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Hyperbaric Oxygen Therapy of Cerebral Ischemia

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Key Words
Acute stroke · Hyperbaric oxygenation · Ischemic stroke

Abstract
Background: Hyperbaric oxygen (HBO) therapy of cerebral ischemia has been evaluated in a number of human and animal studies; however, there is presently no consensus on its efficacy. ***Methods:*** We present a review of animal and human studies on HBO therapy of cerebral ischemia as well as present potential mechanisms of action of HBO. ***Results:*** Animal studies of HBO have shown promise by reducing infarct size and improving neurologic outcome. HBO has also been shown to inhibit inflammation and apoptosis after cerebral ischemia. Early reports in humans also suggested benefit in stroke patients treated with HBO. Recent randomized, controlled human studies, however, have not shown benefit, although all were limited by small sample size. Important differences between animal and human studies suggest HBO might be more effective in stroke within the first few hours and at a pressure of 2–3 ATA. ***Conclusions:*** The clinical usefulness of HBO in the treatment of cerebral ischemia is not yet certain. Attention to emerging pathophysiologic data should be taken into consideration in design of any future clinical trials of HBO in acute ischemic stroke.

Introduction

The use of hyperbaric oxygen therapy (HBO) for treatment of ischemic stroke remains controversial [1]. Proponents suggest that early human research and more recent animal data demonstrate the effectiveness of HBO in ischemic stroke, while others feel that the data are not sufficient to support its clinical use [2].

HBO has been available for more than 100 years and has been investigated as a treatment for numerous disease states [3]. The principal effect of HBO is to increase the solubility of oxygen in plasma to a level sufficient to support tissues with minimal extraction of oxygen carried on hemoglobin [4]. Unsurprisingly, researchers developed great interest in using HBO to treat ischemia, and specifically ischemic stroke [5]. In this review, we will discuss the mechanisms of action of HBO and review basic and clinical data reflecting the impact of HBO in the setting of both focal and global ischemic stroke.

Methods

We performed a systematic review of the literature searching Medline database from 1966–2005 using the terms: hyperbaric, hyperbaric oxygenation, cerebrovascular accident, stroke, ischemia, and infarction. We identified 606 articles and selected 92 as relevant. The reference lists of these articles was further reviewed and articles missed by our initial search were further included.

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Mechanism of Action of HBO

The neuroprotective mechanisms of HBO after ischemia are poorly understood (fig. 1). Originally, the rationale for the use of HBO in cerebral ischemia was centered upon increasing oxygenation to an ischemic penumbra and thus reducing the subsequent effects of hypoxia. In animal studies, PaO_2 was increased in plasma of rats treated with HBO when treated immediately or 1 h after ischemia and correlated with improved outcome and decreased infarct size [6, 7]. In canine experiments, treating dogs with HBO after cardiac arrest, however, increased oxygen saturation but was offset by decreased cerebral blood flow (CBF), such that overall oxygen delivery did not change [8]. A recent study made direct measurements of the regional CBF and tissue pO_2 under HBO in rats. Demchenko et al. [9] showed that despite small decreases in blood flow, brain pO_2 was increased at all levels of HBO compared to 100% O_2 at 1 ATA. Therefore, the effects of HBO might be less straightforward.

Rather, the benefits of HBO may be through an indirect neuroprotective effect. Decreased neuronal shrinkage and edema as well as decreased necrotic damage have been described histologically in animals treated with HBO after ischemia [8, 10, 11, 13]. Also, recent studies have shown a nearly immediate protective effect on apparent diffusion coefficient on HBO treated rats during cerebral ischemia. Furthermore, and perhaps more importantly, far fewer neurons show evidence of having undergone subsequent apoptosis after ischemia in animals treated with HBO [12, 13, 15]. Thus, HBO exposure must produce a lasting physiologic change that interrupts the subsequent cell death cascade. Such a theory would lend support to studies showing a protective benefit to pretreatment with HBO prior to ischemia [16–20].

