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_2) – 13 of them one to five hours post-stroke. We examined patients who received HBO_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_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_2 administration has the most promise for efficacy and improvement of rtPA therapy. HBO_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_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_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_2 would have a positive effect in reversing stroke symptoms. The effect of HBO_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_2 treatment. Initial recovery with application of HBO_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_2 in the hyper-acute time period post-stroke from one hour to five hours. Eight of these patients were obtained for HBO_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_2-treated at four hours post-stroke, and three were treated with HBO_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_2 efficacy. In addition, we present an overall bar graph representation of HBO_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-

hossian and his group in 1995 [3] and Rusyniak and his group in 2003 [4] conducted valuable pilot clinical trials of treatment of human stroke with HBO_2 in the range of five to 24 hours post-stroke with non-conclusive efficacy, but no reference or review of the 1966 Duke work.

The 1995 study [3] detected an outcome trend favoring HBO_2 therapy for stroke, and evaluations were carried out at six months and one year post-stroke of patients treated with HBO_2 within 24 hours post-stroke. No specific hours post-stroke were given for HBO_2 treatment beyond the general 24 hour post-stroke category. The 2003 research [4] studied the effect of HBO_2 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 HBO_2 beyond six hours to 12 hours post-stroke, and 10 patients were treated with HBO_2 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 HBO_2 treatment as the key element determining treatment efficacy, but we broached the subject of using HBO_2 acute stroke treatment as a synergistic bridge to current standard of care tissue plasminogen activator (rtPA) thrombolytic therapy. Also, we proposed that HBO_2 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 HBO_2 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 HBO_2 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 HBO_2 stroke treatment trials conducted at Duke University [1]. The Duke data was published in one fine-print table grouped by HBO_2 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 HBO_2 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,

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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

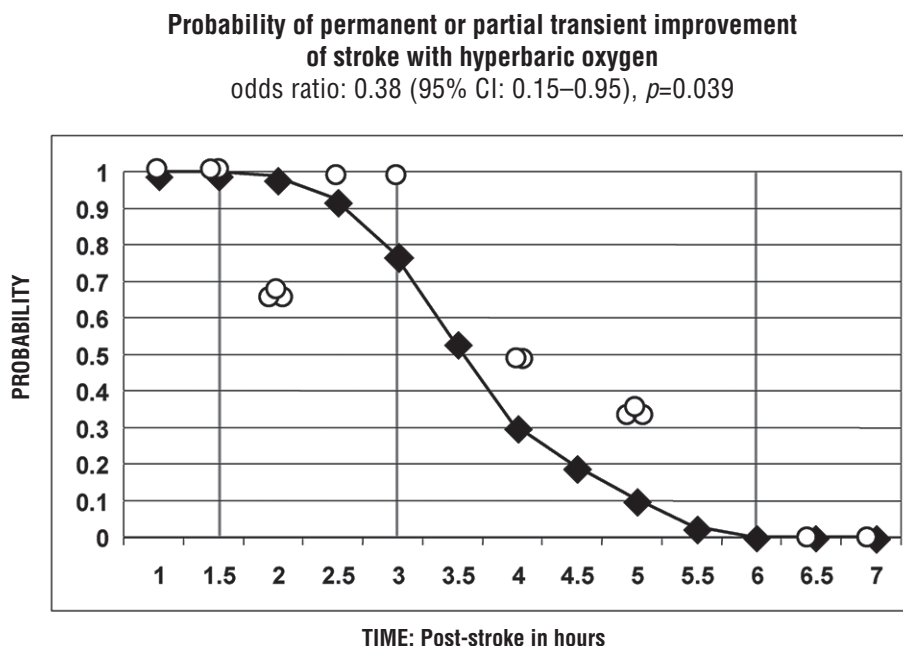**TIME: Post-stroke in hours**

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 HBO_2 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 HBO_2 for treatment of acute stroke at 90 minutes post-stroke, 3 hours post-stroke and 6 hours post-stroke, respectively.

