Treatment of acute stroke with hyperbaric oxygen: Time window for efficacy

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ABSTRACT

We conducted a retrospective statistical analysis of the Heyman, Saltzman, Whalen 1966 study of 22 stroke patients treated with hyperbaric oxygen (HBO\textsubscript{2}) – 13 of them one to five hours post-stroke. We examined patients who received HBO\textsubscript{2} treatment within seven hours post-stroke. An exploratory logistic regression analysis examining the influence of time post-stroke, time in chamber and dose of HBO\textsubscript{2}, range 2.02 atmospheres absolute (ATA) to 3.04 ATA, was conducted. Only time post-stroke was a significant influence for recovery, with each passing hour decreasing the chance of at least partial transient recovery by 62\% – odds ratio: 0.38 (95\% CI: 0.15 – 0.95), \(p=0.039\).

In the one- to five-hour group of 13 patients, nine (41\% of 22) had recovery or recovery with relapse. This represented 69\% (+/- 25\% SE) of this time frame. Only two of the nine had permanent recovery. Past six hours post-stroke, only one patient (11\% +/- 21\% SE) had partial recovery with relapse. The other eight past six hours had no recovery at all. The first three hours post-stroke HBO\textsubscript{2} administration has the most promise for efficacy and improvement of rtPA therapy. HBO\textsubscript{2} may also prove to be a useful challenge pre-rtPA administration to assess the risk-benefit ratio for giving rtPA.

INTRODUCTION

In 1966, Heyman, Saltzman and Whalen at Duke University [1] carried out a landmark study on treatment of human stroke with hyperbaric oxygen (HBO\textsubscript{2}). They studied the treatment effect in 22 human subjects. Also in 1966, Saltzman, Anderson, Whalen, Heyman and Sieker expanded the report of the Duke study of HBO\textsubscript{2} stroke treatment, adding a description of three additional stroke patients [2], but numerical results data were published for the original 22 patients only [1]. These two papers did not involve any statistical analysis or representative graphing of results, but the authors did notice in general that the earlier the patient was treated post-stroke the more likely the HBO\textsubscript{2} would have a positive effect in reversing stroke symptoms. The effect of HBO\textsubscript{2} on stroke symptoms reported for patients was a mixture of recovery maintained, recovery with relapse, partial recovery with relapse, and no recovery – all observed within a matter of hours post-HBO\textsubscript{2} treatment. Initial recovery with application of HBO\textsubscript{2} occurred within minutes, never longer than 30 minutes (personal communication with Dr. Herb Saltzman).

The most remarkable aspect of the Duke study [1] was the ability to obtain 13 human stroke patients for treatment with HBO\textsubscript{2} in the hyper-acute time period post-stroke from one hour to five hours. Eight of these patients were obtained for HBO\textsubscript{2} treatment in three hours or less post-stroke, including one at one hour post-stroke, two at 1.5 hours post-stroke, three at two hours post-stroke, one at 2.5 hours post-stroke, and one at three hours post-stroke. Two were HBO\textsubscript{2}-treated at four hours post-stroke, and three were treated with HBO\textsubscript{2} at five hours post-stroke.

The first main purpose of our paper is to present the original 1966 Duke data in easy-to-read data tables organized according to HBO\textsubscript{2} efficacy. In addition, we present an overall bar graph representation of HBO\textsubscript{2} treatment results so that future researchers may better comprehend the significance of the Duke work. The original paper published raw data in difficult-to-read fine print on two journal pages without statistical analysis of efficacy results.

For many years, the 1966 Duke work was not available online, and many authors in the field were not aware of the study or chose not to cite it. Notably, Nighog-

The 1995 study [3] detected an outcome trend favoring HBO₂ therapy for stroke, and evaluations were carried out at six months and one year post-stroke of patients treated with HBO₂ within 24 hours post-stroke. No specific hours post-stroke were given for HBO₂ treatment beyond the general 24 hour post-stroke category. The 2003 research [4] studied the effect of HBO₂ at the earliest in one patient at five hours post-stroke and one patient six hours post-stroke (personal communication with Dr. Rusyniak). Five patients were treated with HBO₂ beyond six hours to 12 hours post-stroke, and 10 patients were treated with HBO₂ beyond 12 hours post-stroke to 24 hours post-stroke.

At the 2007 Annual Scientific Meeting of the Undersea and Hyperbaric Medical Society (UHMS), we presented [5] the first and only statistical analysis of the 1966 Duke Study. Our paper not only quantitatively identified the early time window post-stroke of HBO₂, but we broached the subject of using HBO₂ acute stroke treatment as a synergistic bridge to current standard of care tissue plasminogen activator (rtPA) thrombolytic therapy. Also, we proposed that HBO₂ challenge pre-rtPA may prove to be a useful assessment of the risk-benefit ratio for giving rtPA, and we speculated that temporary acute stroke recovery stasis afforded by hyperbaric oxygen suggests that HBO₂ could be instrumental in extending the FDA-approved three-hour post-stroke treatment window for rtPA administration.