A prolonged effect of HBO could be explained by alterations in inflammation and excitotoxicity, as well as gene expression of cellular protective enzymes and apoptotic regulators affecting late neuronal damage. Wada et al. [21] described increases in expression of the free-radical scavenger Mn-SOD, as well as Bcl-2, an inhibitor of apoptosis, after repeated HBO exposure in gerbils, which correlated with increased neuronal survival [19]. Furthermore, a recent study of subarachnoid hemorrhage in rats showed HBO to have protective effects on CBF, neuronal damage and neurologic function. These changes were associated with decreased expression of hypoxia-inducible factor-1α, a mediator of hypoxic responses leading to improved blood brain barrier function, mediated by decreased vascular endothelial growth factor expression and decreased apoptosis, through inhibition of the proapototic factor BNIP-1 [22]. Improved blood brain barrier integrity has also been specifically described with the use of HBO in experimental focal cerebral ischemia [23]. Also, numerous studies have evaluated the effects of HBO on inflammatory reactions. Increases in activation and adhesion of leukocytes, especially neutrophils, have been well described after cerebral ischemia, and higher neutrophil counts have been associated with poor outcome [24–26]. Further, inhibition of neutrophil accumulation by blocking ICAM-1 [27–29] or using antineutrophil antibodies [28, 30] has been shown to decrease ischemic injury and limit postischemic apoptosis [31]. HBO may exert its effects through this pathway since decreased levels of ICAM-1 [32] in addition to decreased myeloperoxidase activity, a marker of neutrophil sequestration, which correlated with improved outcome [16, 17] were seen in animals treated with HBO before and after ischemia. These findings suggest that HBO may produce lasting neuroprotection by inhibiting inflammation and late neuronal programmed cell death.

Other effects of HBO, including stimulation of angiogenesis [33–36], and decreased cerebral edema and intracranial pressure [16, 37–40], have also been suggested as mechanisms of protection from cerebral ischemia. These recent studies have shown several pathways as possible targets for neuroprotection from HBO, although a good deal of the data is preliminary and needs to be replicated and expounded upon before a clear picture will arise as to the true mechanisms of HBO.

Table 1. Contraindications to HBO

Condition	Potential harm
Absolute	
Doxorubicin current use	Cardiac toxicity
Bleomycin current or former use	Interstitial pneumonitis
Disulfiram current use (in multiple HBO treatments)	Theoretical increased oxygen toxicity due to decreased SOD levels
Cis-platinum current use	Increased cytotoxic effects
Untreated pneumothorax	Cardiovascular collapse
Relative	
Seizure disorder	Seizure
COPD	Decreased respiratory drive
History of spontaneous pneumothorax or thoracic surgery	Increased risk of pneumothorax
Fever	Seizure
Congenital spherocytosis	Hemolysis
Upper respiratory infections or sinusitis	Ear pain

Potentially Harmful Effects

Unfortunately, the physiologic effects of HBO are quite complex, and have the potential for harm as well as benefit. There are numerous medical conditions and drugs which constitute absolute and relative contraindications to the use of HBO due to these risks (table 1) [41]. The clearest example of the potential for neurotoxicity from HBO is seizure. Prolonged exposure to HBO at high pressures eventually leads to seizures even in healthy individuals [42]. The direct etiology of these seizures is not clear; but oxygen toxicity through free radical formation is one possibility. HBO has been shown to lead to increased levels of free radicals [43–45], and increases in free radicals are reported to precede HBO induced seizures [46], suggesting a causal connection. Despite this, production of free radicals has been hypothesized to play a role in the benefits of HBO in cerebral ischemia [47]. Significant concern still exists, however, regarding the level of oxidative stress created by the use of HBO. Lipid peroxidation has been used as a marker for oxidative damage in several animal studies. Although transient increases in lipid peroxidation have been described following HBO [48], most studies have seen no change in lipid peroxidation in treated animals [6, 49–51] despite one study which showed elevated levels of free radicals in the same animals after HBO [50].

