# Regional CBF in chronic stable TBI treated with hyperbaric oxygen.

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Barrett KF, Masel B, Patterson J, Scheibel RS, Corson KP, Mader JT. Regional CBF in chronic stable TBI treated with hyperbaric oxygen. Undersea Hyperb Med 2004; (31)4:395-406. To investigate whether Hyperbaric Oxygen Therapy ($HBO_2$) could improve neurologic deficits and regional cerebral blood flow (rCBF) in chronic traumatic brain injuries (TBI), the authors employed a nonrandomized control pilot trial. Five subjects, at least three years post head injury, received $HBO_2$. Five head injured controls (HIC) were matched for age, sex, and type of injury. Five healthy subjects served as normal controls. Sixty-eight normal volunteers comprised a reference data bank against which to compare SPECT brain scans. $HBO_2$ subjects received 120 $HBO_2$ in blocks of 80 and 40 treatments with an interval five-month break. Normal controls underwent a single SPECT brain scan, $HBO_2$, and repeat SPECT battery. TBI subjects were evaluated by neurologic, neuropsychometric, exercise testing, and pre and post study MRIs, or CT scans if MRI was contraindicated. Statistical Parametric Mapping was applied to SPECT scans for rCBF analysis. There were no significant objective changes in neurologic, neuropsychometric, exercise testing, MRIs, or rCBF. In this small pilot study, $HBO_2$ did not effect clinical or regional cerebral blood flow improvement in TBI subjects.

*N.B. In Memoriam, Jon T. Mader, Past President, UHMS

## INTRODUCTION

Hyperbaric oxygen therapy has been used in the treatment of traumatic brain injuries. Successful therapy, based on Class II and Class III reports is attributed to a permanent improvement in flow and metabolism and upregulation of "idling neurons" (1-4) that survive long after various cerebral insults(1,5-8). The nature of these surviving neurons is vague. It is unclear whether they are metabolically quiescent as a result of chronic, persistent ischemia or whether there is a primary metabolic down-regulation, presumably resulting from the original injury, with a consequent reduced local CBF. Most authors seem to imply that these represent a form of chronic penumbrae. Conventionally, ischemic penumbrae are thought to be acute phenomenon and are characterized by "critically reduced cerebral blood flow, abolished synaptic activity but preserved structural integrity, and unpredictable outcome depending on the degree and duration of ischemia (9)." This interruption of clinical and electrical function is felt to be reversible, but time limited and of unknown duration (10).

SPECT scans have been used to show the presence of ischemic penumbrae and altered blood flow (1,2,4). Blood flow changes on SPECT imaging after a single $HBO_2$ have been used to predict a response to therapy (1,4). In the presence of clinical change, for SPECT, an area of decreased rCBF that disappears with time or treatment has been used to suggest the presence of an ischemic penumbra (1). Superimposition of SPECT on MRI could then be used as an additional tool to visually identify the existence of a penumbra in a region of identifiable brain injury. Visual analysis of SPECT images alone is subjective, and areas of noise are not filtered

 

out, and may be misinterpreted as areas of activation. Statistical Parametric Mapping (SPM) has been used as an objective method of SPECT analysis utilizing computer-driven, voxel-based analysis of the images (11). Some studies have shown parallel increases in neuropsychological test scores and regional cerebral flow in TBI subjects **(**12**)** and neuropsychometric testing has been shown to predict SPECT abnormalities **(**13**)**.

The goals of this small pilot study were: (1), to generate some clinical observations from a small controlled series of subjects with chronic TBI treated with $HBO_2$ at 1.5ATA; (2), to determine if statistical analysis of SPECT scans could be a useful technique for following these subjects during therapy; (3), to determine if SPECT imaging preceding and following one $HBO_2$ could predict a therapeutic response to a course of treatment.

