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 (ie, 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.2–4 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.5 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.6–10 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.

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Hyperbaric Oxygen in Acute Ischemic Stroke

To the Editor:

Dr Rusnýni& 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 stroke patients have been treated with HBO in previously reported studies. This number exceeds 2000 and references to these studies are easily available in a standard text on this subject. The majority of these patients were treated by HBO pressures under 2 ATA. I do not understand why the authors chose to ignore this experience and decided to follow the results of animal studies, some of which have been conducted at higher pressures but no correlation has been established between pressure and efficacy of HBO treatment in these studies. I am not surprised that the patients who received oxygen at 1.14 ATA did better than those who received it at 2.5 ATA because the former is closer to the ideal pressure of 1.5 ATA.

My other criticism of the study is that it was not restricted to patients in the first 3 hours following stroke or even the first 6 hours. There are logistic problems in applying HBO treatments in a time window that overlaps with thrombolytic therapy. Potential solutions to these 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.

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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 vasodilation 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 IPA 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.

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Response

Dr Jain criticizes this study primarily for its choice of dive pressure at 2.5 ATA. A number of case reports and case series in which HBO has been used in stroke have been published using a variety of pressures ranging from 1.0 to 3.0 ATA with the majority of them suggesting benefit of treatment. Despite these case reports, only 2 randomized trials had been completed prior to our study. Both of these studies used pressures of 1.5 ATA. Their decision seems to be based partially on a study in 1977 by Holbach et al. This study looked at carbohydrate metabolism in 30 patients with traumatic brain injuries and completed strokes (only 7 were strokes and none acute) that underwent hyperbaric oxygen treatment in an unrandomized and unblinded fashion at either 1.5 or 2.0 ATA. By measuring arterial venous (AV) oxygen differences along with AV differences in glucose, lactate, and pyruvate, the authors suggested that at 2 ATA there was increased cerebral anaerobic glycolysis, but at 1.5 ATA glucose metabolism was balanced and oxygen utilization increased. Unfortunately this study does not give any demographics on the patients in the 2 groups and their own data seem to suggest that after the treatment, those patients who underwent treatment at 2.0 ATA had better oxygen utilization. The authors also point out that clinically the patients in the 2.0-ATA group had no adverse events or outcomes. Despite these data, numerous studies in animals have suggested that HBO therapy has benefits that may not occur until pressures are >2.0 ATA.

In animal studies, hyperbaric oxygen treatment at 3 ATA significantly prevented carbon monoxide–induced brain lipid peroxidation, whereas treatments with 1 or 2 ATA oxygen showed no benefit.2 Studies in both humans and rats have shown that the activation of leukocytes through beta-2 integrin receptors can be inhibited by hyperbaric oxygen at pressures greater than 2 atm, but not at pressures less than or equal to 2 ATA.4 HBO has also been shown to downregulate ICAM-1 expression in ischemic cells and that this effect was completely attenuated only at pressures of 2.5 ATA.5 Similarly, HBO therapy at atmospheres of 2.8 ATA has been shown to maintain the integrity of the blood brain barrier after brain ischemia in rabbits.6,7 Numerous animal studies of ischemic stroke have shown HBO therapy at pressures ranging from 1.5 to 3.0 ATA to be beneficial. Another criticism was our inclusion of patients after 6 hours from stroke onset. We chose 24 hours as our inclusion time based on data that have shown viability of the penumbra for up to 24 hours after ischemia.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 24 hours. The clinical cases and studies to which Dr Jain refers in his letter dove patients primarily after the 6-hour time window and in some studies even months and years after the stroke. Lastly, Dr Jain’s comment that we have closed the door to further trials on HBO in stroke is likely a misinterpretation of our final statement. We state that “we will not pursue the use of our protocol in a larger clinical trial.” This, however, does not mean that further studies should not be done using different protocols. Our commitment to this area is demonstrated in our current work with a clinical trial utilizing a pressure at 1.5 ATA.

We agree with the comments of Dr Zhang and colleagues in regard to the outcome interpretation of our study and appreciate their significant contributions to this area of research. Our decision to use a sham treatment at 1.14 ATA was based on our desire to blind the study as much as possible. Our chambers are pressurized with 100% O2 and to simulate the pressure changes on the ear in the sham group the equivalent of approximately 4 feet of sea water was needed, or 1.14 ATA. Other set-ups with our system would likely have decreased our ability to blind the patients. Zhang and colleagues correctly point out that our sham group had impressive results and may reflect a benefit of the sham group compared the treatment group. Although the study by Ronning et al9 showed no benefit on 1-year survival in stroke patients given supplemental O2 for 24 hours compared with placebo, the possibility that higher concentrations of oxygen, for shorter durations, may have benefit is conceivable. In response to whether we have information on tissue perfusion status or stroke subtypes, we did not perform any testing on either of these issues. With regard to immediate response, we did follow up at 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.

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