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Short communication

Pilot case study of the therapeutic potential of hyperbaric oxygen therapy on chronic brain injury

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Abstract

Background: Recently, the effect of hyperbaric oxygen (HBO_2) therapy was explored in the treatment of chronic TBI. It has been speculated that idling neurons in the penumbra zone remain viable several years after injury and might be reactivated by enhanced oxygenation. We studied the therapeutic potential of HBO_2 therapy in a 54-year-old man who had sustained traumatic brain injuries one year before testing that resulted in permanent neurological symptoms.
Methods: Two treatment series separated by a one-year inter-session interval were administered. Treatment series consisted of 20 and 60 daily one-hour exposures to 100% oxygen at 2 ATA. Electrophysiological (event-related potentials), metabolic and behavioral (sensorimotor and neuropsychological) measurements were obtained to evaluate the effects of hyperbaric oxygen therapy on neurocognitive functioning.
Results: Following the initial treatment, the patient showed improvements in sensorimotor functions, as well as enhanced P300 amplitude in the damaged hemisphere. Although most of these gains were no longer observed one year after treatment, these were reinstated with an additional series of 60 exposures. Neuropsychological improvements were also observed after the completion of the second series of treatments.
Conclusion: The present single-case study provides preliminary evidence of neuropsychological and electrophysiological improvements after series of 20 and 60 treatments, although the first dosage appeared to be insufficient to produce permanent benefits. Longitudinal studies using different treatment parameters should be conducted if we are to systematically investigate long-term improvements resulting from HBO_2 therapy.

Keywords: Hyperbaric oxygen; Brain injuries; Neuropsychology; ERPs; P300; SPECT; MRI; Case report

1. Introduction

Despite increasingly rapid intervention, medical experts are still struggling when attempting to reduce the adverse impact of a reduction of cerebral blood flow in the affected area following brain injury (TBI) and cerebrovascular (stroke) accidents. Treatment alternatives offered to TBI and stroke patients are primarily concerned with emerging complications in an attempt to preserve the patients' well-

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being and overall quality of life [1]. Improvements after brain injury resulting from a combination of spontaneous recovery and rehabilitation efforts are well-documented [2]. In fact, intensive functional therapy and rehabilitation programs are considered essential to minimize cognitive and physical sequelae associated with acquired brain injury in order to maximize the patient's quality of life. However, these programs are often only partially successful such that alternative approaches dedicated to the metabolic recovery of vulnerable cerebral tissues and others that attempt to limit the negative impact of ischemic insults need to be further explored in order to improve the functional outcome of a patient's acquired brain injury.

One of the goals in treating cerebral ischemia is to increase cerebral perfusion pressure and blood O_2 content with the use of supplemental O_2 [3]. For this reason, hyperbaric oxygen (HBO_2) therapy has recently been considered to offer new possibilities of recovery for patients with brain injury. However, a conservative approach is mandated due to our insufficient understanding of the underlying effects of high-concentration oxygen therapy on metabolic processes and much uncertainty remains about its potential risks and relatively unexplored long and short-term side effects [4]. So far, the application of HBO_2 has only been approved for medical conditions for which extensive clinical trials have been carried out to document its effectiveness and low risk. Some of these conditions are gas embolism, carbon monoxide poisoning, myonecrosis, crush injury and other acute traumatic ischemic events, as well as decompression sickness, thermal burns and exceptional blood loss [4]. Therefore, further investigations are required before this treatment alternative can be more widely used in the treatment of brain-injured patients.

HBO_2 therapy entails the inhalation of high concentrations of O_2 (94–100%) at pressure higher than sea level. Its effects result from the combined action of hyperoxia and hyperbaria, the pressurized pure O_2 being dissolved in all bodily fluids, especially in the plasma and cerebrospinal fluid [5,6]. At two atmospheres absolute (ATA) for instance, the plasma O_2 tension rises above 1110 mm Hg, whereas it merely reaches 98 mm Hg in normal environmental conditions at sea level. Thus, in the hyperbaric condition there is a ten-fold increase in the amount of O_2 that reaches hypoxic brain tissues. This therapy is well tolerated and considered safe when used according to standard protocols with oxygen pressures not exceeding 3 ATA and treatment sessions limited to a maximum of 120 min [7].