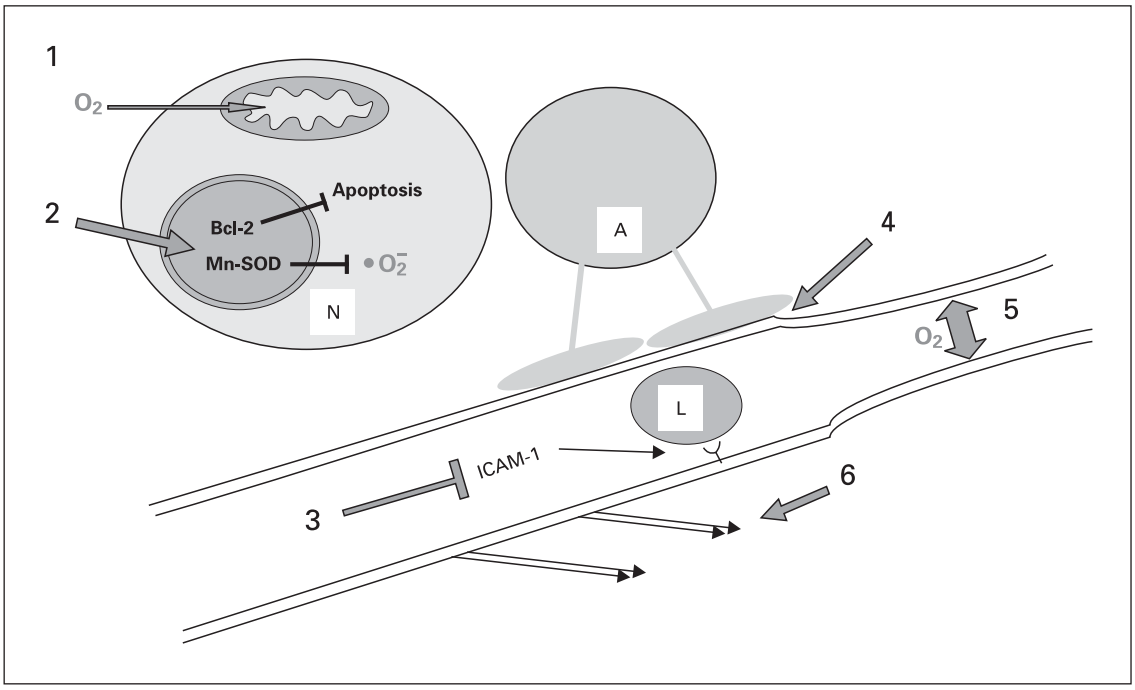

Fig. 1. Potential mechanisms of neuroprotection by hyperbaric oxygen therapy. 1. Increased oxygen delivery to neurons. 2. Stimulation of apoptotic inhibitors and free radical scavengers. 3. Inhibition of leukocyte adhesion through inhibition of ICAM-1. 4. Decreased breakdown of the blood-brain barrier. 5. Decreased edema through oxygen mediated vasoconstriction. 6. Stimulation of angiogenesis. N = Neuron; A = astrocyte; L = leukocyte.

The effects of HBO on CBF might also contribute to potential toxicity. Although the overall effect of HBO is to lower CBF, prior to the development of HBO-induced seizures, there is a significant increase in CBF [52, 53]. This increase has been causally linked to the development of seizures as vasodilation through exposure to CO_2 decreases seizure latency in HBO exposed animals [54]. Also, vasodilatory nitric oxide levels have been found to be increased by HBO [53], and inhibitors of nitric oxide synthase increase seizure latency and attenuate increases in CBF [53, 55]. This suggests that both oxygen toxicity and free radical generation may lead to seizures via NO-induced increases in CBF. Interestingly, NO levels are also decreased by exposure to HBO at lower pressures [56]. Despite these concerns, the pressures and lengths of exposure to HBO that are required to cause seizures in most subjects are greater than those used in trials investigating cerebral ischemia in humans or animals. In routine clinical use of HBO for various indications, the rate of seizures is estimated at 0.03% [57]. In patients treated for carbon-monoxide exposure higher seizures rates were documented with higher pressures. In one series, 0.3% of such patients treated at 2.45 ATA developed seizure, which increased to 2.0% at 2.8 ATA [58].

Additionally there is concern that changes in CBF might have a direct detrimental effect on ischemic brain tissue. Prior to the preseizure increase in CBF, blood flow is significantly reduced, which could extend a stroke through decreased perfusion of an ischemic penumbra. Conversely, however, it has been hypothesized that the early decreases in CBF in normal tissue might cause an inverse steal with an increase in blood flow to unresponsive ischemic areas [1], although it is not clear what effect HBO has on blood flow to ischemic tissue with impaired autoregulation.

Despite these concerns, there has been little evidence that exposure to the levels of HBO utilized in most studies has any detrimental effect in animals or humans. Human trials of HBO for stroke have reported very few adverse events, most of which are of limited severity (e.g. ear pain, claustrophobia).

