Age-related macular degeneration and hyperbaric oxygen

To the Editor:

We read with interest the study by Dr. Jeffrey Weiss concerning age-related macular degeneration (ARMD/AMD) and hyperbaric oxygen [1]. Dr. Weiss is to be commended for his interest in this area of research. However, we disagree with the data Dr. Weiss cites to support his conclusion that all 14 patients showed improvement.

We believe that visual field examination plays no important role in assessing central macular function. Formal visual field testing requires fixation of the macular retina upon an immovable central target. Aside from providing a reproducible result, the macula plays no other role in visual field testing. We believe assessment of changes in ARMD is better managed by ocular computed tomography (OCT) or angiography than peripheral visual field testing, which was developed to test and follow patient responses to threshold targets presented to the non-macular retina.

Visual field testing is also dependent upon the time of day, level of patient fatigue, amount of prior light exposure and the patient's experience with the test and machine. We feel that the results of visual field tests are of limited import regarding patient outcomes in response to hyperbaric oxygen.

We are concerned that Dr. Weiss appears to be the treating ophthalmic physician and the follow-up physician reporting outcomes. The potential for selection and outcome bias is significant in this paper. In addition, all 14 of his patients are reported to have positive outcomes in visual acuity or visual fields examination. This result alone raises further question of treatment and/or observational bias.

We studied six patients with ARMD in a non-randomized fashion similar to the Weiss study. Entrance criteria were that the patient has dry ARMD with no other treatment options. Two of the six patients had geographic atrophy (GA). A general ophthalmologist was the referring physician who recruited patients for our study. All patients met the examination criteria suggested in the Weiss paper. In addition, these patients were seen by one of two retina surgeons for retinal examination and ocular computed tomography (OCT) prior to entering the study. Evaluations in the post-treatment period now date between two and three years.

Hyperbaric oxygen exposure was based on published studies related to traumatic macular edema or cystoid macular edema. While this is not the same etiology or disease process, it was a starting point. Each patient received 20 exposures at 2.2 ATA with 90 minutes of oxygen breathing.

Our patients were followed by using best-corrected acuity to Snellen targets at distance and near, with early treatment diabetic retinopathy study (ETDRS) basis. In addition, Amsler grid testing was performed at the follow-up visits. Each of these tests was performed with a standard, consistent and reproducible lighting source. None of our patients had improvement in visual acuity noted on long-term follow-up examinations. One of the six patients was lost to follow-up, and one with GA had worsened visual acuity since treatment, thought to be due to advancing disease. In the other four patients, no change in visual acuity has been noted. As a group, the patients' perception of vision was improved; however, there was no measurable change in vision.

In addition, these patients were monitored for onset of exudative change, optic nerve atrophy, vasculitis and choroidal effusion. These complications have been noted in other ARMD interventions but were not seen in any patients exposed to hyperbaric oxygen.

While both studies are non-randomized case series, we come to opposite conclusions regarding exposure of ARMD patients, with and without GA, to hyperbaric oxygen in therapeutic settings. We do agree that a randomized controlled trial would determine whether hyperbaric oxygen has any role in stemming the ravages of ARMD.

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Reference

1. Weiss JN. Hyperbaric oxygen therapy and age-related macular degeneration. Undersea Hyperbaric Med 2010; 37:2; 101-105.

Age-related macular degeneration and hyperbaric oxygen: *Response*

To the Editor:

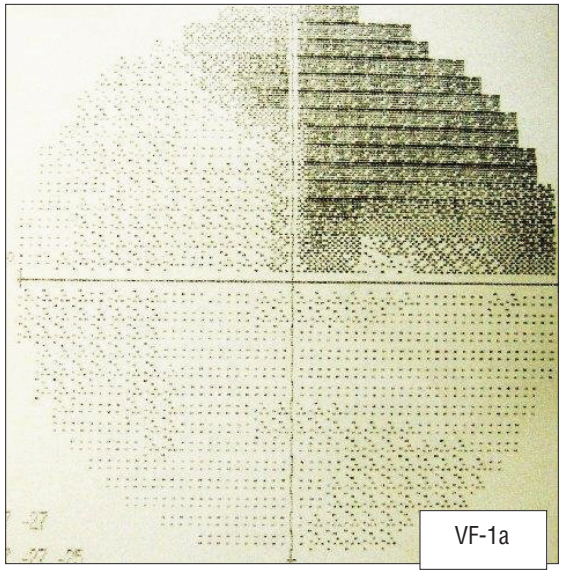
Dr. Worth and Dr. Carver's letter [1] regarding my article [2] represents a misinterpretation of my work. I reported the treatment of 14 patients with visual loss secondary to age-related macular degeneration (AMD/ARMD) with hyperbaric oxygen therapy (HBO_2). I submit that their assertions are incorrect, and I would like to offer some additional information to help clarify my position.