The clinical trial which led to FDA certification of rtPA was carried out and published in 1995 [6] by the National Institute of Neurological Disorders and Stroke rtPA Stroke Study Group under the direction of Dr. John Marler. Intravenous administration of rtPA is the only FDA-approved treatment for acute stroke. The FDA has mandated that intravenous rtPA can be given only in a three-hour window post-stroke.

Accordingly, the second main purpose of this paper is to present and discuss in detail the presentation we made at the 2007 UHMS meeting. We hope that our analysis of the 1966 Duke data will act as a catalyst to energize the Hyperbaric Medicine community to continue to mobilize together to attack the major public health problem of stroke. The important work of the Duke group [1], Nighoghossian’s group [3], Rusyniak’s group [4] and others suggests a need to go forward with additional human clinical trials.

Many of the other significant studies of HBO₂ as a treatment for stroke are mentioned in the excellent review “Animal Experimental Data and Clinical Data Involved in Mechanisms of Hyperbaric Oxygen and Neuroprotection in Stroke,” published in 2005 by Zhang, Lo, Mychaskiw and Colohan [7].

The American Heart Association noted that in the year 2008 the nationwide annual cost of stroke was 65.5 billion dollars. In the State of North Carolina alone in the year 2005, just the cost of stroke hospital care was $540,000,000 (N.C. Hospital Discharge Database, State Center for Health Statistics).

There are approximately 750,000 new strokes in the United States each year. Eighty-five percent of these strokes are ischemic, and the remainder is due to hemorrhage [8]. Thus, of the 750,000 new strokes, 637,500 are possible candidates for FDA-approved rtPA thrombolytic treatment. Of these, only 3-5 percent get treated at nearby approved stroke centers with rtPA. Marler and his group [9] note that “the short time window for rtPA treatment is the greatest barrier to wider application of thrombolytic therapy.” In 2008, only 4.6% of ischemic stroke patients in North Carolina received rtPA treatment (personal communication, Dr. Wayne Rosamond, Professor, Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill).

METHODS

For our analysis we used the data from the published HBO₂ stroke treatment trials conducted at Duke University [1]. The Duke data was published in one fine-print table grouped by HBO₂ efficacy in stroke treatment. For easier interpretation, we organized the Duke data into single separate tables according to similar categories that the Duke paper used:

(a) recovery maintained;
(b) recovery with relapse;
(c) partial recovery with relapse; and
(d) no recovery.

In turn, these data categories were plotted on a bar graph as a function of time post-stroke that the HBO₂ treatment was initiated. To facilitate relating between the data tables and our bar graph, each data table was color-coded according to the same system used on the bar graph.

The original Duke data were listed for each patient by the patient’s initials. To add a layer of patient confidentiality, we converted the patient initials designation to a letter of the alphabet. Upon request by a researcher,
The corresponding author of this paper will provide a translation key for interpolation between the original Duke patient initials and our letter of the alphabet designation. For patients who received HBO₂ treatment within seven hours post-stroke, we carried out an exploratory logistic regression analysis examining the influence of HBO₂ efficacy of time post-stroke, time in-chamber and dose of HBO₂ (range 2.02-3.04 ATA). After this analysis, we proceeded to model a curve for the probability of at least partial transient improvement of stroke with HBO₂ treatment as a function of time post-stroke.

STATISTICAL ANALYSES
All analyses were conducted using SPSS 16.0 (SPSS, Inc., Chicago, Ill.). Where appropriate, all inferences are two-tailed, and point estimates are presented with 95% confidence intervals. For the purpose of analysis, a binary outcome variable was created by dichotomizing the clinical response categories of the original study into one of two groups. Responses were coded as “1” if the participant had a response of “recovery maintained,” “recovery with relapse,” or “partial recovery with relapse”; a “0” response was coded for participants who had “no recovery.” To examine the efficacy of HBO₂ treatment on the participants, we evaluated several logistic regression models examining the univariate influence of time post-stroke, time in-chamber and dose of HBO₂ (range 2.02-3.04 ATA). Descriptive statistics were also presented as frequency counts and percentages (with standard errors).

RESULTS
From the regression analysis for patients who received HBO₂ treatment within seven hours post-stroke, we found that in the Duke study only time post-stroke was a significant influence for recovery, with each passing hour decreasing the chance of at least partial transient recovery by 62% – odds ratio: 0.38 (95% CI: 0.15–0.95), p=0.039 (Figure 1, above). To emphasize the time post-stroke on the results shown in Figure 1, we drew in gray vertical lines at 90 minutes post-stroke, three hours post-stroke and six hours post-stroke, respectively.

