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IMPROVEMENT IN CEREBRAL METABOLISM IN CHRONIC BRAIN INJURY AFTER HYPERBARIC OXYGEN THERAPY

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While no research study has yet demonstrated convincing evidence for the efficacy of Hyperbaric Oxygen Therapy (HBOT) in patients with chronic neurological disorders (CND), anecdotal studies have been supportive of its use in improving healing of the damaged brain. The current study hypothesized that (1) individuals with CND show increases in cerebral blood flow and metabolism as measured by Single Positron Emission Computed Tomography (SPECT) in the cerebral hemispheres, but not on measures of cerebellar and pons blood flow; and (2) younger patients show more improvement than older patients. The study used archival data to compare 25 older and 25 younger subjects who were given SPECT scans pretherapy, midtherapy, and posttherapy. ANOVAs using the SPECT scans as a within subjects variable and age as a between subjects variable confirmed the hypothesis that the cerebral measures all changed but that the cerebellar and pons measures did not. Post-hoc t-tests confirmed that there was improvement in blood flow from the beginning to the end of the study. An age effect was found on only two of the five measures; however, there were no interactions. Analysis by post-hoc t-tests showed that the younger group had higher

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blood flows, but not more improvement than the older group. The results provided the first statistical research data to show the effectiveness of HBOT in improving blood flow in CND. These results indicate that HBOT can be an effective part of the treatment for such clients. The implications of these findings and future research directions were discussed.

Keywords brain injury, head trauma, hyperbaric, oxygen, rehabilitation

Hyperbaric Oxygen Therapy (HBOT) is normally 100% oxygen at greater than the normal pressure of one atmosphere to allow additional oxygen to dissolve into the blood plasma, thereby increasing the amount of oxygen available to the cells of the body and the brain. In theory, HBOT can be employed to supply additional oxygen to help brain cells, which are dormant, to become active and aid intact cells in taking over functions previously completed by ischemic cells (Mehl-Madrona, 2000; Neubauer & James, 1998). Neubauer and Walker (2000) and others have argued that HBOT is an effective treatment for brain injury. However, as Nighoghossian et al. (1995) stated, "The effectiveness of HBOT exposure in humans relies mainly on anecdotal or uncontrolled studies" (p. 1369). A review of the literature on the effectiveness of HBOT in brain injury confirms this. These studies are limited to anecdotal conclusions based on the clinical experience of the author, along with some single-subject or small group studies (Hawkins et al., 2000; Mahi, 1998; Neubauer & Walker, 2000; Neubauer et al., 1994; Walker, 1996).

Previous studies have shared a lack of proper assessment of patient improvement, few subjects, and inadequate lengths of treatment. Few studies have had any physiological measures of change in the clients' brains, and few have used any quantitative measures of change or improvement. A necessary step in showing the effectiveness of this therapy is to show that HBOT actually changes brain activity. Anecdotal cases have suggested that SPELT scans can show such changes in the brain, by showing higher levels of activity as reflected by increased oxygen use. This study attempted to examine this problem and improve the scientific community's understanding of HBOT.

Based on the previous anecdotal research and theory, it was hypothesized that if chronic neurological diseases are treated using HBOT, then there may be a significant improvement in cerebral blood flow as measured by SPECT between a baseline and ending measure after the completion of an average of 70 treatments. This hypothesis is based on the Neubauer and Walker (2000) theory that HBOT can improve cerebral metabolism (as reflected by cerebral blood flow) by improving the functioning of neurons made dormant by a neurological disorder, as well as stimulating axonal growth and increasing the ability of normal neurons to function better and communicate with other neurons. It was further hypothesized that there would be a substantially greater improvement in cerebral blood flow and metabolism at the end of therapy then halfway through therapy. This is based on Neubauer and Walker's (2000) clinical observations that at least 50-80 HBOT treatments are necessary before substantial results can be identified.

