

A Pilot Study of Hyperbaric Oxygen in the Treatment of Human Stroke

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We administered hyperbaric oxygen or air in a double-blind prospective protocol to 39 patients with ischemic cerebral infarction. We interrupted the study when we noticed what appeared to be a trend favoring the air-treated patients, whose neurological deficits were less severe (mean \pm SEM score on graded neurological examination: air, 25.6 ± 4.9 ; oxygen, 34.5 ± 7.5) and whose infarcts were smaller (air, 29.0 ± 12.2 cm³; oxygen, 49.2 ± 11.7 cm³) at 4 months. The trend, we decided, was probably an artifact of the randomization process. Nevertheless, we chose not to resume the trial because the treatment was difficult to administer by schedule (for various reasons the treatment protocol was broken in 15 of the 39 patients), was poorly tolerated (eight of the 39 patients refused to continue treatments), and did not produce dramatic improvement. (*Stroke* 1991;22:1137–1142)

Treatment of acute and subacute focal cerebral ischemia with hyperbaric oxygen (HBO) has been reported in animals^{1–4} and humans.^{5–16} Improved outcome has been demonstrated in most^{1–3} but not all (A.G. Bottini and G.L. Rockswold, unpublished data) controlled experiments in animal models of ischemic stroke. Benefit has also been observed in humans, although clinical reports have been merely anecdotal.

We report the results of a study in which treatment of human stroke with HBO was tested in a controlled, double-blind experimental protocol. The project was originally undertaken to answer the question of whether HBO exposures are safe, practical, and effective in improving neurological outcome when administered according to a defined treatment protocol and given to a broad range of patients sustaining acute cerebral infarction. After enrollment of 39 patients, the study was suspended when a safety monitoring committee detected an outcome trend favoring sham treatment. Concerns about safety, as well as reservations about the prac-

ticality of the HBO treatment modality, led to termination of the project before a definitive answer concerning efficacy could be established. Reported herein are the preliminary results of the trial, along with observations about the practical aspects of HBO treatment in stroke patients.

Subjects and Methods

Considered for inclusion were all nonpregnant patients, aged 20–90 years, with the onset of neurological deficits due to ischemic cerebral infarction in the brain region perfused by one carotid artery during the preceding 2 weeks. All mechanisms of focal ischemia (e.g., atherothrombosis, lacunar disease, cardioembolism, unknown) were permitted. Patients were excluded if their deficits were minor (i.e., score of <20 on a 100-point quantitative scale in which 0 is normal¹⁷), substantially improved or resolved ≤ 3 hours after onset, or could not be clearly distinguished from previously acquired deficits. Also excluded were patients with significant pulmonary disease contraindicating HBO exposure, as well as patients with unstable medical conditions (e.g., cardiac arrhythmia, congestive heart failure) potentially requiring immediate physical access to the patient. Informed consent was obtained from the patient or a surrogate.

Patients were initially managed in a neurological intensive care unit, and standard care was given. All patients received physical and occupational therapy. Patients were randomly assigned to receive either active (i.e., HBO) or sham (hyperbaric air) treatment

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after stratification by clinical severity: at the time of the initial graded neurological examination,¹⁷ each patient's deficit was evaluated as being more severe (score of >40) or less severe (score of ≤40). All patients received hyperbaric exposures in a monoplace chamber (admits only the patient; attendants remain outside). Neither the patients nor the personnel caring for the patients or conducting the study knew which treatment (active or sham) was being administered.

Study protocol specified that the initial pressurization (dive) occur ≤6 hours after entry into the study, with subsequent dives every 8 hours, for a total of 15 dives. The patient was maintained for 1 hour at 1.5 atmospheres absolute (ATA). Compression and decompression rates did not exceed 0.5 psi/min or those tolerated by the patient. Dives were directly supervised by a neurological intensive care unit nurse trained in the administration of hyperbaric gases, and the patient's electrocardiogram was continuously monitored. Sedation with intravenous midazolam, lorazepam, or diazepam was permitted for anxiety or agitation. Vitamin E (400 units every 8 hours during the diving sequence) was given as an antioxidant.

The protocol allowed the diving sequence to be terminated before 15 dives were completed if the neurological deficits resolved entirely, if the patient was discharged from the hospital, or when 14 days had elapsed since the onset of the deficit. Otherwise, if the diving sequence was interrupted before six dives had been completed, a full series of 15 dives was undertaken if and when resumption was possible. If six or more dives had been completed when the diving sequence was interrupted, only those dives required to make a total of 15 were completed.

The primary measure of outcome was score on a graded neurological examination sensitive to deficits referable to the internal carotid artery distribution (specifically, to the middle and anterior cerebral arteries). The examination was devised to assess treatment of acute cerebral ischemic infarction; high interrater reliability and concurrent validity have been shown for this measure.¹⁷ The scale ranges from 0 (no deficit) to 100 (maximal deficit). The examination was administered on entry and at 5 days, 6 weeks, 4 months, and 1 year.

