Oxygen Therapy in Ischemic Stroke

To the Editor:

Previous studies of therapeutic oxygen in stroke have had conflicting results, and the latest study by Rusyniak et al.² seems to suggest that hyperbaric oxygen therapy (HBO) is harmful in ischemic stroke. The authors have already discussed how several inadequacies in trial design might explain their negative results. We wish to draw attention to additional features in their study that might offer important insights into the design of future studies of oxygen in stroke.

The authors evaluated the safety, feasibility, and efficacy of using HBO in a sham-controlled pilot study of 33 patients with acute (<24 hours) ischemic stroke. The HBO group (17 patients) received 100% oxygen at 2.5 atm absolute (ATA), and the sham group (16 patients) received 100% oxygen at 1.14 ATA, both for 60 minutes. Outcomes were measures at 24 hours and 90 days using several clinical stroke scales. Complications related to the use of pressurized chambers were comparable in both groups. There was no difference in stroke outcomes at 24 hours; however, at 90 days a significantly higher percentage of patients in the sham group had good outcome. The authors conclude that their HBO protocol appears feasible and safe (i.e., without significant pressure-related complications) but state that HBO might be harmful in patients with acute ischemic stroke.

As acknowledged by the authors, this study had a small number of patients, which limits data interpretation, and the negative results are probably attributable to factors like late timing of therapy and use of excessively high chamber pressures. It is well known that higher pressures, late timing, and longer duration of HBO produce harmful effects.⁴⁻⁶ In a recent animal study we found that HBO at 3 ATA for 60 minutes (similar to the present study) reduced infarct volumes and improved neurological outcomes when applied at 3 and 6 hours, but enhanced infarct volumes and aggravated neurological deficits when applied at 12 or 24 hours after the onset of reperfusion.⁸ If most patients in this pilot study were treated >12 hours after the onset of stroke (only 15% were treated within 6 hours), it is not surprising that a harmful effect of HBO was observed. Whether early HBO therapy (within 3 to 6 hours) affords benefit remains to be determined.

It is extremely important to note that the sham group was actually treated with 100% oxygen. There was no control group treated with room air at elevated atmospheric pressures, as in previous studies.²⁻³ We have compared the results of different oxygen pressures on brain protection in a neonatal rat model and found that oxygen therapies at 1, 1.5, and 3 ATA produced similar brain protection (measured by brain weight) in pups (Figure; for detailed methods see Ref. 7). Since this study only compared oxygen therapy at different pressures, it is misleading to conclude that HBO itself might be harmful—the only fair conclusion is that (within the limits of this protocol), oxygen therapy at 2.5 ATA is harmful as compared with oxygen therapy at 1.14 ATA.

We were impressed by the excellent results in the sham group: 80% to 91% of patients had good outcome at 90 days, depending on the stroke scale used. Spontaneous reperfusion is common in patients with low NIHSS, and since 15 of 33 patients had NIHSS <7 at onset, factors such as reperfusion might have contributed. However, these excellent outcomes might not be simply fortuitous—an alternate possibility is that low-pressure oxygen therapy is, in fact, highly beneficial. Several recent animal studies have shown that short-duration normobaric oxygen therapy can be highly neuroprotective and does not increase oxidative stress, if started early after stroke onset.⁸⁻¹⁰ Maximum benefit was observed in the cerebral cortex.⁸⁻¹⁰ We ask whether the authors have any information regarding tissue perfusion status, stroke subtypes, and immediate response to oxygen treatment. This information would be extremely useful in analyzing why the sham group had such excellent outcomes.

John H. Zhang, MD, PhD
Department of Neurosurgery
Louisiana State University-Health Science Center
Shreveport, Louisiana

Aneesh B. Singhal, MD
Department of Neurology
Harvard Medical School
Stroke Service
Massachusetts General Hospital
Boston, Massachusetts

James F. Toole, MD
Stroke Research Center
Wake Forest University School of Medicine
Winston-Salem, North Carolina

Hyperbaric Oxygen in Acute Ischemic Stroke
To the Editor:

Dr Rusyniak et al have recently presented the results of a clinical trial of hyperbaric oxygen (HBO) in acute ischemic stroke. The authors are aware of previous human studies in stroke patients indicating that 100% oxygen at pressure of 1.5 atm absolute (ATA) is better tolerated than higher pressures by the brain injured by acute ischemia. Safety of HBO is not an issue here, as pressure of 2.5 ATA is used safely for other indications. The authors mention that 400 ischemia. Safety of HBO is not an issue here, as pressure of 2.5 ATA indicating that 100% oxygen at pressure of 1.5 atm absolute (ATA) reperfusion times.

Hence, any study using HBO has to consider these 2 problems were discussed in a conference more than 5 years ago and the proceedings were published. Since HBO is used as a neuroprotective, it can be combined with thrombolytic therapy, which is directed at the cause. Clinical trials of combination of HBO and thrombolytic therapy are being conducted. I believe that the study did not serve any useful purpose or contribute to knowledge of stroke or HBO beyond what is already known. With negative results, the authors have closed the door to further trials on this topic. It would have been better if they had had another group of patients treated at 1.5 ATA so that the results could be compared with those treated at 2.5 ATA.