Finally, it was hypothesized that if chronic neurological diseases are treated using HBOT, there should be an increase in blood flow and metabolism in the area of the cerebral hemispheres (including the basal ganglia) but not in the brain stem (represented by measurements in the area of the pons) and cerebellum. This is based on the evidence that blood flow is highest in the cerebral hemispheres (including the basal ganglia) and therefore these areas will improve most from HBOT when compared to control areas. In addition, the cerebral hemispheres (including the basal ganglia) represent areas of the brain that are most easily modified by changes in the brain environment as well as experience (Golden et al., 1992). These areas are more able to modify their function in response to numerous factors, which leads to sensitivity to positive influences (such as HBOT), as well as negative conditions (Pinel, 2000).

METHODS

Subjects

The subjects for this study were selected from approximately 300 files of patients who received HBOT from a South Florida medical

clinic from 1997-2000. The first 25 adult and 25 child consecutive subjects who met the following criteria were chosen:

1. Diagnosis of a chronic neurological disease that was permanent and not expected to improve medically on its own.
2. The availability of three SPECT scans: baseline (B), middle of treatment (M), and posttreatment (P).
3. A minimum of 15 treatments prior to the second SPECT (M) scan and a minimum of 50 treatments overall.
4. Were right-handed before the onset of their neurological disorder.

The average age of the 50 subjects selected was 25.00 *(sd* = 22.83). The average length of time since the onset of the neurological disorder was 60.40 months *(sd* = 57.47). Of the 50 subjects 46 were Caucasian, 3 were Asian, and 1 was African-American. The most common diagnoses made by the subject's medical doctor were Cerebral Palsy (30%), Stroke (12%), Traumatic Brain Injury (26%), Lyme Disease (6%), Anoxic Ischemic Encephalopathy (16%), and other (10%). Thirty-one subjects were male and 19 were female.

The younger group consisted of 25 subjects under the age of 18. The older group consisted of 25 subjects ranging in age from 18 to 85. The groups did not differ by chi-square in terms of sex, handedness, or ethnicity. The groups did differ by diagnosis, as the most frequent younger group diagnosis was Cerebral Palsy, while the most frequent older group diagnosis was Traumatic Brain Injury.

Instrumentation and Methodology

HBOT

All clients were administered HBOT under the direction of their physician for the length of time and intensity required for their medical treatment. In all cases, HBOT was administered at 1.25 to 2.5 atmospheres across the series of treatments, with the actual pressure determined by the patients' physician. Patients received treatment in a range from twice a week to 12 times a week (twice a day, everyday except Sunday). When receiving treatment, each patient

was placed in a monoplace (single subject) chamber. Patients were allowed to relax, and even sleep if desired.

SPECT Scans

All subjects received three SPECT scans to measure cerebral blood flow and metabolism. The first SPECT (B) was taken to establish a baseline. The second SPECT (M) was taken about halfway through treatment. The third SPECT scan was taken at the conclusion of this phase of therapy. All subjects received each SPECT scan under standard conditions using a single head multidetector camera system.

The CEL CINT single-head gamma camera allows for rapid scanning of an entire slice of the brain. It is a highly sensitive system that allows good spatial resolution as well as rapid imaging of the brain (or other organs of the body.) When a subject underwent a SPECT scan, they were intravenously injected with Technetium-99 Hexamethyl Propylamine Oxime (Tc-99-HMPAO) (with dose adjusted according to the client's weight) in a dark (dimly lit) room with eyes open. Tc-99-HMPAO, a lipid soluble macrocyclic amine, served as the radiotracer in this study. It has a half-life of 6 hr but only takes 16 min to reach maximum concentration in the brain. The distribution, however, remains constant for many hours after injection. Patients were imaged between 45 min and 1 hr after injection to allow surface scalp activity to dissipate. Each subject was allowed to rest lying down during this time, both to allow relaxation and clearance from the superficial veins around the skull, a period that is very important. Relaxation levels of the patient affect cerebral blood flow just as it does pulse, so agitation or high anxiety can affect results.

