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# Hyperbaric Oxygen for Stroke

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## 1. Introduction

The largest body of evidence involving the use of hyperbaric oxygen for neurologic illness is found in the field of cerebral ischemia. At the center of an infarct, blood flow is completely absent, causing neurons to die within a matter of minutes. This area, therefore, may not be amenable to treatment after the start of symptoms. The region of the brain that draws the most interest is the penumbra, where evidence has shown that blood flow is diminished, but not absent. The cells in this region remain viable for a prolonged period, and can be saved if adequate perfusion is restored. The only FDA approved therapies for acute ischemic stroke include tPA, and interventional intra-arterial treatments aimed at restoring blood flow to the ischemic penumbra, but must be used within the first few hours of the onset of symptoms. There is also evidence that a percentage of the cells subjected to prolonged ischemia will inevitably undergo apoptosis, either after prolonged ischemia or due to reperfusion injury in the case of temporary ischemia. As a result, there has been great interest in using $HBO_2T$ for the added benefit of its anti-inflammatory and anti-apoptotic properties. There is reasonable evidence from animal studies, involving mice, rats, gerbils, and cats that damage from focal cerebral ischemia is ameliorated after treatment with $HBO_2T$. Several human trials investigating the use of $HBO_2T$ for ischemic stroke have also been performed. Most of these lacked controls, as well as uniform standards for inclusion criteria and outcome measurement. There have been three prominent randomized controlled studies that have evaluated $HBO_2T$ in ischemic stroke, none of which where able to demonstrate statistically significant benefit. One might conclude from this that $HBO_2T$ is an ineffective treatment for ischemic stroke, however, it should be noted that these studies enrolled patients well after the therapeutic window of 6 - 12 hours suggested by previous animal studies. Additionally, two of the three also used lower doses of $HBO_2T$ than was found effective in animal studies. Based on our present understanding of ischemia, one would not expect improvement in measured outcomes under these conditions.

It seems therefore reasonable to assess patients presenting for potential $HBO_2T$ for a pattern of penumbra as this provides the strongest evidence of recoverable tissue. As the ischemic penumbra represents the area which is expected to be most salvageable, it is reasonable to determine whether a penumbra is or is not present in patients undergoing experimental treatment with $HBO_2T$. On MRI, penumbra is represented by perfusion-diffusion mismatch. More simply stated, we must find the area of brain which is dying in hope that $HBO_2T$ can still save it before it is dead. This is called ischemic penumbra. In the rat model of focal ischemic stroke produced via thrombotic occlusion of the MCA, MRI revealed perfusion-diffusion mismatch which persists up to 6-12 hours after the occlusion. In patients such

mismatch is usually present during the first 6 hours after stroke. Noticeably, $HBO_2T$ was effective against experimental stroke if administered when a penumbra is typically present in the brain. $HBO_2T$ administered at a time when penumbra is usually gone (e.g. at 23 hours) may even be harmful. The clinical trials done with $HBO_2T$ so far did not follow this paradigm, which creates the most important discrepancy between experimental and clinical work. We propose that the evaluation of patients in any future clinical trial should include separate subgroup analyses of patients with and without confirmed penumbra as the impact on outcomes may be different in these two groups.

As the accepted standards of stroke care are paramount in treatment of any patient presenting with acute stroke, patients presenting within the therapeutic window for tPA should be treated with tPA but should be considered for $HBO_2T$ as well if they have persistent neurologic deficits on physical examination and can be treated within the time window. This is because even in cases of temporary ischemia $HBO_2T$ has shown benefit in animal studies through decreases in reperfusion injury.

## 2. Hyperbaric oxygen for stroke protocol background

This chapter discribes the protocol which we propose ulitmitaly leading to a multicenter trial, as follows.