Visual acuity testing by a trained ophthalmic technician using a standardized eye chart and computerized perimetry (visual field testing) are foundations of ophthalmic examination. Computerized perimetry is used for the detection and monitoring of glaucoma, intracranial tumors, optic nerve disease and other conditions. This is a highly sophisticated and precise test and may be performed in the absence of macular function. In my study, I utilized program 10-2 of the Humphrey Field Analyzer, the most commonly used automated perimeter in the United States. This machine offers a wide range of static field tests, including screening and threshold tests and analysis strategies, with an in-depth statistical analysis of the numerically reported test results. Not only are the results comparable over time, they are comparable from machine to machine. The entire test is automated, and there is no operator-induced bias. Figures *1a* and *2a (below and facing page)* are the pre-HBO_2 visual fields from two representative patients in the study; Figures *1b* and *2b (below and facing page)* are the post-HBO_2 visual fields. The decrease in the size of the scotoma in each case is clear.

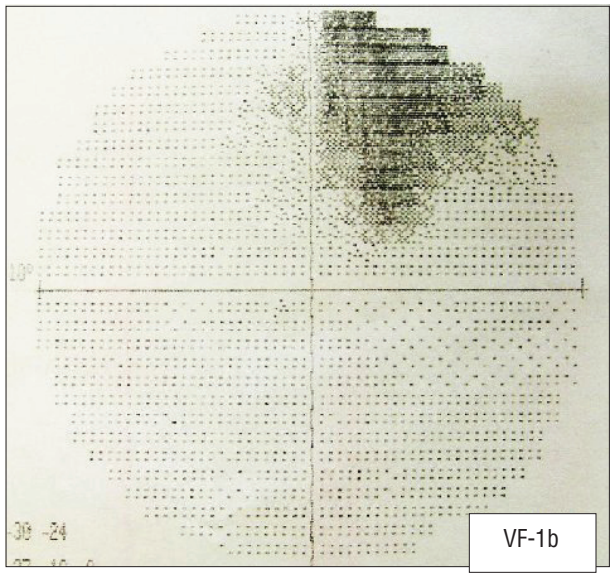
25 patients who met entrance criteria were prospectively offered HBO_2, and 14 of these patients consented to undergo treatment. (I have now treated more than 40 patients, and approximately 90% have experienced an improvement in their visual acuity and/or visual field.) All patients had previously undergone visual field testing and were familiar with the testing procedure. The perimeter uses the 31.5 apostilb (asb) background illumination that was set as a standard by the International Perimetric Society. Projected stimuli are utilized that can be varied in intensity between 0.08 and 10,000 asb, or over a range of greater than 5.1 log units (51 decibels).

Computerized static perimetry varies stimulus intensity in such a manner that all results may be compared directly; no conversion from one spot size to another is necessary. The machine performs a self-diagnostic program prior to use (which includes light intensity), assuring the consistency of results. The patient is automatically monitored for fixation losses using the Heijl-Krakau blind spot monitoring technique, which periodically exposes a stimulus in the blind spot. As the normal blind spot is approximately 5-7 degrees in size, fixation shifts of only a few degrees can be detected. Both false positive and false negative errors are also automatically reported. Time of day as related to patient fatigue would be detected, but this was never an issue in this study.

Visual acuity and computerized perimetry are functional tests. Both optical coherence tomography (OCT) (not ocular computed tomography [1]) and



VF-1a



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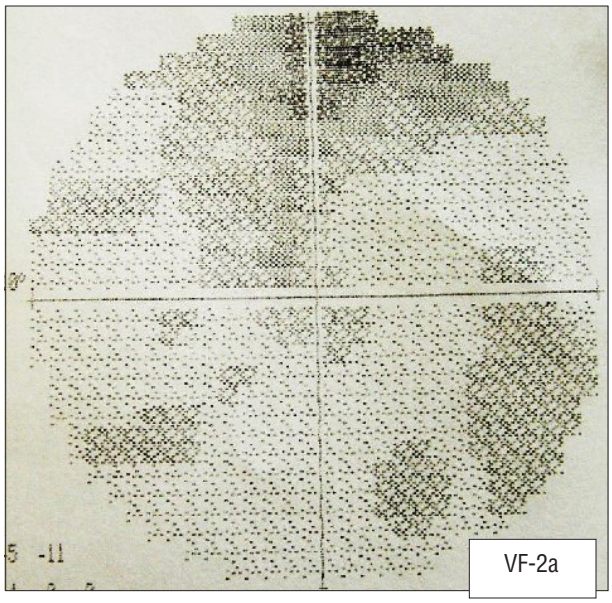
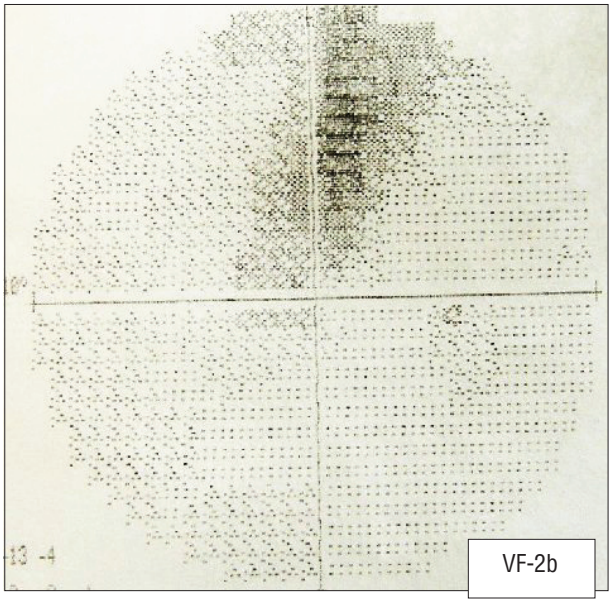