Calculating SPECT Measures

In order to obtain similar data from each subject, brain landmarks are identified in each of the SPECT scans from each subject. Brain landmarks identified in this study included the cerebellum, pons, frontal lobe, temporal lobes, and basal ganglia. Using these landmarks, the SPECT computer calculated cerebral blood flow and

metabolism (which were expressed in terms of expected normal blood flows) for the following areas:

1. **Right and Left Hemispheres at the level of the Basal Ganglia. Figure 1 shows the level of this slice (1) (the highest line) on a lateral image of the brain and the brain structures included in slice 1. The SPECT computer calculated blood *flow* independently for the left and right hemispheres at all four levels indicated in Figure 1. Slices 2, 3, and 4 are directly below slice 1 as indicated in Figure 1. Information from the four slices were summed and averaged to generate average right kemisphere and left hemisphere measures.**
2. **The SPECT computer calculated a single blood *flow* measurement for the pons as a whole.**
3. **The SPECT computer calculated a value for each of the two**

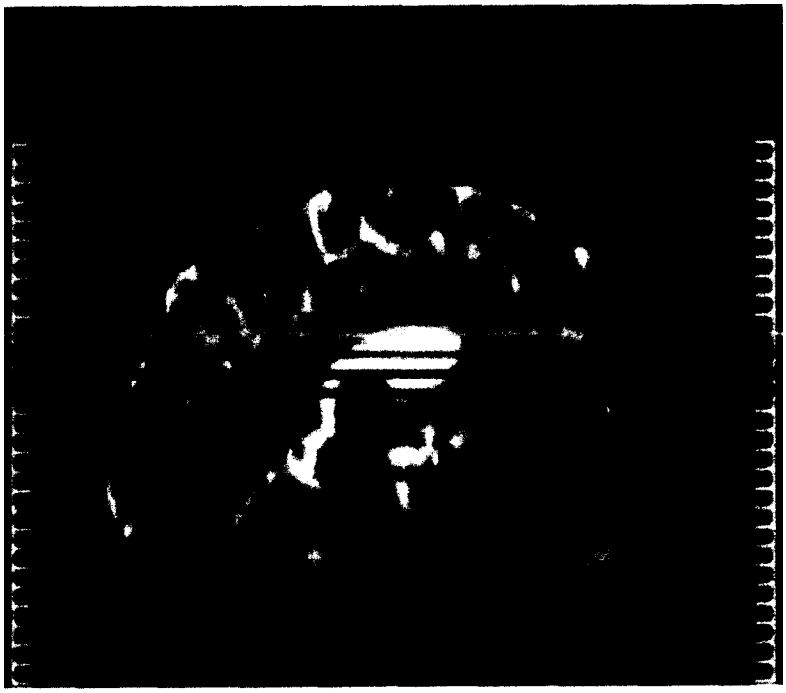

FIGURE 1. Slices for SPECT. See Color Plate I at the back of this issue.

hemispheres of the cerebellum, which were combined into a single average value.

4. The SPELT computer calculated values for frontal and temporal-parietal areas in both hemispheres. A single blood flow measure was generated combining frontal and temporal-parietal flows (right and left).

Each of these measures was calculated on each of the three SPELT scans (B, M, and P) for each of the subjects in the study, yielding 15 dependent measures for each subject.

RESULTS

Prior to the main analyses, the demographic and treatment variables (sex, ethnicity, number of treatments, time between SPELT scans, chronicity) were correlated with the dependent measures to see if they needed to be included in the analysis as additional factors. However, none correlated even at the $p < .20$ level, so none was included in the additional analysis. Means and standard deviations for treatment variables and all dependent measures can be found in Table 1.

According to a series of t-tests, the younger and older groups did not differ in chronicity or the number of treatments. However, they did differ in the length of time between the first SPELT (B) scan and the second SPELT (M) scan, but not in the total amount of time between the first and last SPELT scans. The groups did not differ significantly in terms of the number of treatments completed during this period.