Most studies based on case reports, clinical trials and animal work suggest that patients with neurological conditions such as brain injury and cerebrovascular disease may derive some benefits from HBO_2 therapy, especially in the acute stage, since hypoxia and ischemia are frequently involved in the pathophysiology. Although the efficacy of HBO_2 therapy still remains speculative, its appeal lies in its potential for preserving ischemic tissue by providing enough O_2 for the maintenance of a normal neuronal metabolism [8,9]. It has been assumed that HBO_2 may enhance "idling neurons" function by increasing oxygenation in the cerebral ischemic penumbra where the neurons are thought to be still viable although metabolically "lethargic" and electrically nonresponsive [10,11]. These cells may have sufficient oxygen to maintain ion pump mechanisms but not enough to generate action potentials and be fully functional [12]. The interruption of metabolic and electrical function that characterizes this intermediate zone is thought to be reversible when additional oxygen is made available to these cells [13]. Most researchers believe that physiological recovery of cortical functions is limited to a short period ranging from 30 min to a few hours after injury, depending on the duration of the ischemic event and the magnitude of cerebral perfusion within the cerebral blood flow range that defines the penumbra [13–15]. In fact, HBO_2 research has shown that the time elapsed between the brain insult and treatment is critical for restricting the damage induced by cerebral infarction. According to these studies, the optimal therapeutic window in which to initiate therapy should be within 6 h from the accident [8,16,17]. On the other hand, some investigators suggest that neurons in the ischemic penumbra remain viable for a longer period of time, lasting from 4 months up to several years after brain insult, and that the idling neurons could still be reactivated by exposure to HBO_2 [18–22]. However, there is a paucity of studies that have investigated the effect of HBO_2 therapy in the postacute stage (6 months or more after the insult), at which time brain-injured patients usually experience permanent neurological symptoms.

An important limitation to the study of HBO_2 is that major methodological issues are at the core of most studies reported in the literature. In fact, researchers often have to rely on anecdotal studies that have generally supported the efficacy of HBO_2 in the treatment of TBI. In this context, our group conducted the first double-blind analysis of children suffering from cerebral palsy who were submitted to a series of HBO_2 treatments [23,24] and found that exposure to HBO_2 treatments was no more beneficial than a "placebo treatment". With regard to TBI, a recent meta-analysis has only identified two fair-quality randomized controlled trials of patients with severe brain injury [25]. However, these two studies investigated the effects of this treatment alternative in the acute phase following the injury, which cannot validate the efficacy of HBO_2 offered to patients in the chronic phase following TBI [26]. Therefore, the present case study is intended to provide the first objective examination of the therapeutic value of repeated exposure to HBO_2 after clinical stabilization has taken place in a chronic severe brain-injured patient. This pilot study systematically assessed neurological/neurocognitive changes resulting from series of HBO_2 treatments using event-related potentials, neurobehavioral and metabolic measures.

2. Case history

The patient (M.P.) is a 54-year-old man, who was a senior executive in the civil service when he was involved in a motor vehicle accident that resulted in a polytrauma 11 months prior to his participation in the present study. He sustained a left cervical hematoma, as well as multiple fractures including the sternum, the left orbital floor and left mandibular angle. The neurological examination was normal on admission, but M.P. gradually developed speech problems and a right-sided hemiparesis over the ensuing days. Results of a CT scan and an arteriography performed a few days later revealed the evolution of a left lacunar infarction with associated changes in the territory of the left middle cerebral artery as a result of a thrombosis of the left carotid artery. More precisely, an infarction was localized at the level of the genu and posterior limb of the internal capsule, which is indicative of a lesion of the anterior choroidal artery and an infarction extending to the corona radiata and the semioval center, which reflects an hemodynamic infarction in the territory of the left carotid artery. MRI performed prior to the onset of the study revealed multiple ischemic changes in the left cerebral hemisphere, most likely related to the history of carotid dissection. The T1 weighted images showed multiple hypointense foci involving the left basal ganglia and periventricular white matter, as well as some callosal atrophy. In the T2 weighted and FLAIR sequences, several lacunar infarcts involving the deep white matter and the basal ganglia were noted. Changes were also identified in the left cerebral peduncle and in the area of the cortico-medullary tract, and a lacuna was found most marked in the area of the genu of the left internal capsule. Finally, the left lateral ventricle was dilated as a consequence of neuronal loss. These findings were unchanged at the follow-up examination after completion of the first series of 20 HBO_2 treatments.