FIGURE 1
Probability of permanent or partial transient improvement of stroke with hyperbaric oxygen

Odds ratio: 0.38 (95% CI: 0.15–0.95), p=0.039

Figure 1: The black diamonds represent a curve of our statistical analysis and our model of the probability of at least partial transient improvement for acute stroke patients with HBO₂ treatment in the 1966 Duke Study [1] for the time window 0 to 7 hours post-stroke. The open circles represent the actual patient data points from the Duke study. The vertical gray lines demarcate the relative efficacy of HBO₂ for treatment of acute stroke at 90 minutes post-stroke, 3 hours post-stroke and 6 hours post-stroke, respectively.
In the one- to five-hour post-stroke group of 13 patients, nine (41% of 22) had recovery or recovery with relapse. This represented 69% (+/-25% SE) of this time frame. Only two of the nine had permanent recovery. Past six hours post-stroke, only one patient (11% +/-21% SE) had partial recovery with relapse. The other eight patients who received treatment past six hours had no recovery at all (Figure 2, above).

Individual data tables we constructed organized by response of stroke patients to HBo2 treatment are shown in:
- Table 1 (dramatic recovery maintained) (facing page);
- Table 2 (dramatic recovery with relapse) (facing page);
- Tables 3A and 3B (partial transient recovery) (Page 326); and
- Tables 4A, 4B, 4C and 4D (no response to HBO2) (Pages 327-328).

**DISCUSSION**

**HBO2 time window for efficacy in acute stroke treatment**

Zhang, Lo, Mychaskiw and Colohan [7] reported that “early applications of HBO2 within a therapeutic window of 3-6 hours post stroke or delayed but repeated administration of HBO2 can either salvage injured neuronal tissues or promote neurobehavioral functional recovery.”

Our time window for probability of stroke recovery as a function of time post-stroke shown in Figure 1 is in agreement with the Zhang, Lo, Mychaskiw and Colohan analysis of the literature regarding the efficacy of the three- to six-hour post-stroke window. However, the curve shown in Figure 1 emphasizes that the first 90 minutes post-stroke for the Duke data was best for stroke treatment, with a 100% chance for a positive acute treatment response to HBO2; and out to three hours post-stroke there was still a 78% chance of acute stroke symptom improvement. By six hours post-stroke, Figure 1 shows that an acute positive response to HBO2 drops to 0% of patients treated within the seven-hour post-stroke window for which we calculated the predictive curve of Figure 1.

*Continued on Page 325 ➤*
**Table 1 – Clinical manifestation and blood gas changes during hyperbaric oxygenation**

<table>
<thead>
<tr>
<th>Patient / Age</th>
<th>Onset and Circumstances</th>
<th>Neurologic Deficit</th>
<th>Time Post Stroke to Treatment Initiation</th>
<th>Pressure and Duration of Oxygenation</th>
<th>Arterial Blood pO2 mm Hg</th>
<th>Arterial Blood pCO2 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 61</td>
<td>? embolus; atrial fibrillation</td>
<td>Right hemiparesis, stupor, aphasia</td>
<td>5 hours</td>
<td>2.02 ata. 1 hour</td>
<td>1102</td>
<td>34</td>
</tr>
<tr>
<td>B 58</td>
<td>Arteriographic complications</td>
<td>Right hemiplegia, stupor</td>
<td>2 ½ hours</td>
<td>2.36 ata. 5 hours</td>
<td>1364</td>
<td>32</td>
</tr>
</tbody>
</table>

**Table 2 – Clinical manifestation and blood gas changes during hyperbaric oxygenation**

<table>
<thead>
<tr>
<th>Patient / Age</th>
<th>During Hyperbaric Therapy</th>
<th>At End of Procedure</th>
<th>Clinical Condition at Discharge</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 61</td>
<td>Immediate improvement</td>
<td>Alert, moving all limbs</td>
<td>Improvement maintained with only mild residual hemiparesis</td>
<td></td>
</tr>
<tr>
<td>B 58</td>
<td>Immediate improvement</td>
<td>Alert, moving right arm and hand</td>
<td>Improvement maintained</td>
<td></td>
</tr>
</tbody>
</table>

Raw data adapted from the Duke University article "The Use of Hyperbaric Oxygenation in the Treatment of Cerebral Ischemia and Infarction" by Heyman A, Saltzman HA, and Whalen RE. Circulation, 1966, Supp II, Vols. XXXIII and XXXIV.
### TABLE 3A – Clinical manifestation and blood gas changes during hyperbaric oxygenation