Repeated Measures Analysis of Variance

Five repeated measures ANOVAs were run, one for each of the five dependent variables. Age group was used as a two level between subjects variable, while the three SPELT scans (B, M, and P) served as the repeated within subjects variable. Since five ANOVAs were completed, a $p < .01$ significance level was adopted so that the overall experiment level of significance was .05.

TABLE 1. Means and standard deviations for all study variables

Variable	*Mean*	*Standard deviation*
Age	25.00	22.83
Chronicity	60.40	57.47
Time SPECT 1-SPECT 2	34.00	29.99
Time SPECT 2-SPECT 3	118.48	112.93
Treatments SPECT 1-SPECT 2	32.58	15.28
Treatments SPECT 2-SPECT 3	45.64	25.18
Cerebellum SPECT 1	94.58	7.01
Cerebellum SPECT 2	95.44	7.58
Cerebellum SPECT 3	94.16	17.22
Pons SPECT 1	61.04	10.36
Pons SPECT 2	62.32	10.99
Pons SPECT 3	64.34	12.63
Right Hemisphere SPECT 1	66.62	10.77
Right Hemisphere SPECT 2	68.14	11.34
Right Hemisphere SPECT 3	71.92	13.22
Left Hemisphere SPECT 1	62.05	11.51
Left Hemisphere SPECT 2	64.28	12.51
Left Hemisphere SPECT 3	67.35	14.53
Cortical SPECT 1	67.66	9.97
Cortical SPECT 2	70.21	9.00
Cortical SPECT 3	74.34	12.21

Table 2 presents the results of the repeated measure ANOVAs for all five variables. As can be seen, there were significant differences across the repeated measure for the right hemisphere (RH), left hemisphere (LH), and cortical measures, but not for the pons and cerebellar blood flow measures. Figure 2 shows the percentage changes across SPECT scans for each area of the brain. This figure illustrates the differential effects of HBOT on the percentage increase in cerebral blood flow in these five areas. In addition, there were significant differences for the between group age factor for the

TABLE 2. Results of repeated measures analysis of variance

Variable	*Age*	*Blood flow*	*Interaction*
Pons	0.10	2.86	0.76
Cerebellum	0.13	0.10	0.42
Right hemisphere	10.12*	16.58*	0.24
Left hemisphere	15.06*	18.33*	0.06
Cortical	3.70	21.13*	0.00

*p <.01.

