Adjunctive hyperbaric oxygenation in macular edema of vascular origin

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Krott R, Heller R, Aisenbrey S, Bartz-Schmidt K-U. Adjunctive hyperbaric oxygenation in macular edema of vascular origin. Undersea Hyper Med 2000; 27(4): 195-204. — Macular edema (ME) is a primary reason for permanent decreases of visual acuity (VA) in diabetic retinopathy and retinal vein occlusions. The standard treatment (photocoagulation, rheological treatment) provide only a limited success. We have therefore studied the additional use of hyperbaric oxygenation (HBO2) in patients with persistent ME. Five patients (1 female, 4 male; 7 eyes) were treated by adjunctive HBO2. The average age of the patients was 60.6 (38.9-76.8) yr. The VA was measured with Early Treatment Diabetic Retinopathy Study charts before and after HBO2 with a monthly follow up. Fluorescein angiography was performed before and after HBO2 with a follow up every 3 mo. Each patient received 10-30 HBO2 treatments (median 15). The follow-up period was 15 mo. for every patient. The mean increase in VA was 3.5 (2-4) lines after HBO2. Retinal photocoagulation was performed in six eyes. Diabetic macular edemas showed no morphologic change, while ME originating from retinal vein occlusions (CME) regressed. The VA in our patients with ME of vascular origin seemed to improve with HBO2. Photocoagulation was necessary in most cases. Visual function correlated with the angiographic presentation only for CME.

cystoid macular edema, diabetic retinopathy, hyperbaric oxygenation, photocoagulation, retinal vein occlusion

Macular edema (ME) is a frequent complication of diabetic retinopathy and retinal vein occlusions, often causing severe disturbance of visual acuity (VA). Over a 15-yr period, diabetic macular edema (DME) is detectable in 20% of diabetic retinopathies after the onset of the disease (1-3). Cystoid macular edema (CME) resulting from retinal vein occlusions has an incidence of 30-50% (4-7). General treatment approaches (medication, hemodilution, plasma differential separation) address the underlying cardiovascular disturbances. High-risk diabetic retinopathy and extended ischemia due to retinal vein occlusions are often concomitant with ME and implicate panretinal laser photocoagulation (PRP) to prevent neovascularizations, but there is no specific treatment for ME. Focal laser photocoagulation (PC) as well as macular grid laser photocoagulation (GRID) and hemodilution of CME seem to have a beneficial effect (8-11). According to physiologic considerations and some reported cases (12-17), hyperbaric oxygen (HBO2) promises to be a therapeutic option for ME. Oxygen (FiO2 = 1.0) is administered in a chamber pressurized to above ambient pressure (>100 kPa). A surplus of oxygen is taken to the tissues after alveolar uptake by increased aqueous solution. HBO2 is recommended in the treatment of various infectious and ischemic diseases (18), but long-term follow-up studies of its use in ME of vascular origin have not yet been published.

METHODS AND PATIENTS

Five patients (seven eyes, Table 1), affected by cystoid macular edemas, were treated with adjunctive HBO2. The average age was 60.6 yr. There was no standard treatment protocol before HBO2. Therapeutic decisions were based on the clinical presentation of visual function and ophthalmoscopic findings. Treatment included basic medication, acetazolamide, hemodilution, PC, PRP, and plasma differential separation. VA was assessed according to the Early Treatment Diabetic Retinopathy Study (ETDRS) guidelines before and after HBO2. Follow up was every month thereafter. Additionally, fluorescein angiography was done before and after HBO2 with follow up every 3 mo. Suitability for HBO2 was ascertained in all patients. This evaluation followed the guidelines of the German Diving and Hyperbaric Medical Society (GTÜM e.V., 33) and included medical history, cardiopulmonary examinations with electrocardiogram (ECG) and chest X-rays, as well as measurements of pulmonary volumes (Cardiovit AT-10, Schiller AG, CH-6340 Baar). Threshold and impedance audiometry (DI 920, KIND, D-30928 Burgwedel) with microscopy of the tympanic membrane during Toynbee or Valsalva maneuvers (OPMI 9, Carl Zeiss, D-73446 Oberkochen).
Table 1: Synopsis of Patient Data