<table>
<thead>
<tr>
<th>Strode Patient Diagnosis and Treatment Parameters</th>
<th>Patient/Age</th>
<th>Onset and Circumstances</th>
<th>Neurologic Deficit</th>
<th>Time Post Stroke to Treatment Initiation</th>
<th>Pressure and Duration of Oxygenation</th>
<th>Arterial Blood pO2 mm Hg</th>
<th>Arterial Blood pCO2 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>STROKE PATIENTS WITH PARTIAL TRANSIENT IMPROVEMENT DURING HYPERBARIC OXYGEN THERAPY:</td>
<td>E 58</td>
<td>Old pseudobulbar palsy; sudden worsening</td>
<td>Dysphasic, obtunded, right arm weakness</td>
<td>3 hours</td>
<td>3.04 ata. 30 minutes</td>
<td>1785 49</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F 45</td>
<td>Arteriographic complications</td>
<td>Severe aphasia right hemiplegia</td>
<td>1 ½ hours</td>
<td>2.36 ata. 1 hour</td>
<td>1398 33</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G 57</td>
<td>Gradual deterioration</td>
<td>Coma, quadriplegia, Cheyne-Stokes respiration</td>
<td>4 hours</td>
<td>2.36 ata. 79 minutes</td>
<td>1350 41</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 3B – Clinical manifestation and blood gas changes during hyperbaric oxygenation

<table>
<thead>
<tr>
<th>Strode Patient Response to Hyperbaric Oxygen Treatment:</th>
<th>Patient/Age</th>
<th>During Hyperbaric Therapy</th>
<th>At End of Procedure</th>
<th>Clinical Condition at Discharge</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>STROKE PATIENTS WITH PARTIAL TRANSIENT IMPROVEMENT DURING HYPERBARIC OXYGEN THERAPY:</td>
<td>E 58</td>
<td>Moderate improvement of right hand and movement</td>
<td>Sonnolent and hemiparetic</td>
<td>Died 2 days after therapy; multiple cerebral infarction at autopsy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F 45</td>
<td>Definite improvement in consciousness</td>
<td>Retained aphasia and hemiplegia</td>
<td>Gradual improvement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G 57</td>
<td>Moderate improvement</td>
<td>Relapsed after decompression</td>
<td>Died 1 day after treatment</td>
<td>B.P. rose to 300/150 after decompression</td>
</tr>
</tbody>
</table>

### TABLE 4A – Clinical manifestation and blood gas changes during hyperbaric oxygenation

#### STROKE PATIENTS WITH NO SIGNIFICANT CHANGE DURING HYPERBARIC OXYGEN THERAPY:

<table>
<thead>
<tr>
<th>Patient/Age</th>
<th>Onset and Circumstances</th>
<th>Neurologic Deficit</th>
<th>Time Post Stroke to Treatment Initiation</th>
<th>Pressure and Duration of Oxygenation</th>
<th>Arterial Blood pO2 mm Hg</th>
<th>Arterial Blood pCO2 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>K 54</td>
<td>Embolus, myo-cardiopathy</td>
<td>Coma, quadriplegia, Cheyne-Stokes, respiration, cyanosis</td>
<td>7 hours</td>
<td>2.36 ata. 45 minutes</td>
<td>1348</td>
<td>29</td>
</tr>
<tr>
<td>L 60</td>
<td>Sudden onset</td>
<td>Left hemiplegia, stupor</td>
<td>7 days</td>
<td>2.02 ata. 26 minutes</td>
<td>887</td>
<td>40</td>
</tr>
<tr>
<td>M 63</td>
<td>Left carotid thrombosis</td>
<td>Semi-comatose, right hemiparesis</td>
<td>11 days</td>
<td>2.02 ata. 32 minutes</td>
<td>874</td>
<td>43</td>
</tr>
</tbody>
</table>

#### STROKE PATIENT RESPONSE TO HYPERBARIC OXYGEN TREATMENT:

<table>
<thead>
<tr>
<th>Patient/Age</th>
<th>During Hyperbaric Therapy</th>
<th>At End of Procedure</th>
<th>Clinical Condition at Discharge</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>K 54</td>
<td>No change</td>
<td>No change</td>
<td>Died 2 days later</td>
<td></td>
</tr>
<tr>
<td>L 60</td>
<td>No change</td>
<td>No change</td>
<td>Severe hemolytic reaction</td>
<td>Died 3 months later</td>
</tr>
<tr>
<td>M 63</td>
<td>No change</td>
<td>No change</td>
<td>Died 2 days later</td>
<td></td>
</tr>
</tbody>
</table>

Raw data adapted from the Duke University article "The Use of Hyperbaric Oxygenation in the Treatment of Cerebral Ischemia and Infarction" by Heyman A, Saltzman HA, and Whalen RE. Circulation, 1966, Supp II, Vols. XXXIII and XXXIV.