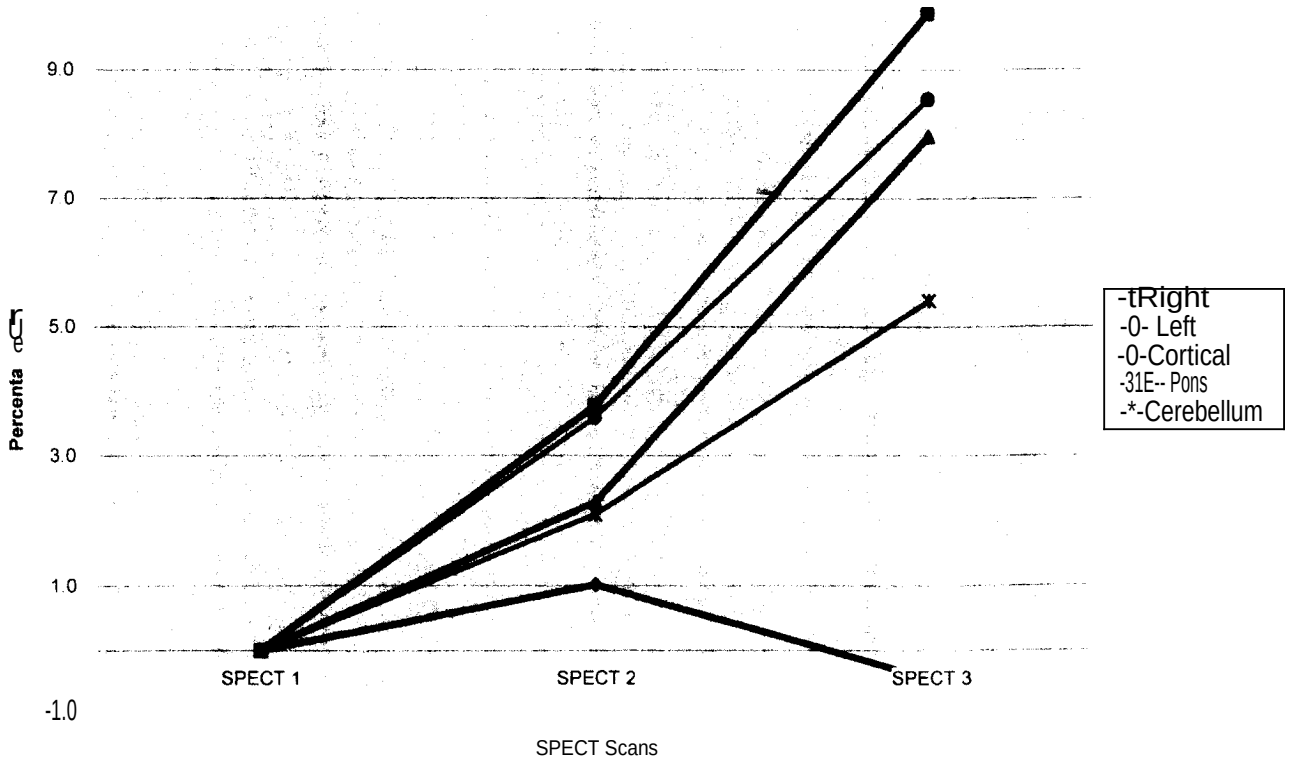

FIGURE 2. Percentage increase of blood flow over baseline.

TABLE 3. Comparison of the older and younger groups

	Younger group		Older group		
Measure	*Mean*	*SD*	*Mean*	*SD*	*T(48)*
Chronicity	56.92	38.08	63.88	72.19	-0.43
Time SPECT 1-SPECT 2	24.80	10.42	43.20	39.39	-2.25*
Time SPECT 2-SPECT 3	124.80	123.03	112.16	104.02	0.39
Treatment SPECT 1-SPECT 2	31.00	9.79	34.16	19.30	-0.73
Treatment SPECT 2-SPECT 3	47.40	21.88	43.88	28.46	0.49

SPECTI = baseline; SPECT2 = middle of treatment; SPECT3 = end of treatment.
*P < .0l

RH and LH measures but not for the remaining measures. There were no interaction effects on any of the measures.

Post-hoc t-tests were run for the age variable on the RH and LH variables across the age groups since age was significant for these variables (see Table 3). The younger group demonstrated significantly higher cerebral blood flow rates at baseline, during treatment, and after treatment on all RH and LH variables. However, since the interactions were all nonsignificant, the degree of improvement for each age group across all of the variables did not differ significantly. Since the repeated measures variable was significant for LH, RH, and cortical blood flows, post-hoc paired t-tests were calculated on each pair of the SPECT variables. The results of these paired t-tests were consistent across all three variables. There was a significant difference between the baseline SPECT (B) and the post-test SPECT (P), as well as the middle SPECT (M) and the post-SPECT (P). There was not a significant difference in any case between the baseline SPECT (B) and the middle SPECT (M). These results indicated that there was a consistent improvement overall, but no significant differences between the baseline SPECT (B) and the SPECT (M) taken during treatment.

DISCUSSION AND CONCLUSION

The three hypotheses were supported by the results. The first hypothesis reasoned that HBOT would leads to significant improvement in cerebral blood flow and metabolism as measured by SPECT

from the baseline measure to the end of the experiment with a minimum average number of treatments of 70 or better. The post-hoc paired t-tests showed that there was an overall increase in blood flow between the baseline SPELT (B) and the post-SPELT (P) for the RH, LH, and cortical measures. It should be noted that a longer length of treatment may have produced larger changes, a hypothesis which needs further study.