## MATERIALS AND METHODS

### $HBO_2$ subjects

Five $HBO_2$ subjects with chronic, stable traumatic brain injuries were recruited from The Transitional Learning Center, a comprehensive neuro-rehabilitation facility in Galveston, Texas. The subjects were adults at least three years post-injury with persistent neurological and neuropsychological deficits. Exclusion criteria were: the presence of significant pulmonary disease, refractory seizure disorder, incapacitating claustrophobia, known current use of drugs or alcohol, pregnancy, and inability to give consent. All subjects gave informed consent. The protocol was approved by The Institutional Review Boards of the University of Texas Medical Branch and The Committee for the Protection of Human Subjects of The Transitional Learning Center at Galveston. The Helsinki principles are inherent in the review boards' standards.

Four subjects sustained closed head injuries (CHI). One subject had a gunshot wound (GSW) with resultant bifrontal lobectomy. Medical records from acute care hospitals were incomplete; therefore, length of coma and the Glasgow Coma Scale Scores were not known.

No medicines were changed specifically for this study. No subjects participated in any formal rehabilitation during this study.

### Control subjects

Two groups of age and sex matched controls were used for this study: five head injured controls (HIC) and five neurologically normal controls. HIC subjects were matched for age, sex, and type of injury (four CHI and one GSW). This group served as control for rCBF changes over time. (Table 1). **Table 1.** Demographics.

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| Groups | Age (years) | Sex | Handedness | Injury Type | Time from Injury |
|---|---|---|---|---|---|
| HBO2 | 35 | 3 M/2 F | 5 Right | 4 CHI/1 GSW | 3 – 19 years |
| HIC | 34.2 | 3 M/2 F | 4 Right/1 Left | 4 CHI/1 GSW | 2.5 –14 years |
| C+D | 34.8 | 3 M/2 F | 4 Right/1 Left | -- | -- |

Legend. **GSW** – Gunshot Wound. **CHI** – Closed Head Injury.

Normal controls underwent a screening questionnaire, and their exclusion criteria included history of brain injury, psychiatric disorder, pulmonary disease, alcohol or substance abuse, or exposure to a pressurized environment or gas including scuba diving. The five normal subjects underwent a SPECT brain scan, single 1.5 ATA $HBO_2$, and a repeat SPECT brain scan to study the effects of one $HBO_2$ upon normal brain. This "control + dive" group is labeled C+D to prevent confusion with the normal control group described below.

**Reference normal subjects**

Sixty-eight normal subjects (mean age 34+/-9.5 years) underwent $^{99m}$Tc-ECD SPECT brain scanning for a previous study (14). This group served as a reference normal bank from which statistical comparisons were made with $HBO_2$, HIC and C+D subjects.

**Hyperbaric oxygen therapy and chamber**

$HBO_2$ subjects and normal controls were treated at the University of Texas Medical Branch in a dual lock, multiplace chamber. All treatments used 1.5 ATA $0_2$ for 60 minutes at maximum pressure for five days per week. Oxygen was administered in the chamber using a Duke hood. There was a physician in constant attendance.

**Testing schedule**

Standard clinical MRI brain scans were performed at the beginning and at the end of the study for both groups of brain injured subjects. The C+D subjects underwent only a single MRI instead of two. Due to metallic scatter, gunshot wound subjects underwent CT scanning. The readers were blinded to treatment.

The $HBO_2$ group was studied with a pretreatment $^{99m}$Tc-ECD SPECT brain scan, progressive exercise testing, and neuropsychometric testing (Table 2).

**Table 2.** Study Time Line for $HBO_2$ Subjects

| HBO2 | T -2weeks | T0 | T1 | T20 | T40 | T60 | T80 | Break | T120 | T +1Year |
|---|---|---|---|---|---|---|---|---|---|---|
| NEUROΨ | Full | Full | -- | Brief | Full | Brief | Full | -- | Full | Full |
| PET | -- | Full | -- | Full | Full | Full | Full | -- | Full | -- |
| EXAM | -- | Neuro | Neuro | Neuro | Neuro | Neuro | Neuro | Neuro | Neuro | Neuro |
| SPECT | -- | SPECT | SPECT | -- | SPECT | -- | SPECT | SPECT | SPECT | SPECT |
| MRI | -- | MRI | -- | -- | -- | -- | -- | -- | MRI | -- |

Legend. **NEUROΨ** - Neuropsychometric testing. **PET** – Progressive Exercise Testing.
**EXAM** – Standard Neurological Exam. **T -2weeks** - Neuropsychometric testing performed 2 weeks before the start of the study. **T0** – Exams performed at 0 $HBO_2$; **T1 – T120** - After 1, 20, 40, 60, 80, and 120 $HBO_2$.
**Break** – 5-month break in study. **T +1year** – Studies performed one year after 120 $HBO_2$.