### TABLE 4B – Clinical manifestation and blood gas changes during hyperbaric oxygenation

#### STROKE PATIENTS WITH NO SIGNIFICANT CHANGE DURING HYPERBARIC OXYGEN THERAPY:

<table>
<thead>
<tr>
<th>Patient/Age</th>
<th>Onset and Circumstances</th>
<th>Neurologic Deficit</th>
<th>Time Post Stroke to Treatment Initiation</th>
<th>Pressure and Duration of Oxygenation</th>
<th>Arterial Blood pO2 mm Hg</th>
<th>Arterial Blood pCO2 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>N 38</td>
<td>Sudden onset</td>
<td>Left hemiplegia</td>
<td>4 days</td>
<td>3.04 ata. 20 minutes</td>
<td>1751</td>
<td>35</td>
</tr>
<tr>
<td>O 55</td>
<td>Sudden onset</td>
<td>Left hemiplegia</td>
<td>5 hours</td>
<td>3.04 ata. 47 minutes</td>
<td>1774</td>
<td>38</td>
</tr>
<tr>
<td>P 62</td>
<td>Left anterior cerebral thrombosis</td>
<td>Right hemiplegia, Cheyne-Stokes respiration</td>
<td>1 month</td>
<td>3.04 ata. 30 minutes</td>
<td>1136</td>
<td>35</td>
</tr>
</tbody>
</table>

#### STROKE PATIENT RESPONSE TO HYPERBARIC OXYGEN TREATMENT:

<table>
<thead>
<tr>
<th>Patient/Age</th>
<th>During Hyperbaric Therapy</th>
<th>At End of Procedure</th>
<th>Clinical Condition at Discharge</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>N 38</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>O 55</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>P 62</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td></td>
</tr>
</tbody>
</table>

Raw data adapted from the Duke University article "The Use of Hyperbaric Oxygenation in the Treatment of Cerebral Ischemia and Infarction" by Heyman A, Saltzman HA, and Whalen RE. Circulation, 1966, Supp II, Vols. XXXIII and XXXIV.
### TABLE 4C – Clinical manifestation and blood gas changes during hyperbaric oxygenation

**STROKE PATIENTS WITH NO SIGNIFICANT CHANGE DURING HYPERBARIC OXYGEN THERAPY:**

<table>
<thead>
<tr>
<th>Patient/ Age</th>
<th>Onset and Circumstances</th>
<th>Neurologic Deficit</th>
<th>Time Post Stroke to Treatment Initiation</th>
<th>Pressure and Duration of Oxygenation</th>
<th>Arterial Blood ( pO_2 ) mm Hg</th>
<th>Arterial Blood ( pCO_2 ) mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q 46</td>
<td>Brain stem infarct</td>
<td>Right hemiplegia, left third nerve palsy</td>
<td>4 weeks</td>
<td>3.04 at a, 30 minutes</td>
<td>1470</td>
<td>42</td>
</tr>
<tr>
<td>R 62</td>
<td>Sudden onset</td>
<td>Right hemiparesis, aphasia</td>
<td>13 days</td>
<td>3.04 at a, 30 minutes</td>
<td>1492</td>
<td>40</td>
</tr>
<tr>
<td>S 41</td>
<td>Cerebral hemorrhage</td>
<td>Left hemiplegia, dysarthria</td>
<td>6 hours</td>
<td>3.04 at a, 30 minutes</td>
<td>1577</td>
<td>40</td>
</tr>
</tbody>
</table>

**STROKE PATIENT RESPONSE TO HYPERBARIC OXYGEN TREATMENT:**

<table>
<thead>
<tr>
<th>Patient/ Age</th>
<th>During Hyperbaric Therapy</th>
<th>At End of Procedure</th>
<th>Clinical Condition at Discharge</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q 46</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>R 62</td>
<td>No change</td>
<td>No change</td>
<td>Died 2 days later</td>
<td></td>
</tr>
<tr>
<td>S 41</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td></td>
</tr>
</tbody>
</table>

Raw data adapted from the Duke University article "The Use of Hyperbaric Oxygenation in the Treatment of Cerebral Ischemia and Infarction" by Heyman A, Saltzman HA, and Whalen RE. Circulation 1966, Supp II, Vols. XXXIII and XXXIV.