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 HBO_2 treatment within seven hours post-stroke, we carried out an exploratory logistic regression analysis examining the influence on HBO_2 efficacy of time post-stroke, time in-chamber and dose of HBO_2 (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 HBO_2 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 HBO_2 treatment on the participants, we evaluated several logistic regression models examining the univariate influence of time post-stroke, time in-chamber and dose of HBO_2 (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 HBO_2 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.
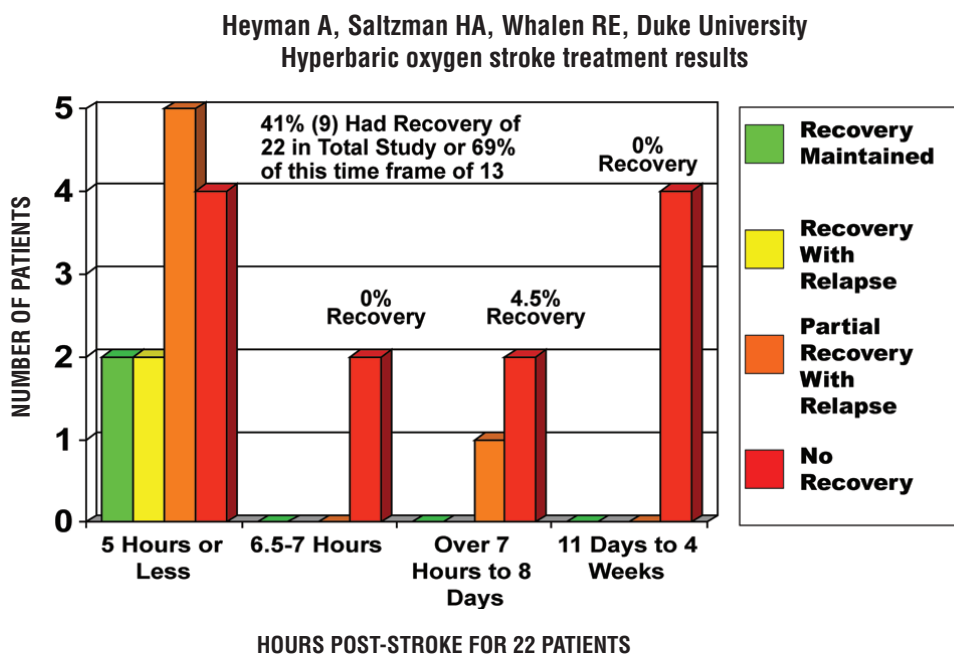
FIGURE 2

Heyman A, Saltzman HA, Whalen RE, Duke University
Hyperbaric oxygen stroke treatment results

FIGURE 2: This bar graph is our representation of the distribution of the HBO$_2$-treated patient stroke data of the 1966 Duke study [1] as a function of time post-stroke. Please refer to this figure to help in understanding Abstract and Results.

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 HBO$_2$ 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 HBO$_2$) *(Pages 327-328)*.

DISCUSSION

HBO$_2$ time window for efficacy in acute stroke treatment

Zhang, Lo, Mychaskiw and Colohan [7] reported that "early applications of HBO$_2$ within a therapeutic window of 3-6 hours post stroke or delayed but repeated administration of HBO$_2$ 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 HBO$_2$; 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 HBO$_2$ drops to 0% of patients treated within the seven-hour post-stroke window for which we calculated the predictive curve of Figure 1.