The second hypothesis argued that there would be a greater improvement in cerebral blood flow at the end of therapy than halfway through therapy. The paired t-tests showed that the post-SPELT blood flows were higher than the midtreatment SPECTs for the RH, LH, and cortical measures. In addition, the tests showed that there was not a significant difference between the baseline SPELT and the midtreatment SPELT for each of these measures. Thus, the improvement in blood flow and metabolism did not occur until there were a substantial number of treatments. The third hypothesis stated that an increase would occur in the area of the cerebral hemispheres (including the basal ganglia), but not in the brain stem (represented by the measurements in the pons) or cerebellum, physiologically older and more basic structures of the brain. This can be seen in both Table 2 and Figure 2.

Despite the overall success of the study in confirming the main hypotheses, the study also had significant limitations. First, only patients who were paying for their own treatment were included in the study. Neither the client nor the physician was blind to the intent of the treatment. This could have created a problem due to a placebo effect, but since SPELT scans rather than client or physician opinions were used as the measure of improvement, this is unlikely.

Second, a traditional control group was unavailable as only referred patients received HBOT. The patients in the present study acted as their own controls, although this may not always control for such extraneous factors as other treatments, medication, and motivation. Use of a control group would have allowed an evaluation of whether just repeated SPECTs were the cause of the increase in blood flow. In addition, it might be suggested that exposure to the HBOT may increase blood flow temporarily even after treatment is completed as a side effect of the treatment rather than reflecting

real change in brain metabolism. These issues were addressed in two ways. The use of the intermediate SPECT scan in the middle of treatment was intended to show that the effect being seen was due to prolonged treatment rather than just exposure. Thus, the intermediate SPECT acted as an additional control, which suggests that extraneous factors were not responsible for the outcome.

In addition, the inclusion of the pons and cerebellar measures, which were not expected to improve, served to make this a multiple baseline study. The absence of change in the pons and cerebellar measures shows that the change in the other three measures were not due to any general factor such as a placebo effect or increased client arousal or other unrelated factors. The use of patients with chronic, stable disorders with long traditional treatment histories also made spontaneous improvement unlikely.

Although there was overall improvement, an inspection of individual data showed that some clients did not improve. In fact, three subjects had cerebral blood flow actually decline over the length of the treatment. In all three cases, the subjects were in the younger age group and took at least five months off between their first and second series of treatments. It is possible that this large amount of time with only a minimal number of treatments, followed by a period of no treatments for a long period of time, may cause regression to baseline levels. Later treatment does not build on the effects of the earlier treatment but rather starts over again. This possible cumulative effect may be necessary for the brain to make permanent improvement or to move towards a self-continuing process, which will persist when treatments are ended. This is supported by the failure to find significant changes at the midtreatment SPECT evaluation.

Pathology may also have an effect on these results. The role of HBOT in different types of disorders has not been well documented or evaluated. Unfortunately, in this study there were inadequate numbers of individuals with any one pathology to be able to test for differences between these groups. Future studies are needed to compare the results of different pathologies when treated by HBOT to see if it is more effective in certain groups. Future studies may also be able to examine improvements in the subject's cognitive skills and activities of daily living to see if there is a correlation

between changes on the SPECT and actual behavioral changes in the subject's life. It is clear that even if blood flow increases, it will not be useful if there are no actual changes in what the client can do.

This study has multiple implications: (1) it can serve as preliminary data to guide future research; (2) it shows for the first time that HBOT can be shown to cause significant changes in the metabolism of the brain; and (3) it can serve as justification for expansion of this treatment to other patients who might show improvement in the quality of their recovery. While other studies are clearly necessary to follow up on this work, these findings suggest that HBOT should be seriously considered as a treatment in chronic brain injury. The potential for this treatment modality is significant for this very impaired population.

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