### TABLE 4D – Clinical manifestation and blood gas changes during hyperbaric oxygenation

**STROKE PATIENTS WITH NO SIGNIFICANT CHANGE DURING HYPERBARIC OXYGEN THERAPY:**

<table>
<thead>
<tr>
<th>Patient/ Age</th>
<th>Onset and Circumstances</th>
<th>Neurologic Deficit</th>
<th>Time Post Stroke to Treatment Initiation</th>
<th>Pressure and Duration of Oxygenation</th>
<th>Arterial Blood ( pO_2 ) mm Hg</th>
<th>Arterial Blood ( pCO_2 ) mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>T 58</td>
<td>Basilar artery thrombosis</td>
<td>Right hemiplegia</td>
<td>6 ½ hours</td>
<td>2.02 at a, 44 minutes</td>
<td>662</td>
<td>45</td>
</tr>
<tr>
<td>U 51</td>
<td>Sudden onset</td>
<td>Right hemiparesis, aphasia, stupor</td>
<td>4 hours</td>
<td>2.02 at a, 1 hour</td>
<td>1155</td>
<td>34</td>
</tr>
<tr>
<td>V 42</td>
<td>Sudden onset</td>
<td>Stupor, dysarthria, left hemiplegia</td>
<td>2 hours</td>
<td>2.36 at a, 50 minutes</td>
<td>1350</td>
<td>No value</td>
</tr>
</tbody>
</table>

**STROKE PATIENT RESPONSE TO HYPERBARIC OXYGEN TREATMENT:**

<table>
<thead>
<tr>
<th>Patient/ Age</th>
<th>During Hyperbaric Therapy</th>
<th>At End of Procedure</th>
<th>Clinical Condition at Discharge</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>T 58</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>B.P. rose from 170 to 240 mm Hg systolic after decompression</td>
</tr>
<tr>
<td>U 51</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>Progressed to quadriplegia and died 3 weeks later</td>
</tr>
<tr>
<td>V 42</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td></td>
</tr>
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Raw data adapted from the Duke University article "The Use of Hyperbaric Oxygenation in the Treatment of Cerebral Ischemia and Infarction" by Heyman A, Saltzman HA, and Whalen RE. Circulation, 1966, Supp II, Vols. XXXIII and XXXIV.
In Table 3B, 37-year-old Subject H responded to HBO₂ at eight days post-stroke by becoming more alert, but the HBO₂ treatment had no effect on his right hemiplegia. No other subject in the Duke study showed signs of recovery past five hours post-stroke.

The fact that we were able to find a statistically significant relationship between time post-stroke and HBO₂ efficacy in the Duke data is indicative of a strong treatment effect of HBO₂ on acute stroke. The treatment effect was so robust that we were able to obtain statistical significance using the Duke patients as their own controls.

Our results presented in Figure 1 for HBO₂ treatment of acute stroke are in good agreement with the time window post-stroke for efficacious treatment of acute stroke with rtPA [9] as shown in Figure 3 (right). For rtPA stroke treatment, similar to our finding, 90 minutes post-stroke is best. Up to three hours post-stroke is still efficacious, and by six hours post-stroke, efficacy is down to control levels. In addition, the results in Figure 1 are in general agreement for the same time windows for electrophysiological, behavioral and histopathological findings for monkeys subjected to experimental induction of ischemic stroke carried out by Jones et al. in 1981 [10]. An adaptation of the Jones group’s findings is presented in Figure 4 (right) for comparison with our data in Figure 1. The Jones et al. [10] work shown in Figure 4 has been discussed in a review by Zivin of factors determining the therapeutic window for stroke [11].

The Duke data we analyzed did not address the issue of efficacy of delayed but repeated administration of HBO₂, except in an acute situation noted for the two stroke patients in Table 2 who had dramatic but temporary recovery of function on second and third HBO₂ treatments after some functional recovery of the initial HBO₂ exposure had relapsed.

Given the positive stroke recovery in the Duke patients occurring within minutes of the application of HBO₂, it is unlikely that the recovery noted for the patients was spontaneous.

**HBO₂ dose response and time in chamber for stroke treatment**

Although our regression analysis did not find a significant relationship between HBO₂ stroke treatment efficacy and the HBO₂ dose used by Duke (2.02-3.04 ATA), we feel it is extremely important to conduct future research designed to elucidate a true dose-response curve for HBO₂ in stroke treatment since the Duke study was not designed to elucidate a dose-response curve.
One of the original Duke authors had the general impression that 2.5 ATA was a good stroke treatment choice to use in future research (personal communication with Dr. Herb Saltzman). Certainly, the 2.5 ATA oxygen pressure would be much less likely to cause oxygen toxicity than the highest (3.04 ATA) pressure used in the Duke study. In an animal study of experimental stroke in 2000, Veltkamp et al. showed efficacy for 2.5 ATA HBO₂, but 1.5 ATA and 1.0 ATA HBO₂ were found ineffective [12].

By the same token, the Duke study was not designed to specifically study time in chamber as a treatment variable, so our finding of no relationship between time in chamber and prediction of stroke recovery bears further research.