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TABLE 1 – Clinical manifestation and blood gas changes during hyperbaric oxygenation

PATIENTS WITH DRAMATIC RECOVERY FROM STROKE DURING HYPERBARIC OXYGEN THERAPY. RECOVERY MAINTAINED POST THERAPY

STROKE PATIENT DIAGNOSIS AND TREATMENT PARAMETERS:

Patient / Age	Onset and Circumstances	Neurologic Deficit	Time Post Stroke to Treatment Initiation	Pressure and Duration of Oxygenation	Arterial Blood pO2 mm Hg	Arterial Blood pCO2 mm Hg
A 61	? embolus; atrial fibrillation	Right hemi-paresis, stupor, aphasia	5 hours	2.02 ata. 1 hour	1102	34
B 58	Arteriographic complications	Right hemi-plegia, stupor	2 ½ hours	2.36 ata. 5 hours	1364	32

STROKE PATIENT RESPONSE TO HYPERBARIC OXYGEN TREATMENT:

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

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.

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TABLE 2 – Clinical manifestation and blood gas changes during hyperbaric oxygenation

STROKE PATIENTS WITH DRAMATIC RECOVERY DURING HYPERBARIC OXYGEN THERAPY WITH RELAPSE SEVERAL HOURS AFTER TREATMENT

STROKE PATIENT DIAGNOSIS AND TREATMENT PARAMETERS:

Patient / Age	Onset and Circumstances	Neurologic Deficit	Time Post Stroke to Treatment Initiation	Pressure and Duration of Oxygenation	Arterial Blood pO2 mm Hg	Arterial Blood pCO2 mm Hg
C 65	Embolus; left heart catheterization	Right hemi-plegia, aphasia, stupor	1 hour	2.36 ata. 1 hour / 2.02 ata. 2 hours	1500 / 1017	43 / 44
D 54	Embolus 6 days after Starr valve surgery	Right hemi-plegia, aphasia	2 hours	2.36 ata. 3 hours	1206	34

STROKE PATIENT RESPONSE TO HYPERBARIC OXYGEN TREATMENT:

Patient / Age	During Hyperbaric Therapy	At End of Procedure	Clinical Condition at Discharge	Remarks
C 65	Regained normal neurologic function in 6 minutes	Normal; relapse 2 hours later	Mild residual hemiparesis and aphasia	Second and third hyperbaric exposure associated with dramatic but temporary improvement
D 54	Dramatic improve-ment with movement of all limbs	Improvement maintained 3 hours, then relapsed	Severe residual neurologic deficit	Second treatment associated with temporary distinct improvement

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

STROKE PATIENTS WITH PARTIAL TRANSIENT IMPROVEMENT DURING HYPERBARIC OXYGEN THERAPY:						
STROKE PATIENT DIAGNOSIS AND TREATMENT PARAMETERS						
Patient/ Age	Onset and Circumstances	Neurologic Deficit	Time Post Stroke to Treatment Initiation	Pressure and Duration of Oxygenation	Arterial Blood pO2 mm Hg	Arterial Blood pCO2 mm Hg
E 56	Old pseudobulbar palsy; sudden worsening	Dysphasic, obtunded, right arm weakness	3 hours	3.04 ata. 30 minutes	1785	49
F 45	Arteriographic complications	Severe aphasia right hemiplegia	1 ½ hours	2.36 ata. 1 hour	1398	33
G 57	Gradual deterioration	Coma, quadriplegia, Cheyne-Stokes respiration	4 hours	2.36 ata. 79 minutes	1350	41
STROKE PATIENT RESPONSE TO HYPERBARIC OXYGEN TREATMENT:						
Patient/ Age	During Hyperbaric Therapy	At End of Procedure	Clinical Condition at Discharge		Remarks	
E 56	Moderate improvement of right hand and movement	Somnolent and hemiparetic	Died 2 days after therapy; multiple cerebral infarction at autopsy			
F 45	Definite improvement in consciousness	Retained aphasia and hemiplegia	Gradual improvement			
G 57	Moderate improvement	Relapsed after decompression	Died 1 day after treatment		B.P. rose to 300/150 after decompression	