Clinically, M.P. presented with a left temporal hemianopsia and a severe hemiparesis affecting the right superior and inferior limbs. He was unable to lift his right arm against gravity, although having a 1/5 motor grip of the right hand. Furthermore the right leg strength was evaluated at 3/5, and the right side was hyperreflexic. In contrast, motor and sensory functions as well as reflexes of his left hemibody were normal. Cognitive functioning was also significantly impaired. Language testing revealed a severe mixed aphasia (mostly expressive) as well as a verbal and buccofacial apraxia. Important deficits were further noted in the areas of attention and working memory, mental control and self-regulation of behavior, executive functions, reasoning ability and praxis. His non-verbal QI assessed on the performance subscale of the Wechsler Adult Intelligence Scale-third edition (WAIS-III), 2 months prior to the exposure to HBO_2 fell in the mildly deficient range.

3. Procedure and materials

The study comprised two phases. The initial phase consisted of 20 daily one-hour exposures to HBO_2, administered over a one-month period. The number of treatments was based upon previous HBO_2 studies with consideration given to the fact that a minimum of 10–15 treatments is necessary to induce observable clinical changes in moderate to severe brain injuries [19]. When positive results were obtained, a second series of treatments comprising 60 additional sessions were provided one year later. The larger number of sessions in Phase 2 was based on research suggesting that improvements are greater with increasing number of HBO_2 treatments [18,27]. Rehabilitation services (speech therapy and physical therapy) were interrupted during the two phases of the study.

After providing full written informed consent, P.M. underwent a medical and neurological examination to obtain medical clearance for HBO_2 therapy. Treatments were administered in a Perry Sigma Plus monoplace chamber (Perry Baromedical, Riviera Beach, FL), at the Cleghorn Hyperbaric Oxygen Laboratory of McGill University under the supervision of a specialized technician and a physician. Treatment sessions consisted in the inhalation of 100% pure oxygen (O_2) at a pressure of 2 ATA for 60 min. Compression and decompression of the chamber was performed at a mean rate of 0.1 ATA/min, for a total duration of approximately 20 min.

In the initial phase, ERPs were used as the main outcome variable. These were accompanied by a brief sensorimotor examination. Testing involved in the initial phase of this pilot study was carried out within 2 days before initiating HBO_2 treatments to collect baseline measures and then 2 days following the completion of the first series of HBO_2 treatments. Phase 2 of this experiment involved a more extensive assessment of brain functioning that included functional neuroimaging (SPECT), a more extensive sensorimotor examination, a complete neuropsychological assessment and ERP recordings. Testing was carried out before and after HBO_2 therapy. In addition, ERP recordings, SPECT and measures of cognitive flexibility were obtained at midpoint that is, after the 30th session.

3.1. Sensorimotor evaluation

Physical functions were assessed using the Berg Balance Scale [28], an instrument that is currently used in clinical practice to evaluate rehabilitation outcome. The scale consists of 14 items of increasing difficulty, graded on a five-point ordinal scale where 0 represents the inability to perform the task and 4 indicates independence (Table 1).