Videotaped non-blinded neurological evaluations were performed by one of the authors (BEM) including testing of cranial nerves, reflexes, sensation, five-point scale motor function, and cerebellar function. SPECT brain scans were performed after one, 40 and 80 $HBO_2$ sessions.

Brain scans were also performed after a five month period immediately before the second set of 40 $HBO_2$, after the 120$^{th}$ total $HBO_2$, and one year after the last treatment. To negate the effects of hyperoxic cerebral vasoconstriction (15), all SPECT brain scans were performed at least 24 hours after $HBO_2$. The HIC group underwent SPECT brain scanning at times that would have corresponded to 0, 40, 80 and 120 $HBO_2$'s for the $HBO_2$ group.

Neuropsychometric testing was performed two weeks before the study, at the beginning, after 20, 40, 60, 80 and 120 $HBO_2$ sessions, and one year after treatment had ceased.

**Image processing**

Seven millimeter thickness axial and sagittal T1, 2D, and axial T2 weighted 2D and T1 axial 2D post Gadolinium images were acquired using a 1.5 T GE scanner. All subjects underwent SPECT brain scanning using 20 milliCuries (740 MegaBecquerels) $^{99m}$Tc-ECD (ethyl cisteine dimer, Dupont, Neurolite®). This tracer was chosen because uptake relates directly to nutritional perfusion and to changes in cerebral metabolism (16). Radiotracer injection was done 30 minutes after starting the intravenous line and after resting in a low stimulus environment, in supine position; eyes and ears open in a darkened quiet room. Thirty to sixty minutes after radiotracer administration, subjects were scanned on a dual-headed rectangular field of view gamma camera (Vertex, ADAC Laboratories, Milpitas, CA) using a high-resolution (12 mm FWHM) collimator. Standardized head position was achieved by aligning the external auditory meati using plastic head holders, and adjusting the camera-head-detector ratio values. Total acquisition time was 35 minutes. Each gamma camera captured 64 projections with a 30-second acquisition time per projection over 180$^{\circ}$ arc for a total of 128 images. Tomograms were generated and transverse images were reconstructed using filtered back projection algorithms employing a Butterworth filter using a Nyquist frequency cutoff of 0.6 and an order of 6. Transverse volume images were then attenuation corrected and the resultant files were transferred to a SUN Sparcstation 20$^{TM}$ for further image processing and analysis.

Image processing and analysis was carried out in SPM (11,17). To facilitate across-subject comparisons, co-registration and spatial normalization were carried out in the following fashion. For the subjects who received multiple scans, all scans were co-registered to the first scan, and a mean image for the subject was created from all the subject's co-registered scans. This mean image was then spatially normalized, and the resulting transformation matrix was applied to all co-registered images of that subject. This was done to reduce variability and error in processing of each subject. Visual inspection of all images was carried out to ensure accuracy of the transformation. For images from the normal control database, co-registration to a group mean was carried out. All images were spatially transformed [17] to the standardized stereotactic space of Talairach and Tournoux [18] using 12-parameter linear affine subroutines, and smoothed with a 12-mm isotropic Gaussian filter.