K.K. Jain, MD, FRACS, FFPM
PharmaBiotech
Basel, Switzerland


Hyperbaric Oxygen Therapy
To the Editor:

We applaud the authors’ efforts in attempting to use randomized controlled trials to study the effects of hyperbaric oxygen (HBO) in acute ischemic strokes. Although we agree that the pressure at which the patients were treated (2.5 atm absolute [ATA]) is appropriate, we feel that several of their other methodologies and interpretations require comments.

First: The time interval from onset of symptoms to the first HBO treatment is critical. The “golden period” from blockage of a vessel of the brain by thrombus or embolus with onset of neurological dysfunction is 3 hours. This is defined as the first reperfusion period. The second reperfusion period occurs from 3 to 5 hours after the occlusion. Successful outcomes in the treatment of cerebral gas embolism with HBO during the second reperfusion have been observed. Hence, any study using HBO has to consider these 2 reperfusion times.

Second: The complication of cerebral edema associated with the treatment of arterial gas embolism has been observed even with immediate HBO treatment. We have reported evidence of a post-HBO exposure vasodilatation occurring in otherwise healthy volunteers. We do not feel these observations are a cause of morbidity.

Third: The minimum of a 1-hour HBO exposure at 2 ATA is required to saturate the mixed venous hemoglobin return to the right atrium in normal resting males. An additional 30 minutes is needed to saturate the other tissues of the body. Treatment duration less than this would not be expected to give optimal results.

Fourth: For optimal results with acute ischemia of the brain, repetitive HBO treatments are recommended. Adequate treatment pressures, durations, and repetitions improve outcomes.

An earlier controlled study, which also showed no benefit from HBO, has some of the same criticisms as this study: for example, treatment durations were 40 minutes and treatment pressures were only 1.5 ATA.

In view of our experience we recommend the following management for all thrombotic/embolic cerebrovascular episodes within 6 hours of onset of symptoms. This management has been used in >80 patients treated in a monoplace chamber compressed in and breathing HBO without using air breaks—improvement percentages using the Rankin scoring system equaled the NIH tPA study.

I. HBO and thrombolytic routine (thrombolysis) is to be used within the first 3 hours from symptom onset prior to CT scan. Note: The combinations of thrombolysis and HBO have been reported as safe and with benefits in myocardial infarction.

II. HBO at 3 ATA for 30 minutes then 2.0 to 2.5 ATA for 60 minutes (with time needed for compression and decompression, total exposure to elevated oxygen pressure approaches 2 hours). (A) Metyldopa 250 mg IV every 6 hours if normotensive and 500 to 1000 mg if hypertensive prior or during first HBO treatment. (B) One-hour air break on the surface. A CT scan is obtained immediately following the first HBO treatment. Additional HBO treatments are based on the following permutations: (1) If CT scan reveals intracranial hemorrhage (ICH): (a) resume HBO if neurological improvement has occurred with first treatment, or (b) stop HBO if neurologically unchanged or deterioration is observed. (2) If CT scan reveals no ICH, continue HBO.

III. HBO 1.5 ATA × 3 hours—may use air breaks at 30-minute intervals.

IV. Eight hours air break with indicated supportive and diagnostic care.

V. Then HBO at 2.0 to 2.5 ATA for 90-minute duration without air breaks twice a day if improvement continues for 7 to 10 days.

G.B. Hart, MD
M.B. Strauss, MD
Department of Baromedicine
Memorial Medical Center
Long Beach, California

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Brain barrier after brain ischemia in rabbits.6,7 Numerous animal studies have shown viability of the penumbra for up to 24 hours after stroke.8 Since it is impossible clinically to determine which patients’ strokes are completed and those in which there is a viable penumbra, we chose to initially include all patients within 12 hours of symptoms or decrease of NIHSS scores at 24 hours on each patient. In those treated within 12 hours of stroke onset 14% in the HBO compared with 33% in sham group and 20% versus 30% in those between 12 and 24 hours had clinical improvement as defined as complete resolution of symptoms or decrease of ≥4 points on the NIHSS.

In response to Drs Hart and Strauss’s question of the duration of treatment, we chose 60 minutes based on prior animal studies showing a sustained benefit from treatments of ≤60 minutes.10,11 Although multiple dives for brain ischemia have been suggested, there have been no controlled trials in humans showing benefit of 1 versus multiple dives, whereas numerous animal studies have shown sustained benefit from a single dive.10,11 Prior randomized trials of HBO for stroke in humans employed multiple dives as part of their protocols.12,13 As mentioned in our article, both of these studies suffered significant protocol violations secondary to the number of dives employed.

It is the conclusion of these authors that the question of the benefit of HBO in acute ischemic stroke is still unanswered and that further studies will be needed to determine if lower pressures and possibly greater number of dives results in improved clinical outcomes.

Daniel E. Rusyniak, MD, for the Hot Stroke Study Group
Departments of Emergency Medicine, Pharmacology & Toxicology & Neurology
Indiana University School of Medicine
Indianapolis, Indiana

Hyperbaric Oxygen in Acute Ischemic Stroke
K.K. Jain

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