The initial assessment of sensory functions consisted of the localization of a light finger touch applied to the face, arms, legs and feet. M.P., with his eyes closed, was asked to lift his left hand every time he felt the stimulation. In the second phase of the study, a more extensive sensorimotor assessment was performed. To evaluate gait velocity, the subject was asked to walk as fast as possible. The time taken to walk 6 m was recorded. Muscular strength of the knee extensors was assessed with a dynamometer (Spark

Table 1
Motor function measures

The Berg Balance Scale items [28] (Berg et al., 1992)
1. Sitting to standing
2. Standing unsupported *
3. Sitting unsupported *
4. Standing to sitting
5. Transfer
6. Standing with eyes closed *
7. Standing with feet together *
8. Reaching forward with outstretched arm *
9. Retrieving shoe from the floor
10. Turning to look behind *
11. Turning 360° *
12. Placing alternate foot on stool *
13. Standing with one foot in front *
14. Standing on one foot *

* For selected items, the subject is asked to maintain position for a given time. Points are progressively deducted when required time limits or distance are not met.

dynamometer). For this test, the subject was seated and instructed to maximally extend the paretic knee. Sensitivity of the elbow, forehead, external maleollus and cheek was measured using Semmes–Winstein filaments. Two measurements were used for each stimulated site. These sensorimotor measures were taken within 48 h before and after HBO_2 therapy.

3.2. SPECT neuroimaging

Cerebral blood flow investigations were performed in the second phase of this study within 2 days prior to, at mid-point and after completion of the HBO_2 therapy using ^{99m}Tc-ECD (Ethylene Cysteinate Dimer; Neurolite®, DuPont; average dose: 925 MBq) and SPECT imaging. Acquisition was initiated approximately 45 min following intravenous injection of the radiopharmaceutical. The camera used was a dual-head system with high-resolution collimators (Vertex, from ADAC Laboratories, Milpitas, CA). Sixty-four (64) projections of a duration of 40 s each were obtained on 64×64 matrices. Two simultaneous acquisition windows were used, centered on 120 keV and 140 keV and both had a 15% width; the first window was used for Compton scattering correction by subtracting 40% of the activity in that window from that in the second peak window on a pixel by pixel basis. After this first correction, the resulting projections were filtered through an in-house developed, adaptative Wiener filter. This was followed by an attenuation correction, using a modified Chang algorithm. The reconstructed volume for each study was then co-registered to the Talairach and Tournoux Atlasm using our adaptation to SPECT of the Minoshima algorithm for ^{18}F-FDG. This allowed for direct comparisons of the slices obtained at pre-, mid- and post-therapy time, and to analyze the chronological changes in cerebral blood flow and metabolism along the course of the treatments.

3.3. Neuropsychological evaluation

A complete neuropsychological assessment, using standardized tests, was performed in Phase 2 of the study, covering domains of attention, executive functions, language, memory and praxis.

3.3.1. Attentional processes

Measures of attention included the auditory and visual versions of the Test of Variables of Attention (TOVA) [29]. This computerized continuous performance test is objective, highly accurate and has been standardized in a large adult population. Four aspects were assessed: 1) Attention, defined by the number of *correct responses*; 2) Self-control, reflected in the number of *correct non-responses*; 3) Processing speed, measured in terms of reaction times in milliseconds; and 4) Fluctuation of attention as reflected in response time variability. The subject had to press the response button as quickly as possible every time he saw or heard the target stimulus (a square with a hole near the top or a high-pitch sound), but to ignore non-targets (a square with a hole near the bottom or a low-pitch sound).

3.3.2. Executive functions

Executive functions can be conceptualized as comprising four components: volition, planning, purposeful action and effective performance [30]. Planning and programming abilities were assessed with the Rey–Osterrieth Complex Figure and the Taylor Complex Figure used at retest [31]. The latter figure contains the same number of elements and has been created as an alternative version to the Rey–Osterrieth figure to control for potential retesting biases. Scores were based on the 36-point scoring system developed by Osterrieth and Taylor [30]. Self-regulatory abilities were assessed using a computerized version of the Stroop Color Word test, originally developed by Stroop [32]. This test purports to assess cognitive flexibility. In the computerized version, the subject has to judge whether the name of a colored word on the screen corresponds to the font color (for example, the word *RED* written in green) by pressing a key located on his left hand-side for congruent stimuli or on his right hand-side for incongruent stimuli as quickly as possible. Reaction times (RT) for incongruent stimuli are usually slower and are thought to reflect the Stroop interference effect. One hundred eighty (180) stimuli were presented on a white background for 100 ms. Congruent and incongruent stimuli were randomly presented in each testing session.