A secondary measure of outcome was quantification of the volume of hypodensity due to infarction, as seen on a computed tomogram (CT scan) performed 4 months after onset. Also recorded were the observations of the nurses supervising the hyperbaric exposures. Stroke progression during hospitalization (as judged by the house staff physicians caring for the patients) was monitored as well.

The primary outcome variable was score on the graded neurological examination performed 4 months after onset. The initial design of the study called for enrollment of 90 patients, with approximately 45 patients in each group. If the true outcome difference were 30% in favor of HBO, this would allow demonstration of a significant difference at an

α level of 0.05 with a power of 0.80. A one-tailed analysis was planned, discounting the possibility that HBO might have an adverse effect compared with sham treatment. An external monitoring committee analyzed the results after 15 and 30 patients had been entered; thereafter, the committee analyzed the study results annually.

Results

Over the 25 months of study enrollment, 92 patients with cerebral infarction in a carotid distribution were admitted to the neurology service. All patients were screened for entry; 53 were excluded from the study for the following reasons: older than age 90 years (one patient), medical contraindication for HBO (eight patients), refusal to participate (nine patients), problematic deficit (score of <20 on graded neurological examination, deficit rapidly improving, or evaluation confounded by presence of old deficits) (32 patients), or treatment status of "supportive care only" (three patients).

Of the 39 patients entered, 19 were randomized to hyperbaric treatments with medical air and 20 to hyperbaric treatments with 100% oxygen. The mean age of the air-treated patients was 69.1 years; the mean age of the oxygen-treated patients was 63.7 years. The groups were similar with respect to sex distribution, risk factors, and presumed mechanisms of cerebral ischemia as determined by standard definitions.¹⁸ Because of stratification, the groups were also evenly matched with respect to baseline scores on the graded neurological examination. In the air-treated patients, the mean and median scores were 43.6 and 42, respectively; in the oxygen-treated patients, the mean and median scores were 45.5 and 38, respectively.

Despite protocol specifications, only 21 (10 air-treated patients, 11 oxygen-treated patients) of the 39 patients dived ≤6 hours after randomization. Reasons for delaying initiation included medical instability, performance of necessary procedures (e.g., arteriography), and temporary unavailability of nursing staff trained to supervise hyperbaric treatment. Average time from onset of symptoms until the first dive was 51.8 (range 10–148) hours. The diving sequence was terminated before the completion of 15 dives in 27 of the 39 patients. In 12 of these patients, diving was discontinued according to protocol (e.g., hospital discharge or resolution of deficit). In 15 patients, however, termination represented a deviation from protocol, most often because the patient refused to continue. For all 39 patients, the average number of dives was 9.4 (air-treated patients, 10; oxygen-treated patients, 8.9).

Patient acceptance of the hyperbaric exposures was a problem. Patients considered them unpleasant for a variety of reasons: difficulty clearing ears (myringotomies were not standard), elevated chamber temperature when pressurized, boredom, disruption of sleep or rest time, and/or claustrophobia. These complaints were dealt with on an ad hoc basis. Diving

TABLE 1. Average Graded Neurological Examination Scores

Time of examination	Treatment group		<i>p</i>
	Air	Oxygen	
Initial			
No.	19	20	
Mean±SEM	44.6±4.8	45.5±5.1	0.908
Day 5			
No.	18	20	
Mean±SEM	38.5±6.3	43.8±5.8	0.538
Week 6			
No.	15	17	
Mean±SEM	28.3±5.9	38.5±6.3	0.248
Month 4			
No.	14	13	
Mean±SEM	25.6±4.9	34.5±7.5	0.327
Year 1			
No.	11	14	
Mean±SEM	25.8±5.4	31.4±6.5	0.529

p values by Student's two-tailed *t* test.

was supervised by the neurological intensive care unit nurses with whom the patients were familiar. Reassurance and encouragement were offered throughout the procedure. Compression and decompression rates were very gentle. A simple cooling system was devised. A television set visible through the glass chamber was installed. Sedation with benzodiazepine was given as needed for anxiety and agitation. Despite these measures, eight patients withdrew from the diving protocol at some point.

Two patients sustained complications. One patient with a history of psychiatric illness became acutely psychotic in the chamber. Another developed atelectasis that we believe was exacerbated by sedation and suspension of pulmonary toilet during diving. Both patients recovered completely. No seizures (a potential toxic complication of HBO) were observed.