The purpose of this study is to determine the safety of hyperbaric oxygen therapy of acute ischemic stroke at a dose of 2.4ATA for 90 minutes administered in the first 12 hours of symptoms. The data obtained will be used to determine safety and to estimate effect size in order to plan a larger, adequately powered, multicenter trial.

Presently, in the US, tPA is the only FDA approved therapy for treatment of acute ischemic stroke (AIS). Unfortunately, only around 3-5% of patients with stroke receive tPA therapy due to the strict time limitations and the high risk of bleeding associated with its use. Therefore, other modalities of treatment for acute ischemic stroke need to be investigated.

Animal studies have suggested that administration of pure oxygen at high pressure can be protective against the effects of cerebral ischemia. Some small uncontrolled studies in humans have shown benefit of HBO. However, no study has tested HBO in stroke at a time and a dose which, based on animal studies, could be expected to be effective.

HBO therapy of cerebral ischemia has been shown to be effective in numerous animal models of AIS (1). Animals treated with HBO after either temporary (2, 3, 4, 5, 6, 7, 8, 9, 10) or permanent (9, 10) cerebral arterial occlusion showed decreased infarct size versus controls. Improved survival, function and behavior in HBO treated animals were also reported (2, 3, 5, 6, 9, 10, 11, 13, 14, 15, 16, 17, 18, 19). Several of the studies used a model involving the nearly immediate institution of HBO, starting treatment immediately (2, 9, 13, 20) or within minutes (8, 11, 12, 14) of ischemia. In models more consistent with conditions in a clinical setting, however, HBO delayed until several hours after the beginning of ischemia was also been shown to be effective. (3, 4, 7, 8, 10, 15) There may, though, be an early window of opportunity after ischemia for HBO to be effective. One study found that treatment after 1 or 3 hours of ischemia decreased infarct size and improved outcome behaviorally, whereas, treatment after 4 hours had no effect on infarct size. (3) A more recent study, however, showed that HBO treatments initiated up to 24 hours after transient cerebral ischemia in rats resulted in decreased infarct size and neurologic deficits at 4 weeks (10).

Human trials of HBO for AIS have been less conclusive. Most of the early trials reported a benefit from treatment of ischemic stroke patients with HBO. (21, 22, 23, 24, 25) These trials,

however, were for the most part, uncontrolled, and utilized greatly disparate criteria for inclusion as well as for evaluation of improvement. Of the three small recent randomized trials of HBO in AIS (26, 27, 28), no significant difference was seen between treatment and sham groups. Significantly, however, treatments were not limited to the hyperacute stage, as patients were enrolled up to 24 hours after symptom onset in 2 studies, and up to 2 weeks in the third. Also, in two of the studies, patients receiving sham treatment were given either hyperbaric air, or 100% O2 at slightly increased pressure, neither of which is known to be clinically insignificant. Further, these studies used a lower dose of HBO than has been shown effective in animal studies, as well as in human clinical use for other approved indications (wound healing, CO poisoning, etc.)

All but one of the studies evaluating HBO therapy of ischemic stroke have used a dose of 1.5 ATA. This was selected based upon concerns for increased risk of oxidative stress with higher doses suggested in a single study from 1977 (29). This study was limited, however, by inclusion of only 7 ischemic stroke patients (the rest had traumatic brain injury) and the administration of HBO several days after the cerebral insult. Despite concerns for increased oxidative stress, the patients who received the higher doses of HBO did not have seizures or worsening of neurologic deficits.

There is a theoretical concern that hyperbaric treatment at a higher dose could cause oxidative stress through free radical damage leading to an increase in neuronal loss and thus a worse clinical outcome. Some animal studies have shown increases in lipid peroxidation (52), a marker of free radical damage, but most have not (12, 53-55). The single study which assessed the use of HBO at 2.5 ATA in acute stroke did raise concerns of worsened stroke outcome at the higher dose, but was limited by several factors (28). First, most of the patients were treated after 12 hours. Second, the control group was subjected to 100% O2 at 1.14 ATA, which is not standard care. Third, there was no cut-off for stroke severity, such that very mild strokes were included, making evaluation of the effect of HBO difficult. Also, the differences seen were not statistically significant.

