secondary stroke prevention, and adjustments were made to his medication regimen to better control hypertension, hyperlipidemia, and diabetes mellitus. Magnetic resonance imaging and angiography of the brain revealed no acute findings, transthoracic echocardiography with bubble study did not reveal any cardiac septal defects, plaques, or emboli, and cardiac telemetry was unconcerning. MR angiography of the neck revealed 60% narrowing of a short segment of the distal internal carotid artery at the level of the C2 vertebrate. Humphrey 24-2 visual field testing revealed a small inferior central scotoma in the RE consistent with the known area of retinal edema (data not shown). The patient received two HBO treatments of 4 h duration each day for 5 days total as per our protocol. On the second day of hospitalization, fluorescein angiogram (FA) of the RE was obtained and showed poor perfusion to the macula (Fig. 2). After completion of the 5-day protocol, the patient was discharged to home with BCVA of 2/200 RE and IOP of 11 mmHg RE. Per our protocol, we monitor all CRAO for development of neovascular glaucoma up to 1 year following the initial insult.

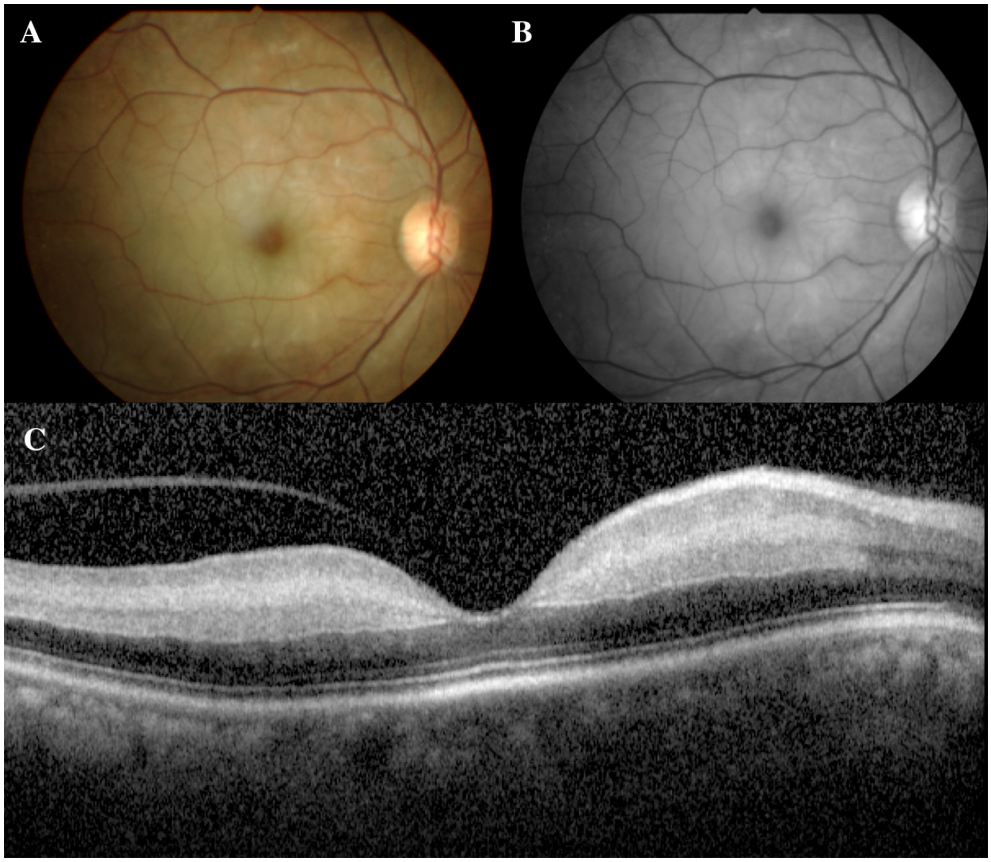

Fig. 1 CRAO in right eye of patient. Images obtained 1 day after presentation include fundus photography exhibiting *cherry red* spot in macula (**a**), red-free photography (**b**), and OCT through fovea showing extensive inner retinal edema (**c**). Humphries 24-2 visual field testing revealed nonspecific defects and a small inferior central scotoma in the right eye consistent with known area of retinal insult (**d**). *CRAO* central retinal artery occlusion, *OCT* optical coherence tomography