3.3.3. Memory processes

In light of M.P.'s severe language difficulties, memory abilities were assessed using tests for which both the material presented and the response to be provided were in the visual modality. Working memory was evaluated with the Spatial Span subtest of the Wechsler Memory Scale-III (Wechsler, 1997). This test features ten cubes that are randomly arranged

on each half of a board. The task requires participants to touch some of the blocks exactly in the same sequence as those just touched by the examiner. Sequences of increasing lengths are administered both forward and backward [31]. Long-term memory was evaluated using the Human Faces subtest of the Denman Neuropsychology Memory Scale (Denman, 1987), as well as the 24-Figure and 24-Sentence subtests of the *Batterie d'Efficience Mnésique* 144 (B.E.M. 144). In these two subtests, subjects were presented 24 target stimuli (either figures or sentences) that had to be recognized among non-target stimuli (figures or sentences). To test incidental visuospatial memory, we used the Complex Figures of Rey–Osterrieth and Taylor described above. M.P. was asked to draw from memory a complex figure respectively 3 min (immediate memory) and 30 min (delayed memory) after its copy.

3.3.4. Linguistic functions

Word comprehension was evaluated with the French version of the 175-item Peabody Picture Vocabulary Test-Revised (EVIP) where M.P. had to choose among a selection of four pictures the one that corresponded with the word given by the examiner. Verbal comprehension was also assessed with the Token Test, which includes a total of 39 verbal commands of increasing length and complexity that the subject has to carry out. The Chapman–Cook Speed of Reading Test was used to investigate the comprehension of written language. In this test, the participant is asked to read silently short paragraphs and to cross out a word from each of them that distorts its meaning. As for expressive language, confrontational naming was assessed with the Boston Naming Test (BNT).

3.3.5. Praxis

Ideational praxis was tested by asking M.P. to perform complex sequences of action involving the use of more than one object (e.g. lighting a candle or putting a letter into an envelope). Assessment of ideomotor praxis included the execution of various activities on verbal command such as pantomiming transitive object-use gestures (e.g., combing hair and painting a wall with a brush) and conventional communication gestures involving symbolic combinations of movements and meanings (e.g. military salute).

3.4. Electrophysiological measurements

Oddball paradigms are typically used in order to elicit prominent P300 waveforms. This paradigm involves the serial presentation of either a frequent stimulus (75% of the total number of trials) or a rare stimulus (remaining 25% of trials). The rare stimulus is known to elicit higher P300 amplitude than the frequent stimulus, especially at parietal electrode sites [33]. For the purpose of this study, a visual Oddball paradigm was used. The stimuli, a star and a circle, of 100 mm × 100 mm dimension, were successively presented in the center of a computer monitor for 100 ms. The shape designated as the rare stimulus was counterbalanced across the different testing intervals according to the following order: 1) baseline = star; 2) mid-testing = circle; 3) post-HBO_2 = star. M.P. was instructed to respond as quickly as possible by pressing the left button of a response box when presented with a rare stimulus while the presentation of a frequent stimulus required the absence of a motor response. The test included a total of 280 trials. Data were collected using an InstEP acquisition device. ERP recordings were obtained from 30 tin electrodes mounted on an E-Cap (Electro-Cap International Inc.). The electrodes were positioned on the scalp at Fp1/Fp2, AF3/AF4, F7/F8, F3/F4, Fz, FC3/FC4, T7/T8, C3/C4, C1/C2, Cz, TP7/TP8, CP3/CP4, P7/P8, P3/P4, Pz, O1/O2, and at Oz according to the standard electrode position nomenclature of the American Electroencephalographic Society [34]. Online reference was based on linked earlobes and the electrodes' impedance was kept below 5 kΩ, with no noticeable asymmetry in resistance. Eye movement artifacts were controlled horizontally with electrooculogram (EOG) electrodes placed at the outer canthi of both eyes and vertically with electrodes placed above and below the right eye. Signals were recorded via a SAI amplifier with filter settings at 1.6 and 30 Hz. After having performed baseline and eye blink corrections, epochs with amplitudes exceeding 150 μV were rejected from data processing and averaging. The P300 wave component was defined as the highest positive deflection occurring within the time window of 250–550 ms post-stimulus, with the Pz peak amplitude and latency being used as basic reference for the remaining electrodes.