The selection of the dose for this study is based on several facts. First, HBO is approved for use by the FDA at a dose of 2.4 ATA for 90 minutes for treatment of numerous conditions and is well tolerated (30). Despite the above stated safety concerns, patients with arterial gas embolism and decompression illness, both of which commonly cause ischemia of the central nervous system, are treated with even higher doses of HBO with good efficacy and acceptable safety levels (31, 32). This cannot, however, be directly compared to ischemic stroke as the pathological mechanism of ischemia is different, and as such, a study is warranted. Second, this dose is more consistent with animal studies which have shown efficacy (see above).

The rationale for the use of HBO in cerebral ischemia centers upon increasing oxygenation to an ischemic penumbra and thus reducing the subsequent effects of hypoxia. Additionally, there may be other effects of HBO contributing to improved outcome after cerebral ischemia. Decrease in cerebral blood flow caused by oxygen induced vasoconstriction, has been shown in humans (35) as well as animals (5, 36) treated with HBO, and may produce a decrease in cerebral edema. Also, HBO may have benefit in the treatment of stroke by exerting 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. (13, 19, 20, 37) Additionally, and perhaps more importantly, far fewer neurons show evidence of having undergone subsequent apoptosis after ischemia in animals treated with HBO. (15, 37, 38) HBO exposures in the first few minutes or hours after

ischemia must, therefore, effect a lasting physiologic change which interrupts the subsequent cell death cascade.

It is felt that this effect may be mediated through inhibiting the inflammatory response to ischemia. Neutrophil accumulation and adhesion have been identified in ischemic brain tissue (39) and are correlated with poor clinical outcome (40, 41). Elevated serum levels of selectin and immunoglobulin-type adhesion molecules have been described after acute stroke (42, 43, 44). In other studies, elevated serum levels of ICAM-1 seen at 12 and 24 hours after symptom onset were shown in humans to be directly related to infarct size on diffusion weighted imaging (45). In the same group of studies matrix mettaloproteinases were also shown to be elevated in ischemia and presentation levels of MMP-9 were correlated with eventual infarct size (45).

Previous studies have shown that administration of antibodies to ICAM-1 after transient cerebral ischemia in animals decreased leukocyte adhesion and limited infarct size as well as the number of apoptotic cells (46, 47, 48) suggesting there is a neuroprotective effect of decreasing ICAM-1 activity after reperfusion. Hyperbaric oxygen therapy may exert its antiapoptotic effects through this pathway, since decreased leukocyte adherence and neutrophil accumulation were seen after cerebral ischemia in HBO treated animals (5, 9). ICAM-1 levels have also been shown to be decreased in ischemic tissues in HBO treated animals (49), as well as in human tissue cultures (50) Interestingly, this effect was not seen in non-reperfused tissue (22, 47). Also, in healthy human volunteers, HBO treatment caused reductions in leukocyte adherence that was seen at 2.8 and 3.0 ATA but not at 1.0 or 2.0 ATA (51).

The outcomes scales selected for the study includes the NIH stroke scale (NIHSS), the modified Rankin scale (mRS), the Barthel index, and the Glasgow Outcome scale. These have been used and validated in numerous stroke studies. As they are non-linear scales, they have been utilized for binary outcomes, good versus poor. Good outcome designations are usually understood to be NIHSS ≤ 1, mRS ≤ 1, Barthel 95-100, Glasgow Outcome scale= 5. (33, 34)

## 3. Hypothesis and objectives

Hyperbaric oxygen therapy administered within twelve hours of symptom onset to patients with acute ischemic stroke at a dose of 2.4 ATA for 90 minutes is safe.