**Image analysis**

*$HBO_2$ Subjects and HI Controls*

A two-step procedure was employed in order to detect changes in regional cerebral blood flow over the multiple patient scans. First, voxel by voxel analysis of the SPECT brain images from each $HBO_2$ and HIC subject was performed by comparing their images to the 68 normal subjects. Because each subject had different lesions, group averaging was not possible, and each subject had to be compared to the normal group individually. Each $HBO_2$ subject had seven scans over the treatment period, and each head-injured control subject had either three or four

scans over time points coinciding with the first three or four scans of the $HBO_2$ group. Variations in inter-individual global intensity were accounted for by scaling all images to a standard intensity level of 50. This was accomplished by deriving a mean global intensity value for each scan, dividing by 50, and multiplying the resultant scaling factor by the original image. For purposes of examining what regions were significantly different in the $HBO_2$ group as compared to the control group, a simple compare-groups design (subject scan vs. the control group) was employed. Age and sex were entered as confounding covariates. This comparison resulted in an SPM(t) map of significance, which was subsequently transformed to the Z statistic. A Bonferroni corrected significance threshold was used for a per-voxel p value $< 0.05$ based on intensity. This comparison revealed significant differences (both increased and decreased rCBF) in each subject's scan. Areas of abnormally decreased blood flow that responded with relative increases in regional perfusion, and which mirrored clinical improvement, would be considered chronic ischemic penumbrae for the purpose of this study.

The second step in evaluation for the effect of $HBO_2$ involved the following procedure. For each subject (either $HBO_2$ or HIC), where there were significant regional perfusion differences in the pretreatment scan compared to normal controls, the most significant (highest Z-score) region of change was located. This coordinate was used as a starting point for a 1cm diameter (81 voxels) of volume of interest (VOI). This VOI was used to measure the intensity at that spot in all subsequent scans of that individual, as well as the control group. The VOI intensity of the pretreatment scan of each subject was compared to that of the other scans as well as to the mean VOI intensity of the controls. This comparison was used to evaluate for significant changes over time, or resulting from an $HBO_2$ effect. Significance for this examination was determined by ANOVA, with a significance threshold of $p < 0.05$ per voxel.

*C+D Subjects*

Normal controls who were scanned both pre and post a single HBO treatment had their functional images processed as above, and were compared in a group-wise fashion using SPM.

**Neuropsychometric testing**

Neuropsychological testing, performed only by the $HBO_2$ subjects, measured the following domains: memory, mental tracking, attention and concentration, executive function, affect, and motor. Specific tests used were: the Adaptive Rate Continuous Performance Test, the Wisconsin Card Sorting Test, the Test of Nonverbal Intelligence-2, the Controlled Oral Word Association test, the Verbal Selective Reminding test, and the Digit Span subtest of the Revised Wechsler Adult Intelligence Scale. The pre-baseline test, T0, also assessed intellectual functioning (Wechsler Adult Intelligence Scale-Reading, WAIS-R); and mood (Geriatric Depression Score). To prevent a practice/learning effect, tests were administered on a random counterbalanced schedule by using one of four parallel packets at each full assessment time point. A brief assessment, testing for mental tracking, concentration, and attention using the above referenced tests was also alternated with full neuropsychometric assessment as an additional measure to preclude against a learning effect.

**Progressive exercise testing**

As complaints of excessive fatigue are common following TBI (19), four of the five $HBO_2$ subjects underwent progressive exercise testing (P.E.T.) as part of the testing battery on a treadmill. One subject could not undergo examination because severe physical disabilities precluded use of a graded treadmill or equivalent testing.

Resting and maximum attained heart rate; respiratory rate, tidal volume, oxygen consumption ($VO_2$) and oxygen consumption per kilogram of body weight ($VO_2$/kg) were studied. Outcome measures were: resting heart rate, anaerobic threshold, oxygen pulse, maximum power output, maximum heart rate, maximum oxygen consumption, and heart rate after 4 minutes of recovery from maximum exercise.

At the beginning of each test, baseline recordings were obtained for three minutes. The subject walked at a fixed speed depending on his physical condition. After two minutes, at a grade of 1%, the inclination was progressively increased by 2% each minute. Exercise testing was terminated when the subject reached the maximum predicted heart rate (2200 bpm - age) or indicated an inability to proceed further. The treadmill speed was then reduced to 1.0-1.5 mph and the grade was lowered to 1% for a four-minute active recovery period.

## RESULTS

There were no significant medical complications during this study. Minor temporary problems occurred with pressure equalization of the Eustachian tubes and were alleviated with the use of intranasal vasoconstrictors.