For each patient, statistical analysis was performed on the difference between the score on the graded neurological examination at onset and that at 4 months. Scores for 14 air-treated patients and 13 oxygen-treated patients were available. Of the five patients lost in the air-treated group, two had died, two had moved away, and one refused follow-up. Seven were lost in oxygen-treated group: two died, one moved away, three refused follow-up, and one had another stroke.

Table 1 shows the results of serial graded neurological examinations. Improvement within groups was analyzed by paired *t* tests, and the groups were compared by two-sample *t* tests (both two-sided). At 4 months, air-treated patients had improved by 15.9±3.2 points (mean±SEM, *p*<0.0003) and oxygen-treated patients by 12.2±4.8 points (*p*<0.03). For completeness the groups were compared at all examination times, and the results were consistent. The difference between groups, although not significant, indicates better im-

provement in the air-treated group, contrary to the assumption made at the design stage.

Based on CT scan data from 12 air-treated patients and 15 oxygen-treated patients, infarct volumes at 4 months were 29.0±12.2 and 49.2±11.7 cm³, respectively (two-tailed *t* test, *p*=0.25). Retrospective review of all 39 entry CT scans demonstrated that more patients with larger infarcts were randomized to the oxygen-treated group, probably explaining the apparent difference in outcome. It is noteworthy that such group differences in entry CT scans were found even though clinical severity stratifications were similar.

Because of the trend toward better outcome in the sham-treated patients, as measured by both clinical and CT scan criteria, the study was suspended for safety reasons. Results of prediving and postdiving examinations were obscured by the frequent use of sedatives. No difference was found in rate of stroke progression during hospitalization.

Discussion

Consideration of HBO treatment for ischemia of the brain derives from the belief that this treatment might salvage the still-viable though nonfunctioning tissue intermixed with and surrounding the nonviable, infarcted tissue.^{19,20} It is hypothesized that HBO exposure might serve as a valuable stopgap cytoprotective measure by supporting the aerobic processes of threatened cells and might even indirectly encourage reperfusion. By enhancing tissue survival, HBO might reduce the formation of edema, which otherwise further compromises local perfusion.²¹ Furthermore, HBO causes vasoconstriction of normal cerebral vessels.²²⁻²⁴ This action might augment blood flow in ischemic regions where it is passive.

Table 2 summarizes reports on experimental brain ischemia in which HBO has been applied.^{1-4,25-36} In some experiments (protection models),²⁵⁻³² the animal was receiving HBO treatment when the ischemia was induced; in other experiments (treatment models),^{1-4,33-36} HBO treatment was initiated at various intervals after ischemia. In general, the results of research in animals have suggested a promising role for the use of HBO.

More than 400 cases of human ischemic stroke treated with HBO have been reported in the English-language literature.⁵⁻¹⁶ In about half of the cases, improvement in status has been claimed on clinical or electroencephalographic grounds, although the observations were uncontrolled. No prospective trial of HBO treatment has been reported.

Our goal was to evaluate HBO treatment under controlled conditions. We developed the experimental design after consideration of both theoretical and practical issues. On theoretical grounds, the ideal candidate circumstances would be focal, incomplete ischemia with potential for reperfusion by clot lysis or recruitment of collaterals. It might be speculated that the patients most likely to respond favorably to HBO therapy are those with large-vessel stenosis or occlusion with insufficient residual blood flow to support

TABLE 2. Animal Studies of Brain Ischemia and Effects of HBO

Author	Year	Animal	Ischemia			Timing of HBO in relation to ischemia	ATA O ₂	Outcome measure	Effect shown?
			Global vs. focal	Complete vs. incomplete	Ischemia reversed?				
Protection models									
Smith et al ²⁵	1961	Dog	Global	Inc	Yes	During	2	EEG	Yes
Fuson et al ²⁶	1965	Dog	Global	Comp	Yes	During	3	EEG	Yes
Moor et al ²⁷	1966	Dog	Global	Comp	Yes	During	3	NF, HC	Yes
McSherry et al ²⁸	1966	Dog	Global	Comp	No	During	2, 3, 4, 5	S, EEG	Yes
Thomas et al ²⁹	1966	Dog	Global	Comp	Yes	During	3	NF, HC	Yes
Whalen et al ³⁰	1966	Dog, monkey	Global	Comp	No	During	3	EEG	Yes
Patterson et al ³¹	1968	Dog	Global	Inc	No	During	3	NF	Yes
Jacobson and Lawson ³²	1963	Dog	Focal	Inc	No	During	2	NF, HC	No
Treatment models									
Kapp et al ³³	1982	Cat	Global	Inc	Yes	Immediately after	1.5	Metab, EEG	Yes
Shiokawa et al ³⁴	1986	Hypertensive rat	Global	Inc	No	1, 3 Hr after	2	S, Metab	Yes
Ruiz et al ³⁵	1986	Dog	Global	Comp	Yes	Immediately after	2	NF	No
Weinstein et al ³⁶	1986	Gerbil	Global	Inc	Yes	Immediately after	1.5	S, HC	Yes
Corkill et al ¹	1985	Gerbil	Focal	Inc	No	1 Hr after	1.5, 2	NF, Vid, S	Yes
Weinstein et al ²	1987	Cat	Focal	Inc	Yes, No	1, 3, 4 Hr after	1.5	NF, HC	Yes
Burt et al ³	1987	Gerbil	Focal	Inc	No	Immediately after	1.5	HC	Yes
Bottini and Rockswold (unpublished)		Hypertensive rat	Focal	Inc	No	1 Hr after	1.5	HC	No
Reitan et al ⁴	1990	Gerbil	Focal	Inc	No	Immediately after	~2.5	S	Yes