**Specific Aim 1:** Safety

We will determine whether patients presenting with acute ischemic stroke with a National Institute of Health Stroke Scale score of ≥4 given one treatment of hyperbaric oxygen at 2.4 ATA for 90 minutes initiated within 12 hours of symptom onset do not have a significantly higher rate of adverse events, or a singificantly increased infarct size by MRI.

**Specific Aim 2:** Pilot data for a larger study

This study will provide pilot data to be used to estimate effect size of the use of HBO on functional outcome of ischemic stroke as stated above in order to determine sample size to adequately power a larger multicenter study to determine efficacy of the treatment.

**Specific Aim 3:** Pilot data on mechanism of HBO

**3a. Perfusion:**

We will gather pilot data on the effect of treatment with HBO as described above on perfusion of the ischemic territory evaluated by pre- and post-treatment perfusion MRI scanning of the brain (in the first 20 patients). This will be used to gain insight into whether a protective effect of HBO is mediated through altered perfusion to the ischemic penumbra,

or if, as is expected, perfusion is not directly affected, but poorly perfused brain territory is protected by other mechanisms.

**3b. Leukocyte adhesion:**

We will test the hypothesis that the mechanism of neuroprotection provided by hyperbaric oxygen therapy exerts itself through changes in leukocyte adhesion. Using MMP-9 levels at presentation, known to be correlated with eventual infarct size, as a standard for stroke severity, we will determine whether the normally exhibited increase in serum levels of ICAM, VCAM and SELAM after onset of acute ischemic stroke, also correlated with infarct size, is attenuated in patients receiving HBO therapy as described above, and if the decrease in leukocyte adhesion factors correlates with decreased infarct size and improved neurologic outcome.

This is how we determined the number of participants necessary to conduct the study:

1. To evaluate efficacy, the first 10 subjects in each group – HBO and non-HBO – will have in addition to their NIHSS, Barthel index and Rankin scale score, an MRI with diffusion and perfusion weighted imaging, which will be performed pre and post treatment (for the first 20 patients and 72 hours post enrollment for the control group). If there is no differential effect between the controls and the HBO on outcome, the study will be terminated for lack of efficacy.
2. To evaluate safety, 36 subjects in each of the HBO and non-HBO stroke treatments would allow a difference of 20% in aspiration pneumonia Adverse Events to be detected with a power of 80% and a type I (alpha) error of 5%. This would also allow detection of a 20% increase in the rate of post-treatment seizures.

The acute stroke team will make first contact when they are consulted for patients with acute ischemic stroke. Patients will be recruited from all emergency room and inpatient consults for acute stroke called to the stroke team. Women and minorities will be included as they present.

Patients and/or involved family members will be presented with the study and the informed consent will be obtained after all questions/concerns are addressed completely. If the patient is unable to give informed consent themselves, then the LAR will give informed consent on their behalf. If the patient does not have a LAR (Living adult relitive), then we will solicit consent from a next of kin (in the following order): the spouse, adult child, parent, adult sibling, grandparent, or adult grandchild. If none of these options are available then we will be unable to consent the patient and they will not be considered for enrollment in the study. If patient's become able to give consent during the study period they will be reconsented at that time.

Potential subjects and their families will be told that this is an emergency treatment study. We will explain that time is of the essence and that if they feel they are unable to make an informed decision in a timely fashion (approx. 20 minutes), they will be unable to participate in the study. We had several people with no medical background who are not involved with the study read the consent form and on average it took them about 20 minutes to read and understand the consent and fill out the consent questionnaire.

The consent questionnaire is used to evaluate the consent process and document the understanding of the patient and/or LAR of his/her obligations as a patient and the obligation of the PI. If the patient or LAR failed to answer more than 50% of the questions we will offer them the opportunity to rereview the consent forms. If they continue lack of understanding of the research study we will no longer consider them for participation.