3.5. Statistical analyses

Based on previous Oddball paradigm studies, the amplitude and latency of the P300 wave were computed in response to the rare stimulus only [35] at the 28 recording sites and averaged for the 280 stimuli, using the StatMap3D program for topographical analysis of EEG brain functioning. To evaluate changes in brain activity before, throughout and after the course of HBO_2 treatments, statistical analyses were performed using Friedman and Wilcoxon signed-rank tests, scalp recordings being subdivided with respect to the central region (Fz, Cz, Pz, Oz), the left hemisphere (AF3, F3, FC3, C1, C3, CP3, P3, F7, T7, TP7, P7, O1) and the right hemisphere (AF4, F4, FC4, C2, C4, CP4, P4, F8, T8, TP8, P8, O2).

For the neuropsychological assessment, M.P.'s performances were scored according to normative data provided in the test manuals. Statistical analysis was carried out for all cognitive domains, using the Sign Test. Significance levels were set at 0.017 for the ERP measurements, using the Bonferroni approach to account for the multiplicity of testing, and at 0.05 for all other measures (neuroimaging, neuropsychological and sensorimotor testing). Reliable Change Index (RCI) was computed to assess the clinical significance of performance differences on neuropsychological tests

administered before and after the second HBO_2 treatment series. Clinically significant performance differences were disclosed whenever RCI > 1.96.

4. Results

4.1. Phase

4.1.1. Sensorimotor evaluation

In the initial phase of the study, physical and sensory functions improved upon completion of the 20 HBO_2 sessions. M.P.'s balance was steadier, as evidenced by scores improving from 46 at baseline to 52 out of 56 possible points on the Berg Balance Scale after HBO_2 therapy. He was able to step on a stool when required to alternate from one supporting leg to the other, a movement that was previously impossible to perform. Furthermore, he could stand on one foot while the other one extended forward for the full time required (30 s), as well as to perform a 360-degree rotation more quickly.

Somatosensory functions also improved after HBO_2 therapy. M.P. was able to localize a few areas on the right hemibody, such as the cheek and the external face of the forearm and foot, where no sensation was reported at baseline. Furthermore, he reported feelings of tingling all over his right hemiface after the first treatment session and, later during the treatments, in his right arm. It was also noticeable that his right feet, which had been red before treatment, regained normal skin color.

4.1.2. Electrophysiological measurements

When electrodes were pooled in regions of interest, the amplitude of the P300 component was found to be significantly enhanced in the damaged hemisphere following HBO_2 therapy (left; $p < 0.01$), whereas the deflection of the P300 component recorded at central electrode sites ($p > 0.27$) and over the right cerebral hemisphere ($p > 0.071$) was unaffected by treatment (refer to Table 2 and Fig. 1). No statistical difference between the latency of the P300 waveform recorded at baseline was found when compared to those obtained following therapy at either central electrode sites ($p > 0.063$), right cerebral hemisphere pooled electrodes ($p > 0.09$), or pooled electrodes from the damaged hemisphere ($p = 0.12$) (refer to Table 2 and Fig. 1).

In sum, marked improvements were noted shortly after the first series of 20 HBO_2 sessions in a number of sensory and motor functions, which were paralleled by electrophysiological measures.

Table 2
Phase 1 — mean P300 amplitude and latency (± standard deviation) elicited by the rare stimulus in the visual oddball task

Subregions	Pre-20 HBO	Post-20 HBO	p value
	Mean ± SD	Mean ± SD	
P3 amplitude (μV) subregions			
Central	5.0 ± 1.9	4.3 ± 2.0	NS
Right hemisphere	3.8 ± 1.8	2.6 ± 2.3	NS
Left hemisphere	3.0 ± 1.4	4.6 ± 1.1	*
P3 latency (m sec) subregions			
Central	492 ± 34	450 ± 40	NS
Right hemisphere	493 ± 57	459 ± 34	NS
Left hemisphere	459 ± 58	465 ± 40	NS

Electrodes values were pooled in subregions.
*Level of significance: $p < 0.017$.