Subsequently, the patient followed up with an outside eye care provider 24 days after the onset of symptoms and was found to have elevated IOP in the RE. He was started on dorzolamide/timolol drop twice per day and referred to our retina service 2 days later. His BCVA was 20/400 and IOP was 28 in the RE upon presentation. Anterior examination revealed neovascularization of the iris and angle on gonioscopy. Posterior examination showed neovascularization of the optic disc with extensive pigmentary alteration in the macula, but no retinal whitening. Optical coherence tomography showed retinal atrophy in the macula, and FA showed retinal ischemia and leakage from neovascularization of the optic disc (Fig. 3). The diagnosis of neovascular glaucoma (NVG) secondary to CRAO was made, and the patient underwent pan-retinal photocoagulation to the RE. One month later, his RE vision and IOP had improved to 20/100 and 20 mmHg, respectively. His neovascularization had fully regressed, and he has remained stable for over 1 year of follow-up with IOP of 12 RE off topical medications.

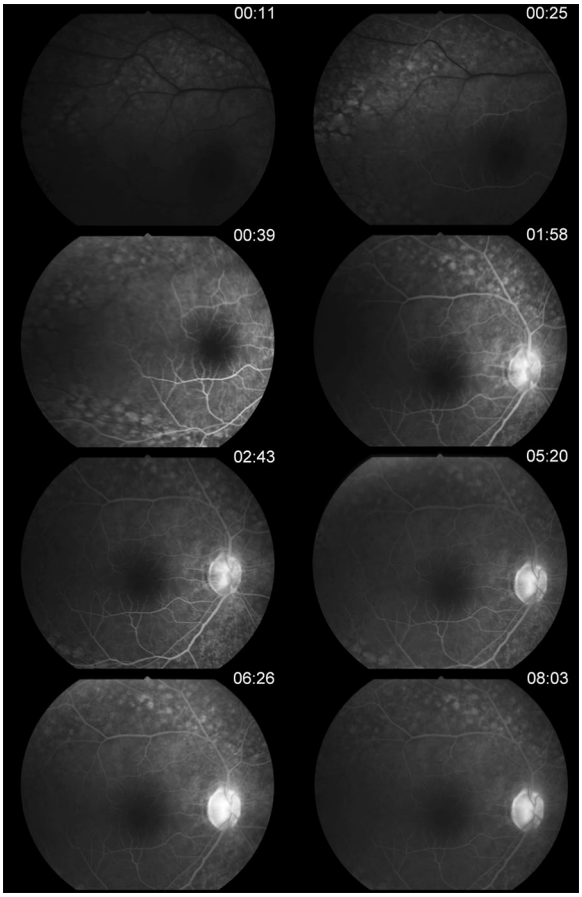

Fig. 2 FA of right eye with CRAO. Images obtained 1 day after presentation show macular ischemia with normal peripheral retinal perfusion. Timing of the study is shown in the *upper right corner* of each image (in minutes). *CRAO* central retinal artery occlusion, *FA* fluorescein angiogram

Compliance with Ethics Guidelines

Informed consent was obtained from the patient for being included in this study.

DISCUSSION

ONV is a serious complication following CRAO with reported incidence ranging up to 19% [1]. There is evidence that CRAO with more severe ischemia may have a higher risk of neovascularization [4–7]. Central retinal vein occlusions have higher rates of neovascularization when there is more ischemia present initially. The literature is lacking in any large or systematic analysis of the complication rate after treatment with HBO or, for that matter, with rapid reperfusion by other means such as digital massage, anterior chamber paracentesis, or hypercapnia.