**Exclusion criteria:**

1. Neuroimaging evidence of ICH, intraventricular or subarachnoid blood, tumor, encephalitis or diagnosis other than stroke.
2. Posterior circulation infarction.
3. Active pulmonary disease, pneumothorax, intubation or possible necessity for intubation. ABG findings of pH < 7.32 or pCO2 >49.
4. Active cardiac disease.
5. Decreased level of consciousness (score > 0 on NIHSS item #1a).
6. Inability to lie flat.
7. Claustrophobia.
8. Life expectancy less than 6 months.
9. Pregnancy or breast feeding.
10. Treatment with any other experimental stroke therapy since symptom onset.
11. Patients requiring continuous IV treatment for elevated or depressed blood pressure.
12. Inability to undergo MRI (pacemaker, AICD, etc.)
13. History of seizure.
14. Diabetic patients with a blood glucose <110
15. A GFR blood test resulting in a value of <30 because then the patient would be unable to undergo MRI with contrast.
16. History of inner or middle ear surgery (other than tube placement)
17. History of pneumothorax.
18. History of exposure to Bleomycin.
19. Presently taking steroids.
20. Presently taking Doxorubicin, cis-platinum or disulfiram.

The target enrollment will be 72 patients. Subjects arriving in the emergency department with a presumptive diagnosis of acute stroke will be evaluated by the on-call neurologist. If the time since symptom onset is less than 12 hours and the subject has no known exclusion criteria, a certified examiner will evaluate them using the NIHSS.

Subjects with at least a score of 4 on the NIHSS who are determined to have anterior circulation ischemia as determined by the clinical judgment of the examiner will be enrolled. The NIHSS will be conducted by a study team member, all of whom are NIHSS certified by the American Heart Association and the National Stroke Association. If a subject is determined to have a NIHSS of less than 4, they will not be considered eligible for the study. Also, if a patient is non-responsive when exmained, they will also be excluded from the study. A copy of the NIHSS is included in the source documents which are attached to section 52 of the study smartform. A pregnancy test will be performed on all women of child-bearing age who have a uterus and ovaries. Premorbid mRS score will be discerned through discussion with the patient or family/friends. If this information if not available in time for randomization, the subject will be excluded. If treatment cannot be started within 12 hours from symptom onset, the subject is excluded. Patients deemed candidates for thrombolytic therapy will be treated accordingly and if the patient is randomized to treatment, the HBO will not begin until the tPA infusion has ended.

A noncontrast head CT is done routinely on all patients presenting to the emergency department with acute stroke. This CT scan will be reviewed for evidence of ICH or other exclusionary pathology prior to randomization.

As part of the normal standard of care for these patients, anyone presenting with a possible stroke has an acute stroke panel blood work-up done. A creatinine test is done as part of this

panel. Patient's need to have normal kidney functions in order to have gadolinium given with their MRI. If a patient has a GFR of < 30, then they will be exlcuded from the study. This would indicate abnormal kidney functions and they would be unable to undergo MRI with contrast.

In all patients enrolled, NIHSS assessment will be repeated at 7 days or at discharge from the hospital, whichever is first. Rankin scale, Barthel index, and Glasgow outcome scale will be assessed at the same time. Subjects will have a follow-up clinic visit at 90 days with repeat NIHSS testing as well as mRS score, Barthel index, and Glasgow outcome scale assessment. (see Appendix A)

If the subject agrees to participate, an arterial blood gas will be drawn for evaluation. Patients exhibiting blood gas abnormalities consistent with underlying pulmonary disease (pH <7.32 or >7.48 or pCO2 > 49) will be excluded. Eligible patients will be randomized in equal numbers to receive HBO treatment or standard of care treatment.

If no exclusions exist, the subjects randomized to HBO therapy will receive one treatment of 100% O2 at 2.4ATA for 90 minutes in a monoplace hyperbaric chamber.