### Neurologic testing

With the exception of aerobic threshold, no objective neurological or P.E.T. changes were seen for the study duration in the $HBO_2$ group (See Table 3). No neurological improvement or deterioration was reported in HIC subjects over time.

### Neuropsychometric testing

One $HBO_2$ subject, (M.S.), exhibited such marked behavioral deterioration that he was removed after completing 110 $HBO_2$'s. Neuropsychometric testing mirrored this event, although there was no significant change in his SPECT. No consistent change was seen in the neuropsychometric scores of the remaining four $HBO_2$ subjects. As large individual variations occurred in all neuropsychometric tests, group trends and consistent correlation to SPECT findings could not be identified. Global depression scores were stable in all $HBO_2$ subjects for the duration of the study.

### Magnetic Resonance Imaging

No structural differences between the pre and post-treatment MRI's were seen in the $HBO_2$ subjects. There were no changes in the MRIs of the HIC subjects over time.

### $^{99m}$Tc-ECD SPECT brain scans

Regions of significant difference were evident in all subjects compared to the normal control group. Visual interpretation of the scans by two blinded nuclear medicine physicians was unable to detect sequential rCBF changes. In addition, visual inspection of SPM(Z) maps resulting from a comparison of each subject's scan to the normal control group revealed no consistent patterns of perfusion changes over time, relative to treatment (data not shown). For each subject, the region with the largest difference in the pre-treatment scan (or first scan for the HIC group) was used to track changes across all the scans within a 1 cm VOI. Significant rCBF changes over time were evident in all $HBO_2$ and HIC subjects with some areas of increased and decreased perfusion enlarging and shrinking in size and intensity over time with no discernible

pattern**.** Figures 1 and 2 show a representative subject from the $HBO_2$ and HIC groups. There were no significant changes after one $HBO_2$ in the SPECT scans of the C+D group (data not shown).

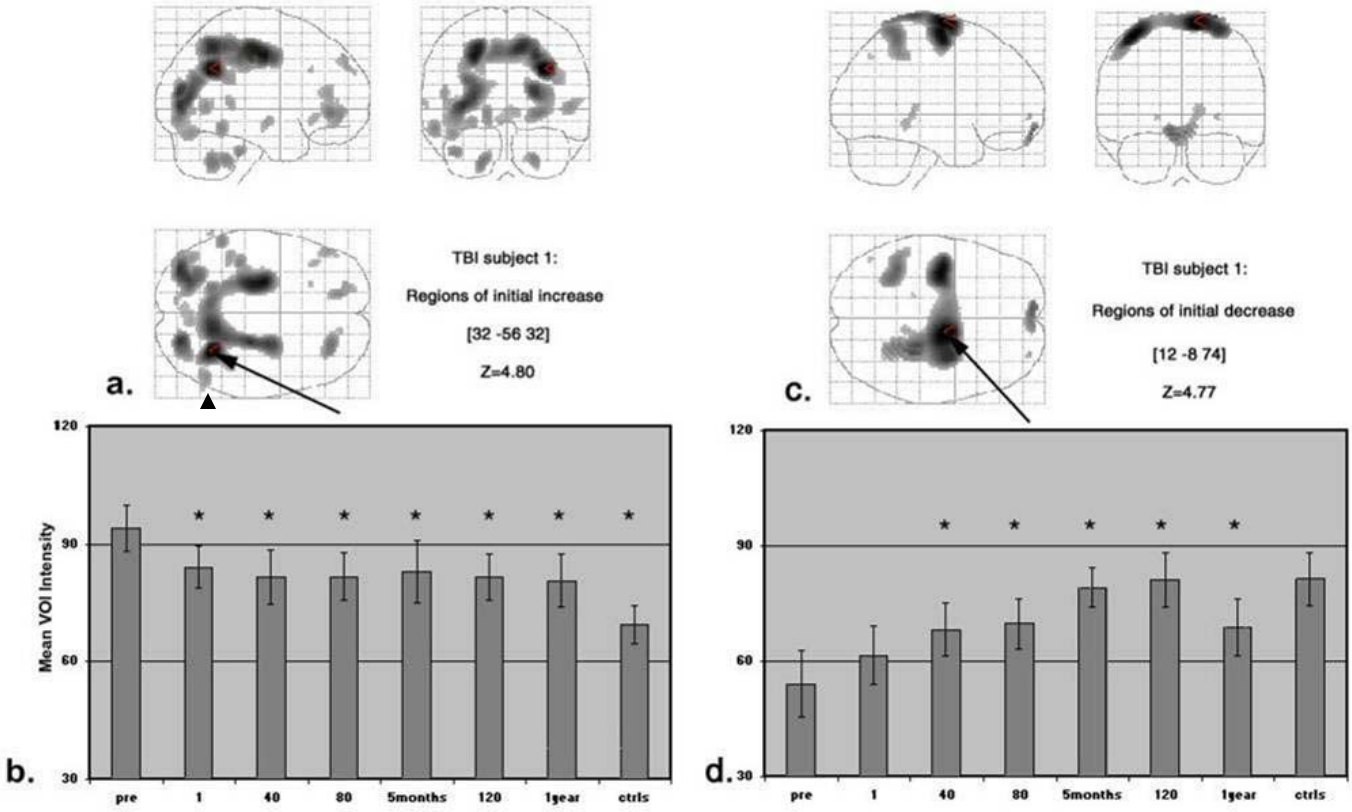
**Table 3.** Graded Treadmill Exercise Test*****