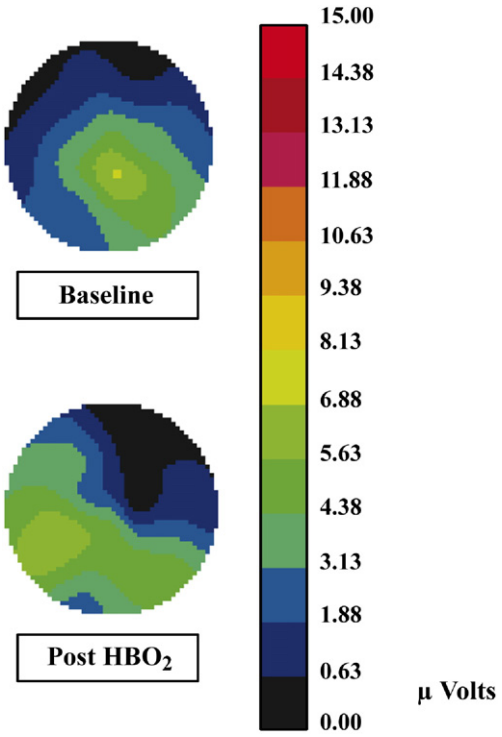

Fig. 1. Phase 1 — M.P.'s P300 amplitude distribution on the scalp, recorded at baseline and post-20 HBO_2 treatments in the visual oddball task. The frontal area of the scalp is represented on top and the occipital one, at the bottom.

4.2. Phase 2 — series of 60 HBO_2 treatments administered one year after Phase 1

4.2.1. Sensorimotor evaluation

The improvements in balance observed in the initial phase were only partially maintained one year after intervention, as revealed by a decrease from 52 to 49 out of a possible total score of 56 on the Berg Balance Scale. Upon completion of an additional 60 HBO_2 sessions, however, the observed loss was fully recovered (see Table 3). In fact, further gains in gait velocity, strength of the knee extensors on the paretic side and an increased sensitivity of the forehead resulted from the second series of HBO_2 treatments when contrasted with measures taken upon completing the initial phase of this study, whereas the sensitivity of the elbow, maleollus and cheek remained unchanged.

Table 3
Phase 2 — summary of sensorimotor measurements

Domains/tests		Baseline	Mid-HBO	Post-HBO
Berg Balance Scale (/56)		49	–	52
Paretic side (right hemibody):				
Gait velocity (meter/sec)	1st measure	0.66	0.76	0.86
	2nd measure	0.81	0.77	0.89
	3rd measure	0.75	0.72	0.88
	Mean	0.74	0.75	0.88
Dynamometer:				
Knee extensors (kg)	1st measure	15.6	15.2	18.8
	2nd measure	15.0	18.0	18.7
	3rd measure	16.0	21.2	19.6
	Mean	15.5	18.1	19.0
Semmes–Weinstein filaments/sensitivity:				
Elbow	Left side	5.88	6.10	5.88
	Right side	5.88	5.88	5.88
External maleollus	Left side	5.88	6.10	5.88
	Right side	5.88	5.88	5.88
Cheek	Left side	5.18	5.28	5.18
	Right side	5.18	5.07	5.18
Forehead	Left side	5.88	5.88	5.18
	Right side	5.88	5.46	5.46

4.2.2. Neuropsychological assessment

A complete battery of neuropsychological tests was administered before initiating the second series of HBO_2 treatments and following its completion. These results are summarized in Table 4. The computed Wilcoxon signed test yielded a significant treatment effect based on a composite neuropsychological test score obtained after 60 HBO_2 treatments when contrasted with that gathered before initiating this second treatment series ($p<0.01$).

4.2.2.1. Attention and executive functions. M.P.'s ability to detect target stimuli included in the auditory TOVA was perfect both at baseline and after having completed the second series of HBO_2 treatments (58th percentile both at baseline and following HBOT). The performance of M.P. was near perfect at the visual counterpart of the TOVA before treatment (baseline: 70th percentile), whereas P.M. missed three extra targets after treatment (post-treatment: <0.1 percentile). However, Reliable Change Index showed that this performance difference was not clinically significant (RCI=1.58; $p>0.05$). M.P.'s ability to inhibit non-target stimuli slightly improved from baseline to post-treatment (baseline: <0.1 percentile; post-HBOT: 68th percentile). This performance difference, however, did not reach clinical significance according to Reliable Change Index (RCI=1.32; $p>0.05$).