VF-2a



VF-2b

fluorescein angiography are imaging studies. Whereas OCT is a noninvasive test that measures retinal thickness, fluorescein angiography is invasive, carries the risk of anaphylactic reaction including death, and is unnecessary in the monitoring of dry AMD.

Dr. Worth and Dr. Carver state that my examination and treatment together raise concerns regarding bias. Physicians advance the practice of medicine by intervening in a well-studied disease process and achieving beneficial results. New findings are the basis for new treatments.

The authors also report that they studied six patients with AMD. They based their treatment on published studies related to traumatic macular edema and cystoid macular edema, while noting that "this is not the same etiology or disease process." Not surprisingly, they report that their treatment wasn't effective.

Their six patients with dry AMD were treated with 20 hyperbaric treatments at 2.2 ATA with 90 minutes of oxygen breathing. The retina is a neural tissue, and my rationale for using 1.5 or 1.75 ATA for 60 minutes was based on the report by Holbach [3], who found that 1.5 ATA resulted in a nearly balanced cerebral glucose metabolism and that 2.0 ATA caused a disturbed oxidative energy formation from an increase in cerebral glycolysis. Oxygen is a drug, the dosage determined by the ATA, duration and frequency of treatment and percentage of oxygen. More is not necessarily better and may be ineffective, or at worse, damaging.

Dr. Worth and Dr. Carver report that "none of our patients had improvement in visual acuity noted on long-term follow-up examinations." This is the most telling statement, for several reasons. If a patient's visual acuity is 20/200 because of an atrophic area centered at the macula, there could not be an improvement in visual acuity with HBO_2 — no more than a missing limb will regrow. Alternatively, if the patient sees 20/20 and has eccentric geographic atrophy not affecting the macula, there also would be no improvement in visual acuity following HBO_2. That is the specific reason visual field testing must be employed to detect the decrease in the size of the scotoma following therapy.

Dr. Worth and Dr. Carver state that "the patient's perception of vision was improved," but by not performing a visual field test, they cannot quantify measurable improvement. Also, the condition is, by definition, age-related. Long-term follow-up does not determine success, because AMD will progress over time. Short-term follow-up will detect the improvement, and subsequent examinations will assess stability. In my patient population, the visual benefit of HBO_2 appeared to last for eight to 17 months before a decrease in the visual acuity or visual field occurred, coincident with an increase in the macular degeneration. Retreatment of two patients resulted in improvement, the degree of improvement dependent on the change in the nature of the retinal condition.

Dr. Worth and Dr. Carver also report that their six patients (with one subsequently lost to follow-up) were monitored for onset of exudative change (I assume that they meant the onset of neovascularization or wet macular degeneration), optic nerve atrophy, vasculitis and choroidal effusion. While optic nerve atrophy may occur from extensive and long-standing AMD, I have never seen the last two "complications" of AMD in my 30 years of medical practice. It is not surprising that, using a different treatment regimen they come to different conclusions regarding the effectiveness of my treatment regimen.

I agree that, to validate this work, a randomized controlled clinical study will be necessary. Many of the current large-scale retinal trials employ a central reading center to confirm the diagnosis and enrollment criteria and allow entry to the study. We must be held to the same standard if this work and its results are to be accepted so that other practitioners will refer their patients for HBO_2. It is exciting that this treatment may be beneficial in the treatment of certain "untreatable" retinal diseases. Perhaps one day in the future there will be certifications in HBO_2 and retinal diseases in collaboration with the ophthalmological societies.

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References

1. Worth ER, Carver JA. Letter to the Editor-Hyperbaric oxygen treatment of macular degeneration. Undersea & Hyperbaric Med 2010; 37:5; 371.

2. Weiss JN. Hyperbaric oxygen treatment of macular degeneration. Undersea & Hyperbaric Med 2010; 37:2; 101-105.

3. Holbach KH, Caroli A, Wassmann H. Cerebral energy metabolism in patients with brain lesions at normo- and hyperbaric oxygen pressures. J Neurol 1977;217:17-30.