Prior to treatment an MRI of the brain with diffusion weighted imaging will be performed. Infarct size will be estimated by selecting the image with the largest area of restricted diffusion. This will be measured by length x width x slice thickness to estimate infarct volume in that slice as an estimate of infarct size. If more than one area of infarction exists, they will be evaluated separately and added together. The first twenty patients randomized will undergo further testing. In those patients, 10 HBO, 10 control, MRI with diffusion and perfusion weighted imaging will be performed within 72 hours following treatment or randomization for the control patients. A liquid containing gadolinium contrast agent will be innjected into a vien prior to the MRI scan. This agent increases the ability of the MRI scan to show abnormal tissues in the brain or elsewhere in the body.

Blood will also be drawn at randomization and at 12 and 24 hours from stroke onset (if different from randomization). These will undergo enzyme-linked immunosorbent assays on plasma for MMP-9 and serum for ICAM-1, VCAM-1, and sELAM-1. Additionally, PFA-100 platelet function tests will be run on blood drawn at enrollment and 24 hours.

Our primary outcomes will be rates of adverse events and infarct size on MRI diffusion weighted imaging (DWI). Adverse events will include pneumonia, seizures, and infarct increase. An infarct increase will be defined as an increase in the area of restricted diffusion on DWI over pretreatment baseline of greater than 10% for patients with no diffusion-perfusion mismatch, or a final DWI lesion size which is greater than 10% larger than the baseline perfusion deficit for patients with a perfusion-diffusion mismatch. The rate of adverse events will be compared between treatment and control groups. If the rate of AEs is not statistically significantly larger in the treatment group, the treatment will be considered safe.

Secondary outcomes will include modified Rankin scale score, NIHSS score, Barthel index score, length of hospital stay, intracerebral hemorrhage and symptomatic intracerebral hemorrhage rates and discharge location. Patients will be categorized as having a good outcome (NIHSS 0 or 1, Rankin 0 or 1) or not. The number of patients in treament and control groups achieving a good outcome will be compared. If there is a significant increase in good outcome in the treatment group, the treatment will be considered effective.

Data collected specifically for research purposes will include: NIHSS scores at 7 days or discharge, and at 30 days, as well as mRS scores, Barthel index, and Glasgow outcome scores at 7 and 30 days.

These are the risks we will explain to patients:

Common:

1. Claustrophobia during HBO treatment or MRI (reversible, treat by terminating HBO or MRI)
2. Ear pain during HBO treatment (reversible, treat by terminating HBO)

Uncommon:

1. Hematoma or bleeding from blood draws (reversible or treatable with transfusion)
2. Infection from blood draws (treatable with antibiotics)
3. Increased likelihood of aspiration pneumonia (treatable with antibiotics)

Very uncommon:

1. Seizure from HBO (reversible, treat by terminating HBO)
2. Barotrauma from HBO including pneumothorax, ruptured eardrum, (usually reversible/treatable)
3. Breach of confidentiality/loss of privacy
4. Allergic reaction to MRI contast medium (treatable with antihistamines, epinephrine). Side effects, such as mild headache, nausea and local burning at the IV site can occur. Patients are occasionally allergic to gadolinium contrast resulting most commonly in hives and itchy eyes, and in very rare cases, a bee-sting type of severe allergic reaction (anaphylactic shock). Use of a gadolinium contrast agent may be linked to a rare but sometimes fatal condition (nephrogenic systemic fibrosis or NSF) in people with severe chronic kidney disease or acute kidney problems. Therefore, before you are given a contrast agent for MRI, your risk factors for kidney disease will be reviewed and a blood test for kidney function will be done to exclude severe kidney disease

Patients will be screened by a physician with specialized training in hyperbaric medicine to exclude patients at higher risk of adverse affects from HBO. Trained technicians will monitor treatment under the supervision of this physician to assess patients during treatment and terminate treatment if necessary. Patients will be monitored through constant verbal and visual contact and if deemed necessary, through continuous pulse oximetry and blood pressure measurements. Blood draws will be performed under usual precautions against infection and bleeding.