<table>
<thead>
<tr>
<th>Patient/Eye</th>
<th>Diagnosis</th>
<th>sph</th>
<th>VA Pre-HBO₂</th>
<th>VA Post-HBO₂</th>
<th>Improvement in Lines</th>
<th>LC Pre-HBO₂</th>
<th>LC Post-HBO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/ RE</td>
<td>DM II</td>
<td>±0.00</td>
<td>0.1</td>
<td>0.2</td>
<td>3</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>1/ LE</td>
<td></td>
<td>+1.00</td>
<td>0.25</td>
<td>0.63</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/ RE</td>
<td>DM II</td>
<td>+2.25</td>
<td>0.1</td>
<td>0.16</td>
<td>2</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>2/ LE</td>
<td></td>
<td>+3.75</td>
<td>0.2</td>
<td>0.4</td>
<td></td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>3/ LE</td>
<td>DM II</td>
<td>+0.75</td>
<td>0.16</td>
<td>0.4</td>
<td>4</td>
<td></td>
<td>yes</td>
</tr>
<tr>
<td>4/ RE</td>
<td>CRVO</td>
<td>−0.75</td>
<td>0.16</td>
<td>0.5</td>
<td>5</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>5/ LE</td>
<td>BRVO</td>
<td>+0.38</td>
<td>0.32</td>
<td>0.8</td>
<td></td>
<td>no</td>
<td>no</td>
</tr>
</tbody>
</table>

Key: LE = left eye; RE = right eye; DM II = diabetes mellitus type II; CRVO = central retinal vein occlusion; BRVO = branch retinal vein occlusion; sph. equivalent = spherical equivalent; HBO₂ = hyperbaric oxygen; VA = visual acuity; LC = retinal laser photoagulation.

were performed. Oxygen (FIO₂ = 1.0) was administered in a multiphase compression chamber (Starmed 2200/5 Eco, HAUX-Life-Support, D-76307 Karlsbad) at an absolute pressure of 240 kPa 3 times for 30 min following the standardized protocol TS 240-90 (GTÜM e.V., 33). Compression velocity up to the attainment of the treatment pressure was titrated under otoscopic monitoring, maximal compression velocity being 14 kPa/min. Regulation of pressures was controlled digitally (DEKOMAT plus V. 1.40, HAUX-Life-Support, D-76307). Monitoring consisted of videographed supervision, supraclavicular transcutaneous oxygen measurements (tcPO₂, Radiometer, D-47862 Willich), and continuous ECG monitoring in cases of cardiac history.

Eight HBO₂ series were performed on the five patients with repetitions on patient 2 (7 and 5 chamber treatments, respectively, interval: 4 mo.), patient 4 (10 and 10 respectively, interval: 1 mo.), and on patient 5 (15 and 15 respectively, interval: 5 mo.). HBO₂ (once daily, 5 times per week) consisted of 5–15 chamber treatments (average: 10.9). During oxygen application an average tcPO₂ of 1,334 mmHg (range: 1,227 to 1,505 mmHg) was attained. The time of follow up after the first HBO₂ series was 14 mo.