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

STROKE PATIENTS WITH PARTIAL TRANSIENT IMPROVEMENT DURING HYPERBARIC OXYGEN THERAPY:						
STROKE PATIENT DIAGNOSIS AND TREATMENT PARAMETERS						
Patient/ Age	Onset and Circumstances	Neurologic Deficit	Time Post Stroke to Treatment Initiation	Pressure and Duration of Oxygenation	Arterial Blood pO2 mm Hg	Arterial Blood pCO2 mm Hg
H 37	Sudden onset on awaking	Right hemi-plegia, aphasia	8 days	2.02 ata. 39 minutes	787	38
I 63	Arteriographic complications	Right hemi-plegia, aphasia	2 hours	2.36 ata. 42 minutes	924	41
J ?	Sudden; after Starr valve surgery	Right hemi-plegia, aphasia	1 ½ hours	2.36 ata. 1 hour	1585	30
STROKE PATIENT RESPONSE TO HYPERBARIC OXYGEN TREATMENT:						
Patient/ Age	During Hyperbaric Therapy	At End of Procedure	Clinical Condition at Discharge		Remarks	
H 37	More alert	Maintained improvement	Slight improvement			
I 63	Slight improvement	Relapsed	Died 2 weeks after cerebral embolus at autopsy			
J ?	Slight improvement	Relapsed	No change			

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.

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

STROKE PATIENTS WITH NO SIGNIFICANT CHANGE DURING HYPERBARIC OXYGEN THERAPY:

STROKE PATIENT DIAGNOSIS AND TREATMENT PARAMETERS

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

STROKE PATIENT RESPONSE TO HYPERBARIC OXYGEN TREATMENT:

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

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.

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

STROKE PATIENTS WITH NO SIGNIFICANT CHANGE DURING HYPERBARIC OXYGEN THERAPY:

STROKE PATIENT DIAGNOSIS AND TREATMENT PARAMETERS

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

STROKE PATIENT RESPONSE TO HYPERBARIC OXYGEN TREATMENT:

Patient/ Age	During Hyperbaric Therapy	At End of Procedure	Clinical Condition at Discharge	Remarks
N 38	No change	No change	No change	
O 55	No change	No change	No change	
P 62	No change	No change	No change	

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.

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

STROKE PATIENTS WITH NO SIGNIFICANT CHANGE DURING HYPERBARIC OXYGEN THERAPY:						
STROKE PATIENT DIAGNOSIS AND TREATMENT PARAMETERS						
Patient/ Age	Onset and Circumstances	Neurologic Deficit	Time Post Stroke to Treatment Initiation	Pressure and Duration of Oxygenation	Arterial Blood pO2 mm Hg	Arterial Blood pCO2 mm Hg
Q 46	Brain stem infarct	Right hemi-plegia, left third nerve palsy	4 weeks	3.04 ata. 30 minutes	1470	42
R 62	Sudden onset	Right hemi-paresis, aphasia	13 days	3.04 ata. 30 minutes	1492	40
S 41	Cerebral hemorrhage	Left hemi-plegia, dysarthria	5 hours	3.04 ata. 30 minutes	1577	40

STROKE PATIENT RESPONSE TO HYPERBARIC OXYGEN TREATMENT:				
Patient/ Age	During Hyperbaric Therapy	At End of Procedure	Clinical Condition at Discharge	Remarks
Q 46	No change	No change	No change	
R 62	No change	No change	Died 2 days later	
S 41	No change	No change	No change	

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.

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

STROKE PATIENTS WITH NO SIGNIFICANT CHANGE DURING HYPERBARIC OXYGEN THERAPY:						
STROKE PATIENT DIAGNOSIS AND TREATMENT PARAMETERS						
Patient/ Age	Onset and Circumstances	Neurologic Deficit	Time Post Stroke to Treatment Initiation	Pressure and Duration of Oxygenation	Arterial Blood pO2 mm Hg	Arterial Blood pCO2 mm Hg
T 58	Basilar artery thrombosis	Right hemi-plegia	6 ½ hours	2.02 ata. 44 minutes	662	45
U 51	Sudden onset	Right hemi-paresis, aphasia, stupor	4 hours	2.02 ata. 1 hour	1155	34
V 42	Sudden onset	Stupor, dysarthria, left hemiplegia	2 hours	2.36 ata. 50 minutes	1350	No value