Animal Studies

HBO in Focal Ischemia

Interest in the use of HBO therapy in treatment of AIS has been fueled by findings from various animal studies showing efficacy. Tables 2 and 3 give details of animal studies of HBO treatment of focal cerebral ischemia reported since 1985. Most showed a benefit to animals treated with HBO. Models of stroke examined cerebral ischemia with and without reperfusion through either temporary [7, 10, 11, 13, 14, 16, 17, 59–65] (table 2) or permanent [6, 49, 50, 65–68] (table 3) occlusion of cerebral arteries. Timing of temporary occlusions ranged from 20 min [11] to 24 h [59]. Several studies used a model involving very early institution of HBO therapy, starting treatment immediately [7, 10, 11, 17] or within minutes [6, 14, 62, 67, 68] of ischemia. Improved survival, smaller infarct size, and better neurologic function were seen in the HBO-treated animals.

Table 2. Animal studies of hyperbaric oxygen treatment of temporary focal ischemia

Name year	Time of ischemia	Time from onset	HBO treatment	Number × length of treatment	Animal	Findings	Time at evaluation
Weinstein 1986	20 min CCA	0 min	100% O_2 1.5 ATA	1 × 15 min	gerbil	increased survival, improved function, decreased neuronal damage	10 days
Weinstein 1987	6 h or 24 h MCA	1, 3 or 4 h plus 6 h, or before during, and after 24 h	100% O_2 1.5 ATA	1 × 40 min	cat	smaller infarcts in 1 and 3 h treatment, no change in 4 h, smaller infarcts in 3 h treatment of 24 h, improved function at all times in 6 h and in 3 h of 24 h	10 days
Kawamura 1990	4 h MCA	2.5–3.5 h	100% O_2 2 ATA	1 × 30 min	rat	smaller infarcts with later treatment, decreased edema with later treatment	4 h
Roos 1998	variable ICA	variable 3–90 min	100% O_2 2 ATA	1 × 30 min or 5 × 30 min	rat	no difference in time to create deficit	4 days
Atochin 2000	2 h MCA	before	100% O_2 2.8 ATA	1 × 45 min	rat	smaller infarcts, improved function, decreased neutrophil accumulation	46 h
Chang 2000	1 h MCA	0 min or 60 min	100% O_2 3 ATA or Air 3 ATA	2 × 1.5 h	rat	smaller infarcts, improved motor function, intermediate effect from hyperbaric air	24 h
Veltkamp 2000	75 min MCA	12 min	100% O_2 1.5 ATA 2.5 ATA, 100% O_2 as control	1 × 1 h	rat	smaller infarcts at 2.5 ATA, improved behavioral function, no effect of 1.5 ATA	7 days
Badr 2001	2 h MCA	6 h	100% O_2 3 ATA	1 × 1 h	rat	smaller infarcts, decreased glutamate, glucose, pyruvate	24 h
Yang 2002	1 h MCA	0 min	100% O_2 2.8 ATA	1 × 1 h	rat	decreased edema and neuronal shrinkage, lesser dopamine increase	120 min
Yin 2002	2 h MCA	6 h	100% O_2 3 ATA	1 × 1 h	rat	smaller infarcts, smaller increase in COX-2	24 h
Miljkovic-Lolic 2003	60 min MCA	before or 0 min	100% O_2 3 ATA	1 × 1 h	rat	improved outcomes, smaller infarcts, decreased leukocyte infiltration	24 h
Yin 2003	2 h MCA	8 h	100% O_2 2.5 ATA	1 × 2 h	rat	improved outcomes, fewer apoptotic bodies and less DNA fragmentation	7 days
Lou 2004	90 min MCA	3, 6 or 12 h	100% O_2 3 ATA	1 × 1 h	rat	improved outcome and smaller infarct in 3 and 6 h, worse outcome and larger infarct in 12 h	7 days
Veltkamp 2005	120 min MCA	40 min	100% O_2 3 ATA	1 × 1 h	rat	reduced volume of restricted diffusion, histologically smaller infarcts	24 h

Unfortunately, treatment of stroke in humans can rarely be instituted so quickly. In models more consistent with conditions in a clinical setting, HBO treatments delayed until several hours after the beginning of ischemia were also shown to be effective in reducing infarct size and improving outcome [11, 13, 50, 60, 63–65].