HBO, hyperbaric oxygen; ATA O₂, atmospheres oxygen absolute; Inc, incomplete; Comp, complete; EEG, electrical activity demonstrated by electroencephalography; NF, neurological function; HC, histopathologic changes; S, survival; Metab, metabolic consequences of ischemia; Vid, ischemic blanching as demonstrated by videodensitometry.

cerebral function. In support of this are reports claiming a favorable transient or, less often, permanent response to HBO in cases selected for demonstrated carotid occlusion.¹¹⁻¹³ Results have not been reported for patient groups with other, specifically defined mechanisms of brain ischemia. Because of this lack of information and because the mechanism of ischemia is often not apparent during the initial assessment, when early treatment might be important, we admitted patients with all presumptive mechanisms of ischemic stroke.

Like case selection, the diving protocol was developed empirically since the literature offers little guidance. Practicality and the trade-offs between efficacy and oxygen toxicity must be considered when developing experimental parameters for treating cerebral ischemia (e.g., timing of the initial dive, depth and duration of dives, diving frequency, total number of hyperbaric exposures). As shown in Table 2, experimental strokes have been uniformly treated early (immediately to 4 hours after occlusion). In one experiment, treatment at 1 and 3 hours after occlusion was effective, while delay until 4 hours or longer was associated with no benefit.² This observation suggests that there are definite time limits on the viability of marginally perfused cells, which is consistent with the generally held notion that early application is crucial for any treatment of evolving brain infarction.^{37,38} Perhaps unexpectedly, the experience in human stroke suggests that the timing of initial

HBO exposure is not as important, with equally high response rates reported with exposures during the subacute and chronic phases.^{8-11,14,15}

Oxygen toxicity, which is related to the partial pressure of oxygen and the duration of exposure, must also be considered when determining the diving depth and schedule. The mechanism of damage is not well established, but generation of free radicals is thought to initiate the process.^{39,40} One would speculate that if this were so, oxygen toxicity would be intensified under conditions of ischemia, in which free radical generation is also postulated to play a role.⁴¹ Using measures of carbohydrate metabolism as indicators of cerebral well-being in cases of human head trauma and stroke, Holbach et al⁴² determined that HBO at 1.5 ATA was associated with the most normal respiratory quotient; at lower and higher pressures, products of anaerobic metabolism were apparent. We depended on this relatively meager data in establishing our experimental diving pressure. Our schedule of dive duration and frequency was also similar to that of Holbach et al.⁴²

In developing the diving protocol, one must also consider the labor-intensiveness and unique patient care aspects of hyperbaric treatment. Even the use of a monoplace device (in which the attendant is not enclosed with the patient) places a significant burden on the staff.

In spite of the appeal of the idea of using HBO as a treatment for cerebral ischemia, the promising

experimental observations, and the sanguine clinical anecdotes, we found the protocol-governed administration of hyperbaric treatment (active or sham) to be problematic at best. Patients were often unstable, and there were competing demands on their time, making strict adherence to the protocol difficult. Most patients found the diving experience aversive, and one fifth of the patients ultimately refused to continue. In the limited data we did gather, we found no dramatic benefit favoring HBO treatment; in fact, the results raise the possibility that such treatment might worsen outcome.

In summary, this sham-controlled, double-blind study of HBO as a treatment for ischemic stroke encountered practical problems and was terminated before an answer about efficacy was reached. We were unable to test the hypothesis that treatment with HBO delivered within a few hours after the onset of symptoms might improve outcome. If a study were undertaken in the future, more than the 90 patients we originally projected would be required since, from our pilot study data, dramatic benefit is highly unlikely. Frequent deviations from protocol (15 of 39 patients in our experience) should be anticipated, thus requiring a larger number of initially recruited patients for a statistically valid analysis of treatment effectiveness. A one-tailed analysis would be inappropriate since our data suggest that HBO treatment for ischemic stroke could be harmful. Given all of these considerations, it is clear that our study as originally designed could not allow the question of the efficacy of HBO to be answered.

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