STROKE PATIENT RESPONSE TO HYPERBARIC OXYGEN TREATMENT:				
Patient/ Age	During Hyperbaric Therapy	At End of Procedure	Clinical Condition at Discharge	Remarks
T 58	No change	No change	No change	B.P. rose from 170 to 240 mm Hg systolic after decompression
U 51	No change	No change	No change	Progressed to quadriplegia and died 3 weeks later
V 42	No change	No change	No change	

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 HBO$_2$ at eight days post-stroke by becoming more alert, but the HBO$_2$ 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 HBO$_2$ efficacy in the Duke data is indicative of a strong treatment effect of HBO$_2$ 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 HBO$_2$ 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 HBO$_2$, 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 HBO$_2$ treatments after some functional recovery of the initial HBO$_2$ exposure had relapsed.

Given the positive stroke recovery in the Duke patients occurring within minutes of the application of HBO$_2$, it is unlikely that the recovery noted for the patients was spontaneous.

HBO$_2$ dose response and time in chamber for stroke treatment

Although our regression analysis did not find a significant relationship between HBO$_2$ stroke treatment efficacy and the HBO$_2$ 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 HBO$_2$ in stroke treatment since the Duke study was not designed to elucidate a dose-response curve.

FIGURE 3

The ATLANTIS, ECASS and NINDS rtPA study model estimating odds ratio for favorable outcome at 3 months in rtPA-treated patients compared with controls
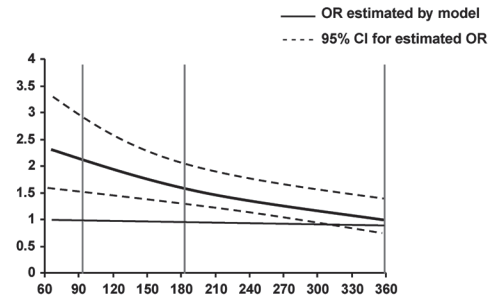

Adjusted for age, baseline glucose concentration, baseline NIHSS measurement, baseline diastolic blood pressure, previous hypertension, and interaction between age and baseline NIHSS measurement

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FIGURE 3: For comparison to our results shown in Figure 1, the vertical gray lines denote the relative efficacy of rtPA for treatment of acute stroke when given at 90 minutes post-stroke, 3 hours post-stroke and 6 hours post-stroke, respectively. *Reprinted from The Lancet, Volume 363, The ATLANTIS, ECASS and NINDS rtPA Study Group Investigator. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS and NINDS rtPA stroke trials, pages 768-774, 2004, with permission from Elsevier.*

FIGURE 4

Degree of neurologic injury as a function of the duration of focal cerebral ischemia in awake monkeys
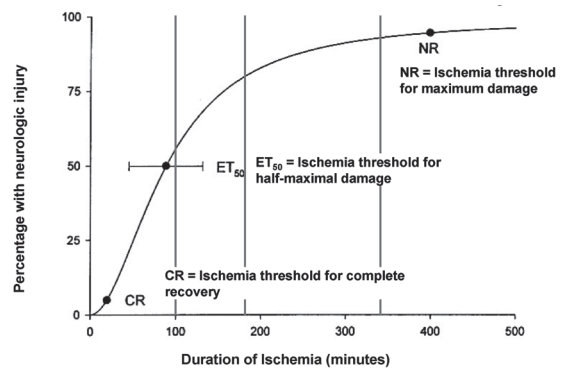
Constructed from the data of Jones, TH Journal of Neurosurgery 1981; 54:773-782 by Zivin, JA, Neurology 1998;50(3), 599-603