A proposed mechanism of HBO therapy is that the elevated blood oxygen content achieved through HBO allows oxygen to diffuse more effectively into the retina from choroidal circulation. The inner retina that normally relies on central retinal artery perfusion receives sufficient oxygenation from both the choroidal vasculature and any residual retinal artery perfusion to survive until the central retinal artery recanalizes [15, 16]. This is predicated on applying the HBO while the retinal ischemia is still reversible, typically within the first 2 days after the inciting event.

The vision in our patient did improve with HBO, but remained poorer than it was prior to the CRAO, and far poorer than that of many other eyes at our institution that undergo prompt HBO therapy for CRAO. This was most likely due to our inability to fully reverse the initial ischemic retinal insult. He probably sustained a large component of irreversible macular ischemia from the series of transient amaurosis episodes and the 24 h of CRAO prior to onset of HBO therapy. This may well be the reason for his development of ONV and it would have happened regardless of whether he underwent HBO therapy. His ONV developed a little less than a month after the CRAO, within a time range that has certainly been reported after untreated CRAO, although it is on the earlier side of the spectrum.

A potential mechanism beyond just profound initial ischemia may involve the HBO therapy itself. The acute HBO protocol for CRAO at our institution during the time of this study included two treatments per day for a

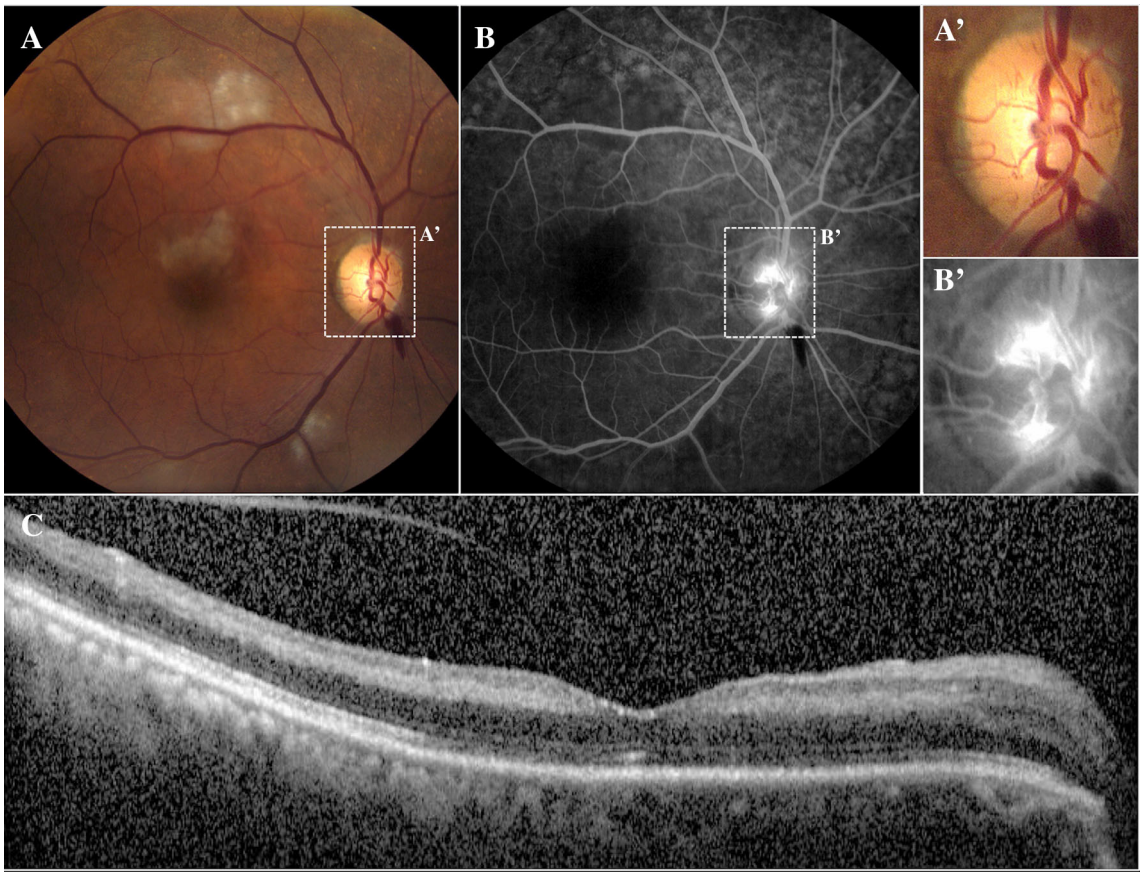

Fig. 3 Imaging from our patient 24 days after CRAO. Fundus photo shows improved retinal whitening and pigmentary mottling throughout (a). FA shows persistent retinal ischemia along with leakage from neovascularization of the disc (**b**). *Enlarged images* better characterize neovascularization of the disc (**A′**) and FA leakage (**B′**). Inner retinal edema has improved, but still mildly present along with significant atrophy (**c**). *CRAO* central retinal artery occlusion, *FA* fluorescein angiogram