The optimal dose for HBO to be effective in cerebral ischemia is not clear from these reports. The dosing of HBO varied between studies with various pressures and treatment duration in animals. Most animals were given one treatment lasting 1 h, although times as brief as 15 min [11] and as long as 36 h [67] were evaluated. Pressures ranged from 1.5 ATA to 3 ATA. No clear minimum or maximum effective pressure or time can be deduced, as positive results were seen in various studies throughout these ranges. A dose-response effect might be inferred from Veltkamp et al. [62] who compared HBO at 2.5 ATA and 1.5 ATA to 100% O_2 and found only the 2.5 ATA dose to be effective. In contrast, the time from the onset of ischemia to initiation of treatment does appear to be important. Weinstein et al. [59] administered HBO after MCA occlusion in cats and found that treatment after 1 or 3 h of ischemia was effective in decreasing infarct size and improving outcome behaviorally. Treatment after 4 h, however, had no effect on the size of the infarction, although HBO treated animals still had better functional outcome than controls. Similarly, Lou et al. [65] administered HBO at 3, 6 or 12 h after 90 min of focal ischemia to rats and found significant neurological improvement and decreased infarct size in animals treated 3 or 6 h after ischemia. Conversely, rats treated with

Table 3. Animal trials of hyperbaric oxygen in permanent focal ischemia

Name year	Site	Time from onset	HBO treatment	Number × length of treatment	Animal	Findings	Time at evaluation
Corkill 1985	CCA	<1 h	100% O_2 2 ATA or 1.5 ATA	1 × 1 h or 1 × 30 min	gerbil	decreased interhemisphere differences	3 days
Burt 1987	CCA	<30 min	100% O_2 1.5 ATA	1 × 36 h or 1 × 18 h or on/off × 36 h	gerbil	36-hour treatment all died, others had greater survival and fewer infarcts	36 h
Reitan 1990	ICA	40 min	100% O_2 1,875 mm Hg	1 × 2 h, or 1 × 4 h	gerbil	increased survival	5 days
Sunami 2000	MCA	10 min	100% O_2 3 ATA	1 × 2 h	rat	smaller infarcts, no change in CBF, no change in lipid peroxidation	24 h
Hjelde 2002	MCA	10 min	100% O_2 2 ATA	1 × 230 min	rat	no change in DWI image, no change in MPO	4 h
Schäbitz 2004	MCA	2 h	100% O_2 2 ATA	1 × 1 h	rat	decreased DWI and T_2 image, improved outcome, no change in lipid peroxidation	5 days
Lou 2004	MCA	3 or 6 h	100% O_2 3 ATA	1 × 1 h	rat	no difference in infarct size, no difference in outcome	7 days

HBO 12 h after ischemia had worse neurologic outcomes and larger infarcts than controls. Further, in the same set of experiments, rats subjected to permanent MCA occlusion given HBO at 3 or 6 h showed no benefit or harm compared to controls. This suggests that there may be a window of opportunity between 6 and 12 h after transient ischemia for HBO to be effective and raises concerns that beyond that window, HBO may actually be harmful. Permanent ischemia may have an even shorter window as studies treating within 2 h showed a benefit from HBO [6, 49, 51, 66–68] whereas one study treating at 3 or 6 h after ischemia did not [65].

A common factor between several negative studies was delayed initiation of treatment. Weinstein et al. [59] and Lou et al. [65] compared treatments at various times after transient ischemia and found less efficacy of treatments given later after onset. Lou et al. [65] also found no effect of HBO administered 3 or 6 h after permanent focal ischemia, which was a greater delay to treatment than in studies with positive results.

Only few animal studies failed to find any benefit from HBO therapy of cerebral ischemia. Using a unique experimental design, Roos et al. [61] tested rats treated with HBO at 2 ATA for 30 min after various times of ischemia to determine the average duration of arterial occlusion required to create a neurologic deficit. No difference was seen in this evaluation between treated and control animals. Hjelde et al. [49] used a design, timing, and dosage similar to other studies, treating rats with HBO at 2 ATA for 230 min beginning 10 min after permanent MCA occlusion and yet found no improvement in infarct size compared to control animals.

What is apparent from these various studies is the effectiveness of HBO in ameliorating the effects of cerebral ischemia. Numerous variables, including dose, timing, and number and length of treatments merit further evaluation to identify the optimal treatment regimen.