| Subject | $HBO_2$ | Treadmill Speed | Maximum Grade | $VO_2$ Maximum | $VO_2$/kg Rest | $VO_2$/kg Maximum | A. T. $VO_2$ | A.T. $VO_2$/kg |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |
| L.T. | | 2 | 19 | 2647 | 3.5 | 35.58 | 1852 | 24.89 |
| | | 2 | 15 | 2236 | 3.5 | 30.63 | 1965 | 26.92 |
| | | 2 | 19 | 2380 | 2.4 | 31.99 | 1389 | 18.67 |
| | | | | | | | | |
| J.E. | | 2.5 | 25 | 1903 | 3.5 | 25.98 | 1586 | 20.57 |
| | | 2.5 | 23 | 1996 | 2.5 | 26.83 | 1400 | 18.82 |
| | | 2.5 | 23 | 1956 | 2.5 | 24.74 | 1272 | 16.69 |
| | | | | | | | | |
| M.R. | | 2.7 | 13 | 1681 | 2.4 | 20.35 | 1334 | 16.15 |
| | | 2.7 | 15 | 1705 | 2.5 | 21 | 1181 | 14.54 |
| | | 2.7 | 15 | 1625 | 2.4 | 19.25 | 1036 | 12.27 |
| | | | | | | | | |
| R.H. | | 3 | 15 | -- | -- | -- | | |
| | | 3 | 15 | 1725 | 2.1 | 20.13 | 1531 | 17.86 |
| | | 3 | 15 | 1876 | 2.2 | 21.89 | 1293 | 15.09 |
| | | | | | | | | |
| | RM ANOVA | | | 0.66 | 0.25 | 0.42 | 0.06 | 0.06 |
| | | | | | | | | |
| | t-TEST Pre/Post | | | 0.44 | 0.18 | 0.13 | 0.02 | 0.03 |

**Table 3** Legend. ***** One $HBO_2$ subject could not participate in either the graded treadmill or bicycle ergometer tests because of severe physical handicaps. $VO_2$ – Oxygen Consumption. A.T. – Aerobic Threshold.

Because subjects were not pre-selected on the basis of MRI findings, only one subject was found to have a gliotic lesion on MRI. SPECT scans superimposed on the MRI showed an area of decreased blood flow around this lesion; however, there was no change with treatment.

**Fig. 1.** Representative $HBO_2$ subject. Panels a and c - SPM pretreatment scan showing increased or decreased intensity voxels (corrected $p < 0.05$/voxel, T=4.56). Arrow denotes 1 cm maximal intensity difference VOI. Panels b and d - Mean VOI intensity per scan. Control indicates normal group grand mean. (*) corrected $p \leq 0.0006$ from pre-treatment scan VOI by ANOVA.