total of ten sessions or 5 days, which is derived from previous studies and treatment algorithms proposed by other groups [9, 12]. Even though the patient initially presented possibly outside of the 24 h treatment window, we felt compelled to offer HBO to provide as much potential as possible for him to recover vision in his RE in the monocular setting. ONV is driven by vascular endothelial growth factor (VEGF) released from ischemic retinal tissue that is not dead. When initial infarction occurs, the retina declines to an ischemic state, and VEGF begins to be released. Over time, the ischemic retina in an untreated patient declines further into necrosis and atrophy; thus, VEGF secretion is stopped. It is conceivable that in the HBO-treated patient, the ischemic phase is prolonged by the improvement in retinal oxygen saturation, thus enhancing VEGF release and potentially worsening ONV (Fig. 4). Further clinical studies will be essential to further elucidate this process.

CONCLUSION

Ultimately, HBO remains a controversial treatment modality for CRAO, a condition for which we are still without a proven and widely

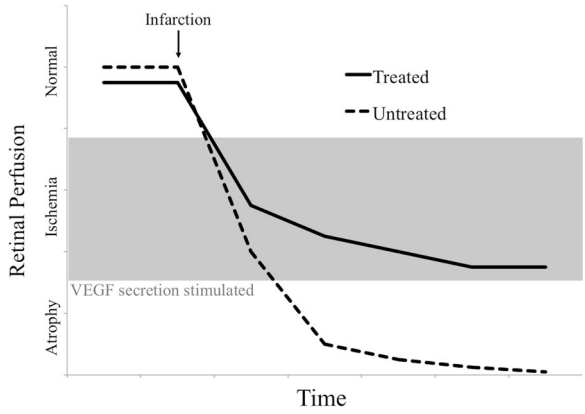

Fig. 4 The proposed mechanism of VEGF elevation by HBO therapy in CRAO. After acute infarction, profound retinal ischemia induces a period of time where VEGF is released in response. While the untreated retina eventually declines into atrophy and death (*dotted line*), the HBO-treated retina is maintained in a prolonged ischemic state (*solid line*). This can promote prolonged VEGF release to result in a relatively quicker onset of ONV compared to the untreated retina. *VEGF* vascular endothelial growth factor, *HBO* hyperbaric oxygen therapy, *CRAO* central retinal artery occlusion, *ONV* ocular neovascularization

accepted means of improving vision. The NVG was treated effectively in this patient, and his current level of vision in the RE is most likely due to the original CRAO rather than the subsequent ONV. This case does underscore, however, that patients undergoing HBO for CRAO may need to be followed more closely for the development of secondary CRAO complications such as ONV compared to those who have not undergone HBO.

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Compliance with Ethics Guidelines. Informed consent was obtained from the patient being included in the study.

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