CASE REPORTS

Case 1: This 63-yr-old man has suffered from diabetes mellitus type II for the last 18 yr; he has received insulin for the last 6 yr. Fasting blood glucose values were in the normal range. We measured 6.4 mmol/liter postprandially and after chamber treatment. There was no history of arterial hypertension or other cardiopulmonary disorders. No ophthalmologic diseases had been diagnosed until 1991. In 1993 the patient received PRP for the onset of high-risk diabetic retinopathy. DME with visual impairment developed in 1994. In October 1994, VA best-corrected (bc) was 0.4 in the right eye (RE) and 1.0 in the left eye (LE). He received PC in 1996 for his RE, but his visual performance declined progressively. In October 1997, VA was 0.4 in the RE and 0.5 in the LE. He initially came to our department in December 1997. At that time, VA was 0.2 (bc with +0.5 to −1.0/100) in the RE and 0.4 (bc with +1.0) in the LE. Macular PC of the LE and peripheral PRP of the RE were added and resulted in a further deterioration of vision (RE: bc 0.1; LE: bc 0.25). In February 1998, HBO₂ was initiated over a period of 2 wk. Improvement of VA to 0.25 in the RE and 0.5 in the LE were noted. Later, VA rose to 0.63 in the LE, whereas the RE lost one line to 0.2. To treat retinal ischemia, both eyes received a PRP (1,000 burns, applied in fractions of 250 burns, 200 μm) 2 mo. after HBO₂ treatment (Fig. 1) without alteration of central retinal function. There was no significant change in the angiographic presentation of his cystoid macular edema (Fig. 2).

Case 2: This 76-yr-old man reported a history of diabetes mellitus type II over the last 20 yr. Insulin had been prescribed for 17 yr and has resulted in sufficient
regulation of blood glucose (fasting: 6.7 mmol/liter). Further medical history revealed coronary artery disease (posterior myocardial infarction in 1994, coronary artery bypass grafts in 1995, right bundle-branch block). With a medication of lisinopril, isosorbide dinitrate, and sotalol, blood pressure and cardiac performance were normalized. Since 1992 a progressive impairment of visual function had been observed in both eyes. When first seen in April 1996, we observed a bilateral incipient cataract. VA was 0.2 (bc with +3.5/-1.5/97) in the RE and 0.25 (bc with +4.25/-1.0/82) in the LE. In May and September 1996 the patient underwent PRP of the LE and both eyes, respectively. A course of acetazolamide was added in November. After this treatment, VA was 0.16 in the RE and 0.32 in the LE. Between April and November 1997, a plasma differential separation was performed 4 times. At the end of the fourth treatment, VA rose to 0.25 in the RE and to 0.4 in the LE, but subsided below pretreatment values by January 1998 (0.1 in the RE and to 0.2 in the LE). In February 1998, HBO₂ was initiated over a period of 2 wk. VA rose to 0.25 in the RE and 0.5 in the LE. Four weeks later we observed a recurring decline of VA to 0.1 in both eyes. Fluorescein angiography revealed an increase of macular edema and peripheral ischemia. A decision was made to perform another PRP with 2,000 burns (in fractions of 400 burns every 2nd day) to each eye. After treatment, VA was 0.16 in both eyes. Eight weeks later, a second HBO₂ was performed for 2 wk. VA stabilized at 0.16 in the RE and rose to 0.4 in the LE (Fig. 3). There was no change in the angiographic presentation of the cystoid macular edema (Fig. 4).

Case 3: This 60-yr-old man came to us in September 1997. His diabetes mellitus type II had been stable for 9 yr with glibenclamide medication. He had a history of slight arterial hypertension, which had been normalized by betablocking eyedrops (timolol) and systemic acetazolamide. Other antihypertensive medications had been discontinued. Rheologically active treatment was implemented with pentoxifylline and low-dose acetylsalicylic acid. Indometacin was also given orally.

Due to a rubetic secondary glaucoma, he was amaurotic with no light perception in the RE. Both eyes were phakic with a mature cataract on the right and incipient cataract of the left side. VA of the remaining LE had rapidly decreased to 0.16 (bc with +0.75). In the absence of retinal ischemia we started HBO₂ without PC for a duration of 2 wk in October 1997. VA rose to 0.4. Two months later, fluorescein angiography revealed ischemia of the central retina and PC (200 burns, 200 μm) of the posterior pole was applied. In April 1998, DME was still evident and progression of ischemia to the peripheral areas occurred. A PRP (1,000 burns applied in fraction of 250 burns, 200 μm) was performed (Fig. 5). No change was observed in VA or in the angiographic presentation of the cystoid macular edema (Fig. 6).