**HBO₂ treatment vs. type of stroke**

Future HBO₂ stroke treatment research should attempt to study how the type of stroke and stroke etiology relate to HBO₂ treatment efficacy. This factor was not controlled in the Duke study. Many animal models of experimentally induced stroke use a middle cerebral artery variable [7]; thus, human acute stroke studies that focus on middle cerebral artery strokes are good for comparison to the animal data. Besides the type of stroke under study, just as important a variable is the collateral circulation of the particular subject. As noted previously, 85% of strokes are ischemic, and the other 15% are hemorrhagic. The cutting-edge pioneering work at Duke in 1966 pre-dated CT scans, which are now routinely used in stroke centers to diagnose and eliminate hemorrhagic strokes as part of the triage procedure for rtPA thrombolytic treatment. Relative to the hemorrhagic stroke issue, Qin et al. in 2007 [13] discovered in rats that “early intraischemic HBO₂ treatment reduces the blood-brain barrier disruption, hemorrhagic transformation and mortality after focal cerebral ischemia, suggesting that HBO₂ could be used to reduce hemorrhagic conversion in patients with stroke.” Also noteworthy is the fact that clinical treatment of strokes with thrombolytics did not exist in 1966 at the time of the Duke work.

**Mechanisms of HBO₂ in stroke**

Zhang and his colleagues discuss mechanisms of HBO₂ in stroke [7]. The first obvious benefit of HBO₂ for ischemic stroke was presented by the Duke group [1] in a figure where they demonstrated an average increase in the arterial pO₂ from 1 ATA of 450mm Hg to an average of 1800mm Hg for HBO₂ at 3.04 ATA. The solubility of oxygen in the blood is a linear function of the partial pressure inhalation of this gas in a hyperbaric environment. The tension of oxygen in arterial blood rises proportionally to the rise in atmospheric pressure [1].

The pressures of HBO₂ in the range used in the Duke study are high enough to dissolve significant amounts of oxygen in the plasma of the blood. With existence of partial thrombotic vessel ischemic blockages large enough to block red cells from passing to deliver their oxygen to brain tissue — but not large enough to stop plasma delivery — the oxygen dissolved in the plasma may mitigate the anoxia of brain tissue [14]. In addition to possible plasma provision of oxygen, the maximum distance in the brain from capillary to cell, allowing for transport of oxygen by extravascular diffusion, is 0.1mm [15]. Brown and colleagues, 1965, have calculated that 3 atmospheres of oxygen provides an increase in the theoretical limiting distance from capillary to cell of 0.073mm [16].

Treatment of the pathophysiology of cerebral ischemia depends on time (the sooner the better), blood flow and oxygenation, but hyperbaric oxygen is also known to reduce vasogenic edema and will not impair neuronal function. Rabbits subjected to global ischemia followed by HBO₂ had better electrophysiological function despite an increase in oxidative stress documented by levels of oxidized glutathione [17].

HBO₂ treatment oxidative stress does not have to be interpreted as negative for patients. Thom discusses how reactive hyperoxia species contribute to reduced adherence of circulating leukocytes, which has been linked in animal models with therapeutic benefit of HBO₂ in reperfusion injuries of brain, skeletal muscle and intestine [18].

**The synergistic relationship between HBO₂ and rtPA**

HBO₂ has been shown to stimulate an increase in the human body’s production of rtPA by inhibiting the PAI-1 activity which suppresses rtPA production in the body [19]. Thus, we speculate that such an endogenous upregulation of rtPA could benefit to some degree the resolution in part of thrombogenic-induced ischemic stroke.

The activation of thrombosis by gas bubbles in decompression sickness (DCS) has been demonstrated and discussed by Hallenbeck and Anderson [20] and others. McCormick et al. demonstrated the thrombogenic action of bubbles in decompression sickness as the etiology of...
inner ear deafness from DCS, and they went on to show protection against the DCS-induced deafness with prophylactic administration of heparin anticoagulant [21, 22,23]. Given the increase in endogenous production of rtPA with HBO₂, we speculate that the thrombolytic activity of such an increase in rtPA could possibly mitigate part of the activation of thrombosis in DCS. An experimental thrombogenic myocardial infarction model for left anterior descending artery (LAD) occlusion by Thomas et al., 1990 [24], using the dog, with no treatment (control), HBO₂ alone (2 ATA), rtPA alone, or HBO₂ plus rtPA, showed a true positive synergistic response between rtPA and HBO₂ in the resolution of cardiac thrombosis, with subsequent restoration of enzyme activity (Figure 5, right). Given the elevation of endogenous rtPA by HBO₂ discussed above, this factor could possibly contribute to the synergistic therapeutic effect of HBO₂ and rtPA on the myocardial infarction observed by Thomas et al. Further, we speculate that the same synergistic response between HBO₂ and rtPA in myocardial infarction could possibly aid in the resolution of ischemic stroke. Figure 5 shows that the restoration of enzyme activity after LAD occlusion for two hours was greater with HBO₂ plus rtPA than it was either with HBO₂ alone or rtPA alone. All three of these conditions were better than the control group.