HBO in Global Ischemia

HBO has also been investigated as a treatment for global cerebral ischemia. Most of the reports to date have been limited to animal models (table 4). Similarly to the focal cerebral ischemia studies in animals, the results are quite promising. In an effort to simulate global ischemia similar to a clinical setting, most groups instituted ischemia for only 10–15 min, such as might be sustained during cardiac arrest. Krakovsky et al. [69], however, subjected rats to 1 h of ischemia before treatment with HBO, and Shiokawa et al. [70] treated rats after 1 or 3 h of ischemia. HBO therapy was instituted either immediately [50, 69] or, in a more clinically relevant model, after a period of several minutes to hours [8, 12, 15, 23, 70–73]. In an effort to simulate a hypoxic-ischemic insult, Calvert et al. [15] permanently occluded the common carotid artery in rats. Two hours later they subjected them to 2.5 h of hypoxia followed 1 h later by treatment with HBO. In all but two studies where 2 ATA was administered [12, 70], high doses of HBO were used (2.7–3 ATA). Treatments ranged from 30 min to 2 h. In the study by Shiokawa et al. [70], rats treated with HBO 3 h after onset of ischemia showed a statistically significant increase in survival, while those treated after 1 h showed only a trend towards longer survival. In each of the other studies, all animals treated with HBO after global ischemia had better survival and physical outcomes [8, 15, 50, 61, 71, 72] as well as less microscopic evidence of ischemic damage [8, 12, 15, 23, 50, 73] than did control animals.

Human Studies

HBO therapy has been utilized in more than 1,000 stroke patients in numerous trials over the last 40 years. Despite this, it is difficult to determine the true benefit or harm from HBO for isch-

Table 4. Animal studies of global ischemia and hypoxia

Name year	Length of ischemia	Time from onset	HBO treatment	Number × length of treatment	Animal	Findings	Time at evaluation
Shiokawa 1986	permanent	1 h or 3 h	100% O_2 2 ATA	1 × 30 min	rat	lengthened survival in 3 h, trend toward same in 1 h	8 h
Takahashi 1992	15 min	3 h	100% O_2 3 ATA	3 × 1 h	dog	improved survival, improved function, improved EEG	2 weeks
Iwatsuki 1994	15 min	3 h	100% O_2 3 ATA and nicardipine	3 × 1 h	dog	improved survival, improved function, improved EEG	2 weeks
Mink 1995	10 min	1 min	100% O_2 2.8 ATA	1 × 75 min	rabbit	improved recovery, increased free radicals, no change in lipid peroxidation	immediate
Mink 1995	10 min	40 min	100% O_2 2.8 ATA	1 × 125 min	rabbit	decreased vascular permeability, decreased CBF, no change in SSEP	240 min
Kondo 1996	10 min	6 h or 24 h	100% O_2 2 ATA		gerbil	less neuronal death, decreased heat shock proteins	3 weeks
Krakovsky 1998	60 min	'brief delay'	100% O_2 3 ATA	1 × 1 h	rat	greater survival	2 weeks
Calvert 2002	CCA occlusion, wait 2 h, 2.5 h hypoxia	5.5 h	100% O_2 3 ATA	1 × 1 h	rat	decreased atrophy, decreased apoptosis, improved function	6 weeks
Rosenthal 2003	10 min	70 min	100% O_2 2.7 ATA	1 × 85 min	dog	improved function, decreased neuronal death	24 h
Zhou 2003	10 min	1 h	100% O_2 3 ATA	1 × 2 h	rat	decreased neuronal death	7 days

emic stroke due to the heterogeneity of patients, treatments and experimental designs (table 5). Most of the early trials reported a benefit from treatment of ischemic stroke patients with HBO [4, 74–77]. Unfortunately, these trials were for the most part, uncontrolled, and utilized greatly disparate criteria for inclusion as well as for evaluation of improvement.

The three most recent studies, however, were double-blind, randomized, controlled trials. Anderson et al. [78] randomized 39 patients within 2 weeks of cerebral infarction to multiple treatments of either HBO at 1.5 ATA or hyperbaric air at similar pressure. At 4 months, no significant difference was seen on a graded neurologic exam or in stroke volume by CT. A trend towards better outcome in the hyperbaric air group had been noted, and thus the trial was stopped early. Nighoghossian et al. [79] treated 34 patients presenting with MCA symptoms within 24 h of onset with multiple treatments at 1.5 ATA or sham treatment with air and a 'minimal pressure increase'. There was no difference in the mean Rankin scores at 1 year, whereas the Orgogozo and Trouillas outcome scores were significantly higher in the treatment group. This difference was lost when pre- versus posttreatment scores were compared. These conflicting data suggest that if there was an effect of this regimen it was not robust.