FIGURE 4: For comparison to our results shown in Figure 1, the vertical gray lines demarcate the time line of neurological injury for focal ischemia in monkeys in the study of Jones [10] as a function of time from the start of focal ischemia at 90 minutes, 3 hours and 6 hours. *Reprinted with minor modification from Neurology, Volume 50, Justin A. Zivin. Factors determining the therapeutic window for stroke, pages 599-603, 1998, with permission from Wolters Kluwer Health.*

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 stoke in 2000, Veltkamp *et al.* showed efficacy for 2.5 ATA HBO_2, but 1.5 ATA and 1.0 ATA HBO_2 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.

HBO_2 treatment *vs.* type of stroke

Future HBO_2 stroke treatment research should attempt to study how the type of stroke and stroke etiology relate to HBO_2 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 HBO_2 treatment reduces the blood-brain barrier disruption, hemorrhagic transformation and mortality after focal cerebral ischemia, suggesting that HBO_2 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 HBO_2 in stroke

Zhang and his colleagues discuss mechanisms of HBO_2 in stroke [7]. The first obvious benefit of HBO_2 for ischemic stroke was presented by the Duke group [1] in a figure where they demonstrated an average increase in the arterial pO_2 from 1 ATA of 450mm Hg to an average of 1800mm Hg for HBO_2 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 HBO_2 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 HBO_2 had better electrophysiological function despite an increase in oxidative stress documented by levels of oxidized glutathione [17].

HBO_2 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 HBO_2 in reperfusion injuries of brain, skeletal muscle and intestine [18].

The synergistic relationship between HBO_2 and rtPA

HBO_2 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 HBO_2, 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), HBO_2 alone (2 ATA), rtPA alone, or HBO_2 plus rtPA, showed a true positive synergistic response between rtPA and HBO_2 in the resolution of cardiac thrombosis, with subsequent restoration of enzyme activity *(Figure 5, right)*. Given the elevation of endogenous rtPA by HBO_2 discussed above, this factor could possibly contribute to the synergistic therapeutic effect of HBO_2 and rtPA on the myocardial infarction observed by Thomas *et al*. Further, we speculate that the same synergistic response between HBO_2 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 HBO_2 plus rtPA than it was either with HBO_2 alone or rtPA alone. All three of these conditions were better than the control group.

The safety of rtPA plus HBO_2 administered to humans

The safety and efficacy of HBO_2 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 HBO_2 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.

HBO_2 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.

FIGURE 5

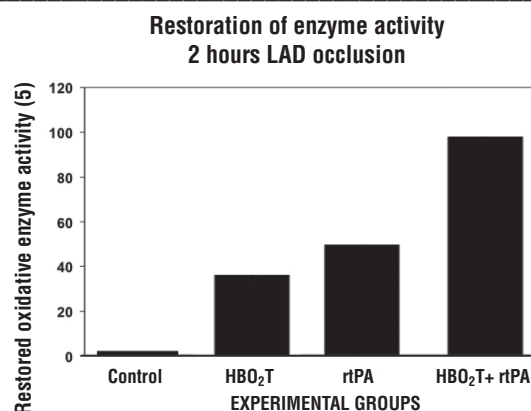**Restoration of enzyme activity
2 hours LAD occlusion**

FIGURE 5: An experimental thrombogenic myocardial infarction model for left anterior descending artery (LAD) occlusion by Thomas MP et al. [24], using the dog, treated with control, HBO_2 alone (2 ATA), rtPA alone, or HBO_2 plus rtPA, showed a true positive synergistic response between rtPA and HBO_2 in the resolution of cardiac thrombosis with subsequent restoration of enzyme activity. *Reprinted from American Heart Journal, Volume 120, Thomas MP, Brown LA, Sponseller DR, Williamson SE, Diaz JA, Guyton DP. Myocardial infarct size reduction by the synergistic effect of hyperbaric oxygen and recombinant tissue plasminogen activator, pages 791-800, 1990, with permission from Elsevier.*

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 HBO_2 provided to an acute stroke patient in the first three hours post-stroke could potentially put the brain in a stasis that, while under HBO_2, would "stop the clock" on the three-hour rtPA FDA administration window. This would greatly extend the range that a dedicated HBO_2 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.