Case 4: A 38-yr-old occupational motorist with an uneventful medical history was admitted to our department in August 1997 for PRP of an ischemic central retinal vein occlusion. Impairment of VA in the RE had occurred in April. Internal and neurologic medical workups were normal except for slight hypertriglyceridemia (2.4 mmol/liter) and hypercholesteremia (8.3 mmol/liter). No cataracts were present and intraocular pressures were normal. Initial VA was 0.32 (bc with +0.75) in the RE and 1.0 (bc with -0.75) in the LE. Aggregation inhibitor therapy was started with low-dose acetylsalicylic acid (100 mg) once daily. Fluorescein angiography disclosed ischemia of the peripheral retina, and PRP was performed with a total of

![FIG. 1—Visual acuity, follow up of case 1 (diabetic macular edema). Solid triangles = FE; solid squares = LE.](http://rubicon-foundation.org)

HD in CME of vasculitis profile.
1,000 burns (applied in fractions of 250 burns, 20 μm). Within 2 mo. after laser treatment, VA further declined to 0.16 (December 1997). Hematocrit was 46% and isovolemic hemodilution was initiated with no effect on visual performance. Therefore the patient underwent HBO₂ that was interrupted for 2 wk because of a tubal catarrh. HBO₂ resulted in immediate improvement of VA to 0.32 and a further increase to 0.5 until March 1998 (Fig. 7). Morphology correlated to VA. We observed moderate regression in the cystoid macular edema (Fig. 8).

**Case 5**: A 65-yr-old woman was referred to our institution as an emergency in April 1997. A rapid decline in VA of the LE had developed during the 2 wk before admission. She reported a history of hypercholesteremia and arterial hypertension, which were controlled with fluvastatin and captopril. Supraventricular cardiac dysrhythmia was suspected to derive from coronary arteriopathosis. Heart failure had not been observed. Medication comprised diltiazem, isosorbid dinitrate, and low-dose acetylsalicylic acid (100 mg). The cardiovascular situation remained stable throughout the course with normal blood pressures (RR <160/90 mmHg). Cranial computed tomography showed no abnormalities. We diagnosed a branch retinal vein occlusion of the upper temporal vein with macular edema and retinal bleeding near the papilla. Intraocular pressures were normal and there was incipient cataract in both eyes. VA was 0.32 (bc with +0.5/-0.75/117). Hematocrit was elevated to 53%. Since hemodilution was not successful, she was given HBO₂ for 2 wk. VA rose to 0.5 after treatment. No resolution occurred within the next 5 mo. of follow up. We proposed farther HBO₂ in September 1997. VA again rose from 0.63 to 0.8 (bc +0.5/-0.25/120) (Fig. 9) and her macular edema regressed almost completely (Fig. 10).

**DISCUSSION**

The therapeutic advance of HBO₂ in ME consists of effective retinal and macular oxygenation, especially in areas with deficient perfusion and interstitial edema or thickened basal membranes (19,20). Pao₂ with air respiration at ambient pressure is approximately 100 mmHg. This may be increased to almost 1,500 mmHg with HBO₂ at 240 kPa (21). Using the Krogh–Erlang diffusion model (22), the diffusion radius of oxygen is markedly enlarged. The gradients of oxygen partial pressures from blood to the tissues increase and the oxygen diffusion cylinders around the capillaries enhance. Thus, oxygen may reach ischemic retinal areas from the choroid circulation and by the enhanced oxygen content of the remaining plasma perfusion in regions of hemostasis. Due to the low oxygen extraction, the choroid has a high potential to oxygenate the whole retina (23). In primates, complete ischemia of the retina is tolerated up to 97 min (24). Experimental data showed improved erythrocyte flexibility (25) with HBO₂.