The most recent trial by Rusyniak et al. [80] randomized 33 patients presenting in less than 24 h to one treatment of HBO at 2.5 ATA or a sham of 100% O_2 at 1.14 ATA. Analysis at 3 months showed a better outcome in the control group on the NIHSS and Rankin scales, suggesting a potentially harmful effect of HBO, but intention-to-treat analysis showed no statistical difference between the groups.

Interestingly, a recent analysis of human trials by Rogatsky et al. [81] attempted to compare studies based on a determination of the 'total dose' of HBO given to each patient calculated as the product of pO_2 used, treatment time, and number of chamber treatments. In their analysis, a strong correlation was seen between average total HBO 'dose' and patient outcome.

As no statistically significant differences were shown, it appears that HBO is ineffective in treatment of stroke; however, this must be considered in light of several factors. First, the control treatments used to maintain blinding are important. Anderson et al. [78] treated control patients with hyperbaric air, which in one animal study showed a trend towards improved outcome over controls treated with air at normal pressure [7]. Rusyniak et al. [80] used normobaric oxygen, which has been found to have benefit over air in ischemia [82–84] and thus should be considered a treatment arm as well.

Table 5. Human studies of hyperbaric oxygen in acute ischemic stroke

Name year	Time from onset	HBO	Control	Number of patients	Number and length of treatments	Findings	Time at evaluation
Neubauer 1980	0–4 h >4 h	100% O_2 2.0 ATA	none	122 HBO; 16, 0–4 h; 106, 4 h – 10 years	16 × 1 h	improved neurologic function, decreased length of stay in <4 h	varied
Kapp 1981	0–2 weeks	100% O_2 1.5 ATA	none	22 HBO	14 × 65 min	improved neurologic function in 43%	varied
Anderson 1991	0–7 days	100% O_2 1.5 ATA	air 1.5 ATA	20 HBO; 19 control	8.9 × 1 h	no significant effect, trend towards improved outcome in hyperbaric air	1 year
Nighoghossian 1995	0–24 h	100% O_2 1.5 ATA	air and 'minimal pressure increase'	17 HBO; 17 control	10 × 40 min	no significant effect, trend towards improved outcome in HBO	1 year
Rusyniak 2003	0–24 h	100% O_2 2.5 ATA	100% O_2 1.14 ATA	17 HBO; 7, <12 h; 16 control; 6, <12 h	1 × 1 h	no improvement in HBO, trend towards improved outcome in sham	90 days

Nighoghossian et al. [79] used nearly normobaric air, which is most like standard therapy. Nevertheless, it must be restated that no statistically significant differences between treatment and controls were seen on intention-to-treat analysis in any of these studies.

Second, the timing of treatment should be considered. Animal studies suggest that treatment beyond 4–6 h is less beneficial and may be harmful. In humans, Neubauer and End [74] reported 16 patients who were treated with HBO within 4 h of stroke and observed a shorter length of stay and better outcome, as determined by discharge location, than for age- and severity-matched patients at another institution. Similarly Kapp [75] administered HBO to 2 patients within 1 h after stroke onset and described complete resolution of symptoms, whereas patients treated later did not have such a dramatic response. Although these findings are the results of uncontrolled, unblinded observations, they do suggest that early HBO therapy may be beneficial.

Limitations and Future Directions

To date, no adequately powered, well-controlled clinical trial has been carried out to evaluate the true efficacy of HBO in acute ischemic stroke. As such, discordance still exists between the animal data and ischemic stroke clinical trials. This has been a problem for many promising neuroprotective stroke treatments. Two reports have discussed the pitfalls of translational research in stroke treatment and recommended standards for such studies [85, 86]. Several of the issues discussed are particularly important in the case of HBO preclinical and clinical studies. First, timing of treatment in most studies of HBO was immediate or very early after ischemia in animal models, yet up to days or weeks after index stroke in clinical trials. Thus, it should not be surprising that they achieved different results. Second, animal studies used primarily transient ischemia as a model for stroke, but clinical trials did not limit patients to those with thrombolysis or reperfusion, and since the bulk of patients do not undergo recanalization, these results are not comparable. Further, although most animal models that did evaluate HBO in permanent cerebral arterial occlusion reported benefit, most administered treatment almost immediately after ischemia [6, 50, 51, 66–68]. Only one study evaluated HBO treatment within a window more consistent with patient care (3–6 h) and showed no benefit in permanent arterial occlusion [65].