FIGURE 6

15 minutes (11 miles)
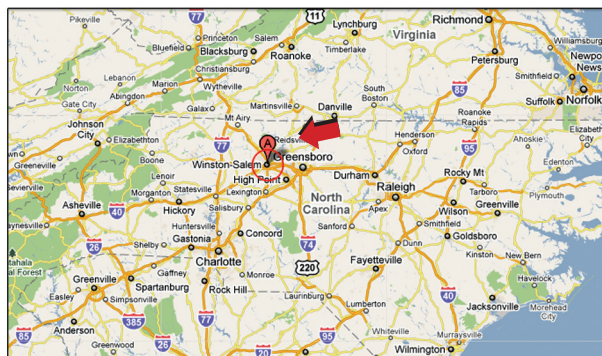**Standard ambulance**

FIGURE 6: Range a standard ambulance can go to get an acute stroke patient and still have time to work up the patient at the hospital stroke center for rtPA within the FDA 3-hour post-stroke window.
Map is by ©2011 Google - Map data.

FIGURE 7
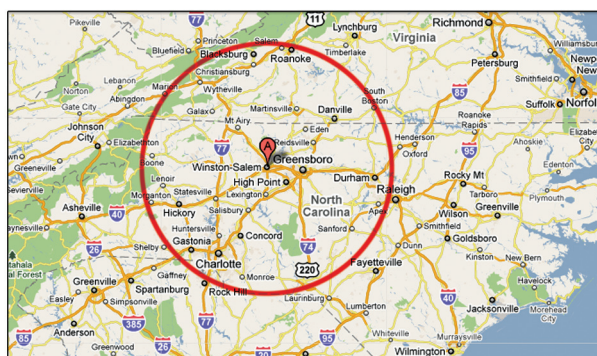
2 hours (90 miles)
HBO₂ ambulance

FIGURE 7: The dramatic rapid HBO$_2$-induced acute stroke recovery observed in the 1966 Duke Study [1] suggests that an HBO$_2$ chamber-equipped stroke ambulance would improve the triage of acute stroke patients to a stroke center for standard of care rtPA treatment by stopping the clock on the 3-hour FDA post-stroke rtPA window for administration. Compared to a standard ambulance, the HBO$_2$ stroke treatment ambulance would have a greatly extended range, with time to work up the patient at the hospital stroke center for rtPA. Clinical trials are needed for proof of concept.
Map is by ©2011 Google - Map data.

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 HBO$_2$. The dramatic rapid degree of HBO$_2$-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 HBO$_2$ 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 HBO$_2$ chamber would not only extend the range for stroke patient triage, but for the reasons discussed above, would potentially provide an HBO$_2$ treatment en route to the stroke center, which would be synergistic with rtPA standard of care acute stroke treatment. Plus, the HBO$_2$ stroke ambulance would have completed the functional HBO$_2$ challenge test for rtPA administration assessment by arrival at the hospital. To this end, our group is designing and building a prototype HBO$_2$ 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 HBO$_2$ 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 HBO$_2$ environment of our mobile chamber-equipped ambulance could facilitate ambulance-based rtPA administration.

FIGURE 8

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.

FIGURE 9

FIGURE 9: An inside view of the two-place mobile Cowan Manufacturing Company Transportable Recompression Chamber to be used in our prototype HBO₂ acute stroke treatment ambulance. Pure oxygen will be delivered to the patient via mask or hood, and the chamber itself will be pressurized with air at 2.5 ATA.
Photograph used with permission of Cowan Manufacturing Company. Manufacturing Company Transportable Recompression Chamber.

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