In ME, fluid containing a low level of lipid and protein collects pericapillary or with classic CME in cystic cavities between the external plexiform or the internal granular layer or both. The important gangliocytes situated in these layers are affected (26,27). In retinal vein occlusions (28) and in diabetic retinopathy (29), ME is caused by chronic perfusion disorders, whereas aphakic or pseudophakic ME is predominately an adverse reaction after complicated cataract surgery. It is related to surgical trauma and mediated by inflammation (27,30). In 1987, Pföff and Thom (12) found HBO₂ to ameliorate VA in five patients with this diagnosis compared to controls (follow up: 3 mo.). There was, however, no reduction in the horizontal edema extension in three patients. With the improvement of cataract surgery [intracapsular cataract extraction without intraocular lens (IOL) implantation vs. phacoemulsifica-
FIG. 4—Fluorescein angiography, follow-up of case 2.

HBO in CME of vascular origin

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HBO in MACULAR EDEMA OF VASCULAR ORIGIN

FIG. 5—Visual acuity, follow up of case 3 (diabetic macular edema). Solid symbols = LE

FIG. 6—Fluoresceinangiography, follow up of case 3.

tion with IOL], ME became rarer (31,32). But, a controlled trial with HBO in aphakic ME was never done. Our results on the other hand seem to confirm Pfoff and Thom’s observations even in primary vascular pathogenesis.

Regulation of cardiovascular risk factors may act prophylactically, but scarcely results in any improvement of visual performance. Cardiovascular conditions and risk factors in our patients were stabilized before the onset of visual impairment and within the observation period. Deterioration occurred without any cardiovascular crisis except for elevation of hematocrit (>45%). Yet hemodilution remained ineffective. The rationale for hemodilution was based on controlled trials showing a benefit on central vision and retinal circulation in retinal vein occlusions (8–10) but CME was not particularly addressed. Focal laser PC and macular GRID were stated to reduce exudation or improve VA (33–36). However, referring to recently published data (36,37) and our own observations, GRID is ineffective at least in CME. Though PRP may improve DME (38) it is also likely to cause it (39). PRP of retinal ischemia, neovascularizations, and microaneurysms is a necessity in the treatment of the underlying retinal disease, but it is also prone to destabilize ME. PC did not markedly improve VA in our patients. Plasma differential separation lowers blood viscosity and improves flow properties (40), but its cost-effectiveness remains questionable. Follow-up showed no sustained effect in our patient (case and Fig. 2).

Arteriovenous adventitial sheathotomy in CME associated with branch retinal vein occlusions was recently reported to gain excellent long-term results in four of five cases (41). This surgical procedure aims to correct pathomorphology but carries with it the risk of grave complications. It should only be considered in patients with very poor vision.

All the patients benefited from adjunctive HBO, after most other approaches had failed, with an average gain of 3.5 lines in VA. Our angiographic findings did not always correlate with the increase in function, findings consistent with those in other publications (17,42). HBO.
temporarily relieved the oxygen deficit and might have induced a long-lasting regeneration of retinal cell metabolism in our patients. This would explain improved VA extending beyond the time of mere hyperoxygenation. Restoration of vascular tight junctions induced by antihydrosic effects of HBO₂ is discussed elsewhere (12). This mechanism, however, cannot be claimed to work in DME because fluorescein angiography showed no change in our patients. Its role in aphakic ME and in CME is supported from our data. Improvement in VA correlated to the angiographic edema reduction only in our cases with retinal vein occlusion.

A randomized clinical trial is needed to further assess beneficial influences of adjunctive HBO₂ in ME of vascular origin. This should include HBO₂ as a first line treatment after rheologic medication, eventually after hemodilution in CME, and before PC or GRID. Its usefulness after deterioration following PRP must be addressed and it should be applied before extended retinal ischemia has developed.

FIG. 7—Visual acuity, follow up of case 4 (macular edema in CRVO). Solid symbols = FE.

REFERENCES

FIG. 9—Visual acuity, follow up case 5 (macular edema in BRVO)
FIG 8 (top) — Fluorescein angiography, follow up of case 4.
FIG 10 (bottom) — Fluorescein angiography, follow up of case 5.


22. Krog A. The number and distribution of capillaries in muscles with calculations of the oxygen pressure head necessary for supplying the tissue. J Physiol 1919; 52:409-415.