Third, the type of stroke was considered in only one study where treatment was limited to patients with MCA occlusion [79]. In all other human studies, no distinction of stroke etiology was made. Since all of the animal data is limited to large vessel occlusion, it is not clear that other etiologies, such as lacunar or subcortical strokes, would benefit from HBO treatment and thus may dilute any benefit seen in trials. Fourth, the appropriate dose of HBO for maximal benefit has not yet been determined, so trials have varied greatly in the regimen of HBO administered, with a particular discrepancy between preclinical and human trials. Animal studies that have shown benefit from HBO in cerebral ischemia have used pressures ranging from 2.5 to 3.5 ATA. In contrast, the human studies used lower pressures, from 1.5 to 2.5 ATA. Interestingly, in one study, 1.5 ATA, a level tested as potentially therapeutic in human studies was used as a sham protocol in animal testing and showed no significant effect on outcome [62]. Similar discrepancies are seen in number and length of treatments.

Also, given the logistical difficulty of treatment with HBO in the setting of acute stroke, it is imperative that its superiority over the simpler use of normobaric hyperoxia be assured, as animal models have shown normobaric 100% oxygen to reduce infarct size in ex-

perimental stroke [82–84]. Several studies suggest that HBO is, in fact, more effective than normobaric hyperoxia. Weinstein et al. [59] compared neurologic function and infarct size in cats receiving room air, normobaric 100% oxygen or HBO after MCA occlusion and found that only groups treated with HBO had significantly better neurologic outcomes, and smaller infarct sizes. In another study, Veltkamp et al. [14] administered HBO or 100% O_2 at ambient pressure during experimental stroke in rats and found immediate protection in the form of smaller infarcts and less restricted diffusion on MRI scan only in HBO-treated animals. The same group had previously shown similar results of animals treated with 100% O_2 at 2.5 ATA versus 1.5 ATA or 1 ATA. Rats treated with 2.5 ATA had smaller infarcts, and better neurologic function at 7 days than those treated with 100% O_2 at lower pressures [62]. Additionally, Chang et al. [7] showed that the increased pressure itself may contribute therapeutic effect as control rats receiving air at 3 ATA had intermediate reductions in infarct size compared to HBO and normobaric air-treated animals. These findings suggest that HBO has effects above and beyond those achievable through the use of oxygen at normal pressure.

Finally, outcome measures are not consistent between animal and human studies. Animal models, if they recorded functional outcome at all, evaluated animals at a few hours to at most a few weeks. Also, most studies actually used more anatomic measures, such as infarct size, as a measure of efficacy. In contrast, most human trials looked solely at functional outcome after several months or even years making comparison between them difficult if not impossible.

These various discrepancies between the promising animal research and human trials would need to be reconciled in design of any future clinical trials of HBO. Several questions remain unanswered. First, what is the optimal dose of HBO, including pressure, length and number of treatments? Second, is there a limited window of opportunity after which HBO is ineffective or even harmful? Third, is HBO effective for only a subset of strokes, such as large vessel occlusion, or reperfused tissue? Further animal studies would be useful to more clearly understand these issues. Presently, a human protocol would only be valuable if it reflected closely the HBO treatments used in successful animal studies. This would require limiting the treatment to the first several hours and to patients with large vessel occlusion. Also, since transient and permanent arterial occlusion appear to respond differently, monitoring for recanalization by transcranial doppler or MR or CT angiography would be useful. Dosing of HBO should also be similar to the animal studies using pressures of 2.5–3 ATA, although a preliminary dose-finding trial might be useful as well. Controls should breathe air close to ambient pressure, though a small increase would be needed to maintain patient blinding. Such an approach might more clearly answer the question of the efficacy of HBO in stroke. Until that time, the clinical use of HBO for the treatment of acute ischemic stroke cannot be advocated outside of a well-designed experimental protocol.

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