The safety of rtPA plus HBO₂ administered to humans
The safety and efficacy of HBO₂ used at 2.0 ATA plus rtPA or streptokinase has been tested in studies of 178 human myocardial infarction patients [25,26]. In these studies, treatment of acute myocardial infarction patients with HBO₂ combined with thrombolysis appeared to be feasible and safe and trended towards an attenuated CPK rise, more rapid resolution of pain and improved ejection fractions.

HBO₂ as a bridge to rtPA therapy for stroke
To be sure, treatment of acute stroke in humans with rtPA involves community education on the fact that stroke is an emergency requiring immediate transportation to a certified stroke center. The first link in the chain to successful transport of patients to a stroke center quickly for stroke care is educating the public about the symptoms of stroke.

The need for the FDA to mandate the three-hour post-stroke time window to give rtPA for ischemic stroke is a major impediment to rtPA treatment. Even with the best possible education of the public, practically speaking, in order for a ground ambulance to transport an acute stroke patient from their home to a stroke center with time to spare to work up the patient for possible rtPA at the hospital, the ambulance can travel approximately 15 minutes one way (11 miles) from home base (Figure 6, Page 332). The dramatic recovery from hyper acute stroke symptoms demonstrated in Figure 1 and Tables 1, 2 – and perhaps even the partial recovery shown in Tables 3A and 3B – suggest the possibility that HBO₂ provided to an acute stroke patient in the first three hours post-stroke could potentially put the brain in a stasis that, while under HBO₂, would “stop the clock” on the three-hour rtPA FDA administration window. This would greatly extend the range that a dedicated HBO₂ chamber-equipped stroke ambulance could travel to serve acute stroke patients (Figure 7, Page 332), resulting in a major public health advance that would greatly mitigate the appalling low 3-5 percent treatment rate for stroke centers.
HBO₂ as a functional test for acute stroke risk-benefit ratio for rtPA administration

Presently clinicians rely on an NIH Stroke Scale clinical exam [27] and a CT scan of the acute stroke patient’s brain to gain an estimation of whether enough viable brain function remains to justify the risk of giving rtPA therapy, which in itself carries an increased risk of induction of cerebral hemorrhage [6]. It should be far superior to conduct a functional challenge of the acute stroke patient with HBO₂. The dramatic rapid degree of HBO₂-induced stroke symptom recovery demonstrated in the 1966 Duke study and elucidated in our paper would give the emergency room neurological stroke team invaluable insight as to the patient’s remaining brain function.

Clinical trials should be instituted to establish the validity of using an HBO₂ challenge of acute stroke patients as an indicator for safe and efficacious administration of rtPA in place of the arbitrary three-hour post-stroke time limit imposed by the FDA. This would allow for testing the possibility of functionally justifying administration of rtPA beyond the arbitrary three-hour FDA window – perhaps for some stroke patients out to the six-hour limit for efficacy shown in Figure 1.

Another big shortcoming with the three-hour post-stroke FDA window for approved rtPA administration is that it requires an accurate observation by a competent observer of the start time of the patient’s stroke. If, for example, a patient has a stroke in their sleep, the FDA rules require that the three-hour clock be started when the patient went to bed.

We believe a dedicated stroke ambulance with a two-place HBO₂ chamber would not only extend the range for stroke patient triage, but for the reasons discussed above, would potentially provide an HBO₂ treatment en route to the stroke center, which would be synergistic with rtPA standard of care acute stroke treatment. Plus, the HBO₂ stroke ambulance would have completed the functional HBO₂ challenge test for rtPA administration assessment by arrival at the hospital. To this end, our group is designing and building a prototype HBO₂ chamber-equipped stroke ambulance which, when completed, will be used in clinical trials to test the postulates outlined here (Figures 8 and 9, facing page). Also, the HBO₂ stroke ambulance could be used in conjunction with ambulance-based telemedicine techniques [28]. We are undertaking this venture in collaboration with the Undersea and Hyperbaric Medical Society.

Future development of a CT scanner operable in the HBO₂ environment of our mobile chamber-equipped ambulance could facilitate ambulance-based rtPA administration.
FIGURE 8: For the construction of our prototype HBO2 chamber-equipped Acute Stroke Ambulance, we are using the two-place mobile Cowan Manufacturing Company Transportable Recompression Chamber.

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REFERENCES