## DISCUSSION

This pilot study investigated the hypotheses that 1.5 ATA $HBO_2$ has significant effects on several neurological and neuropsychological variables, as well as cerebral perfusion. This is the only longitudinal investigation of $HBO_2$'s effects on chronic TBI that employed head injured and non-head injured controls and that also used objective statistic based computer algorithms (SPM) to evaluate temporal rCBF changes. We chose SPM because of reported poor intra/inter observer concordance in subjective readings among trained neuroradiologists (20). We believed objective SPM analysis would be superior at detecting the previously reported increased cerebral blood flow accompanying the electrophysiologic upregulation of "idling neurons" by $HBO_2$ (4). We hypothesized that these metabolically quiescent "idling" neurons were a form of chronic penumbrae and would be physically near or adjacent to anatomically identifiable areas of injury when SPM-SPECT scans were superimposed on MRI images. We were unable to do so principally because most of the patients had sustained diffuse axonal injury. Thus, only one $HBO_2$ patient had identifiable areas of injury on MRI.

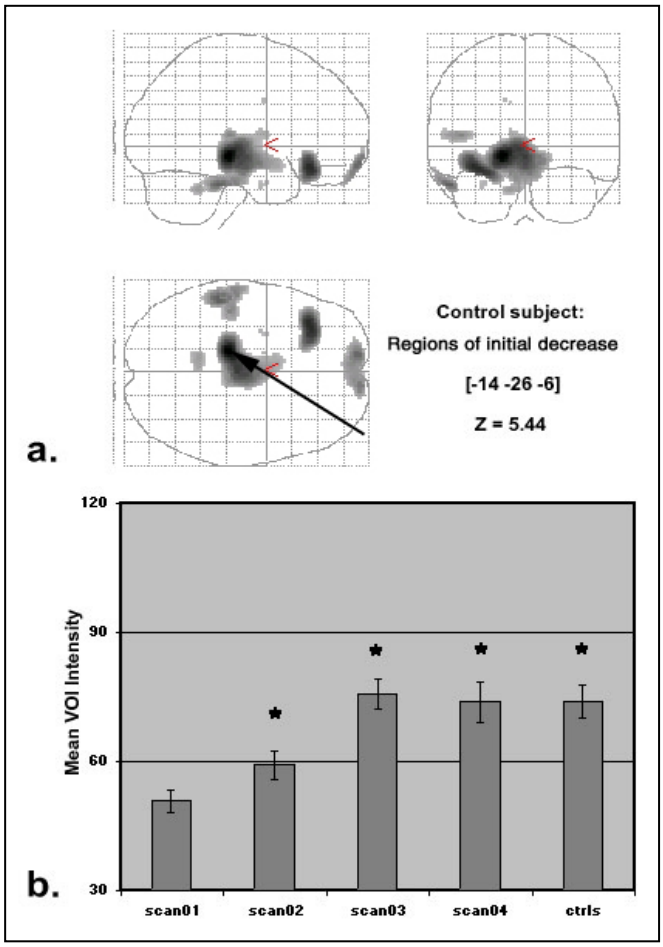



**Fig. 2.**- Representative HIC subject. Panel (a) shows a Z-map having only regions of decreased perfusion by SPM analysis. No regions of increased perfusion passed the corrected threshold of T=4.56. The arrow indicates the VOI. Panel b displays the results of the VOI analysis. See Figure 1 for legend and statistics. (*) significantly different from pre-treatment scan

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Some $HBO_2$ subjects had regions of decreased rCBF that did not change with time or treatment. This was also apparent in the non-treated head-injured control group. $^{99m}$Tc-ECD uptake is felt to be a marker for nutritional blood flow or metabolism (21). Therefore, rather than areas of marginal perfusion suggesting penumbrae of chronic persistent ischemia, these areas of low CBF could be attributed to impaired neuronal metabolism caused by chronic regional deafferentation, and consequent reduced metabolic demand (22). It is possible, but unlikely, that some areas of decreased rCBF are artifacts inherent in the SPM technique of spatial transformation of images from patients with brain lesions, because spatial normalization of brain scans with large abnormal regions of perfusion can be problematic (23). However, all scans were visually inspected for goodness of fit of the transform, and the same transform was applied to all scans of a given subject after coregistration to a mean subject image. Although there could be small penumbrae beyond the limits of detection by SPECT imaging, it is possible that none exist in chronic TBI patients.