All patient data will have most identifiers removed (except age, which may include those >89 years old) and will be stored on a password-protected computer database. Additionally a checklist for side effects and their severity will be filled out at completion of the HBO treatment and at discharge or 7 days whichever is earlier. In the case of ear pain which does not resolve after return to normal pressure, ENT will be consulted for evaluation and quantification of any damage using the Teed Scale for quantification.

Patients will be monitored clinically while receiving hyperbaric treatment by the technician and the physician. Patients will be monitored by constant visual and verbal contact and when deemed necessary by the treating physician, by continuous pulse oximetry and blood pressure monitor. Patients will be monitored while inpatient by one of the study physicians or nurses for AEs or SAEs. AEs or SAEs occurring after discharge will be assessed at the follow-up visit. Any adverse events or serious adverse events will be reported to the PI immediately.

The potential benefit to the subject is improved outcome in terms of neurologic function by limiting the damage to the brain from ischemia. Other patients and society could benefit by

the development of an additional therapy to limit brain damage from acute ischemic stroke, particularly in patients who are not thrombolytic candidates. Data will be kept on a password-protected database. Only participating study team members will have access to the database. Specimins of serum and plasma will be kept in a locked freezer prior to analysis. Only study team members will have access to the freezer.

## 4. Conclusions

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. 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 603 articles and selected 89 as relevant. Animal studies of HBO have shown promise by reducing infarct size and improving neurologic outcome. Early reports in humans also suggested benefit in stroke patients treated with HBO. Recent randomized, controlled human studies, however, have not shown benefit. All but one of the studies evaluating HBO therapy of ischemic stroke have used a dose of 1.5 ATA, based upon concerns for increased risk of oxidative stress with higher doses suggested in a single study from 1977. Despite concerns for increased oxidative stress, the patients who received the higher doses of HBO did not have seizures or worsening of neurologic deficits. The single study which assessed the use of HBO at 2.5 ATA in acute stroke did raise concerns of worsened stroke outcome at the higher dose, but was limited by several factors. First, most patients were treated after 12 hours. Second, the control group was subjected to 100% O2 at 1.14 ATA, which is not standard care. Third, there was no cut-off for stroke severity, such that very mild strokes were included, making evaluation of the effect of HBO difficult. 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 to 3 ATA. Therefore, clinical trials of HBO in acute ischemic stroke should be designed to evaluate treatment administered earlier and in higher doses to more clearly address its efficacy. We propose such a clinical trial, in this chapter.

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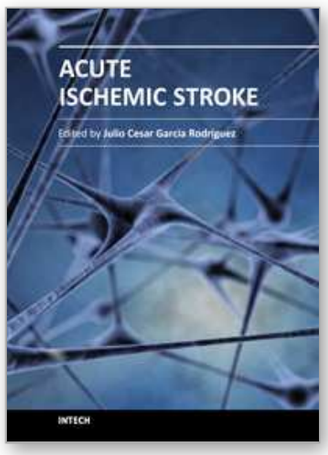


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Despite significant technological advances in recent years, their impact on our overall health and social, well-being is not always clear to see. Perhaps, one of the best examples of this can be highlighted by the fact that mortality rates as a result of cerebrovascular diseases have hardly changed, if at all. This places cerebrovascular diseases as one of the most prominent causes of both disability and death. In Cuba, for instance, a total of 22,000 cases of cerebrovascular diseases are reported each year in a country where life expectancy should increase to 80 years in the near future. In such a situation, to have a book that includes in a clear and summarized way, a group of topics directly related to the preclinical investigations advances and the therapeutic procedures for the cerebrovascular disease in its acute phase constitutes a useful tool for the wide range of the contributors to this affection's problems solution. In this group is included students, professors, researchers, and health policy makers whose work represents one of the greatest social and human impact challenges of the XXI century basic and clinical neurosciences.



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