While rCBF regressions towards baseline were evident in the $HBO_2$ subjects, these changes were also seen in the HIC group. These changes, therefore, may not be consequential to $HBO_2$, but might be attributable to the decreased effects of novelty and anxiety over time as subjects became more comfortable and familiar with repeated scans in that environment. A similar finding was noted for "semiglobal CBF" in subacute TBI subjects treated with $HBO_2$ (24). Our cohort of five normal subjects scanned before and after one $HBO_2$ showed no significant change in regional perfusion. As there was no significant treatment effect in the head-injured group with one treatment with hyperbaric oxygen, there was no predictive value to this treatment in our study.

Both groups showed areas of significantly increased rCBF that would enlarge, decrease, or variably disappear and reappear over time. The nature of areas of increased rCBF in chronic TBI is unclear, but has been reported previously in stroke (25) and brain trauma (12) using different methodologies. Several possibilities might explain these changes. They may represent a persistence of chronic luxury perfusion (26), due to an irreversible breakdown of regulatory mechanisms that normally couple rCBF and metabolic need. They could also represent an

activation of redundant neurons, where an assumption of function by uninjured and previously underutilized neurons within a damaged area takes place. [27] The areas of increased rCBF might also be explained by vicariation, taking on functions formerly assigned to the damaged areas by other cortical areas as part of the mechanism of brain plasticity. [27]

Complications of $HBO_2$ did not occur. [28] One subject displayed increased agitation and decreased alertness after 110 $HBO_2$, necessitating his removal from the study. Although reduced frontal rCBF on SPECT has been found to correlate with behavioral disinhibition, and aggression has been correlated with reduced right hemispheric blood flow in severe TBI patients [29], we found no significant change in this subject's SPECT. Because his mental status returned to baseline two weeks after cessation of treatment, CNS oxygen toxicity is suspected.

We found wide variations in individual neuropsychometric testing in the $HBO_2$ subjects; consequently no correlation could be made to rCBF findings. Few longitudinal studies have examined serial SPECT brain scans in chronic TBI. A one year longitudinal study of patients with mild, acute TBI using a standardized radiological evaluation technique showed improvement in some SPECT lesions, which correlated in many cases with clinical findings over time. [30] A $Xenon^{133}$ inhalation study measuring global cerebral perfusion also reported correlations between higher global flow and higher cognitive scores as long as ten years post injury. [31] A retrospective study of 50 subjects having chronic traumatic brain injury and cerebral palsy showed at least 70 $HBO_2$s were necessary to achieve clinical improvement and increased cortical and hemispheric blood flow using sequential SPECT brain scanning. [32] None of these studies employed head injured controls. We were unable to find other studies of chronic head-injured patients that statistically analyzed regional perfusion changes in sequential SPECT scans using either voxel-by-voxel analyses, or region of interest analyses. In our small set of treated subjects who were at least three years post injury, we found no significant objective clinical or rCBF improvement.

Regarding the three goals of this study, our findings indicate: 1.5 ATA $HBO_2$ did not produce any clinical change in subjects with chronic TBI; statistical analysis of SPECT showed no evidence of chronic ischemic penumbrae in these subjects or changes in rCBF attributable to $HBO_2$; no evidence that SPECT preceding and following one $HBO_2$ could predict outcome. These results must be evaluated critically due to the extremely small sample size and lack of homogeneity in cerebral pathology inherent in a small group of individuals with TBI. Future research in this area may answer the question of whether $HBO_2$ has utility in the treatment of stroke or acute brain injury, as well as possible in-depth evaluation of other cerebral lesions.

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