When we investigated the effects of HBO_2 therapy on information processing speed, the mean RT obtained either in the auditory or the visual conditions of the TOVA were below normal range before initiating the second treatment series and hardly changed as a result of therapy (auditory modality at baseline: 9th percentile; and post-HBO_2: 3rd percentile; visual modality at baseline: 5th percentile; and post- HBO_2: 16th percentile). In contrast, RT variability at the auditory TOVA was significantly reduced after treatment (baseline: 5th percentile; post-treatment: 61st percentile) (RCI=2.68; $p<0.05$), whereas that of its visual counterpart remained unaffected by treatment (baseline: <0.1 percentile; post-treatment: <0.1 percentile) (RCI=1.07; $p>0.05$). Similarly, we found a gradual decrease in RT on the Stroop test, although remaining severely impaired (baseline: <1st percentile; post-HBOT: <1st percentile). This improvement was mainly attributed to faster reaction time to process incongruent stimuli. However, no improvement was made in terms of perseverative errors following the second treatment series as his performance remained well below average (baseline: <1st percentile; post-treatment: <1st percentile). Reliable Change Index used to test for clinical significance could not be computed as test–retest reliability has yet to be determined for the version of the Stroop test used in this study.

4.2.2.2. Visuospatial abilities. The copy of the Rey–Osterrieth Complex Figure performed at baseline and that of Taylor was equivalently impaired as the slight improvement post-treatment was not found to be clinically significant (baseline: <1st percentile; post-treatment <1st percentile) (RCI=1.33; $p>0.05$).

4.2.2.3. Memory processes. As for working memory abilities, M.P.'s performance on the spatial span significantly increased after HBO_2 therapy (RCI=2.06; $p<0.05$); his level of performance improving from very inferior to within normal range (baseline: 12th percentile; post-HBO_2: 42nd percentile). Long-term memory for faces (Denman) was kept constant in the high average range both prior to treatment and following HBO_2 therapy (baseline: 55th percentile; post-HBO_2: 62nd percentile) (RCI=0.71; $p>0.05$).

Visual recognition of the 24 figures of the BEM-144 was initially inferior to the normal range and improved after having completed the second treatment series up to within the low average range (baseline: <3rd percentile; post-HBO_2: 44th percentile). Reliable Change Index used to test for clinical significance could not be computed as test–retest reliability for the latter measure has yet to be determined.

Similarly, delayed recall of the Rey–Osterrieth Complex Figure, which was far below average at baseline, improved up to the low average range after treatment on the Taylor Complex Figure (baseline: <1st percentile; post-HBO_2: 24th percentile). However, Reliable Change Index did not reach clinical significance (RCI=0.76; $p>0.05$).

Table 4
Phase 2 — summary of neuropsychological test scores

Cognitive domain and test	Phase 2						
	Pre-HBO		Mid-HBO		Post-HBO		RCI
	Score	Rank	Score	Rank	Score	Rank	$p=1.96$
Attention/executive functions							
T.O.V.A. — auditory							
Mean RT[1]	0.599	9th perc	–	–	0.641	3rd perc	$p>0.05$
Variability in RT[1]	0.188	5th perc	–	–	0.097	61st perc	$p<0.05$
Correct Responses (/72)	72	58th perc	–	–	72	58th perc	$p>0.05$
Correct Non-Responses /252)	250	<0.1 perc	–	–	252	68th perc	$p>0.05$
T.O.V.A. — visual							
Mean RT[1]	0.558	5th perc	–	–	0.523	16th perc	$p>0.05$
Variability in RT[1]	0.128	<0.1 perc	–	–	0.125	<0.1 perc	$p>0.05$
Correct responses (/72)	71	70th perc	–	–	68	<0.1 perc	$p>0.05$
Correct non-responses (/252)	248	<0.1 perc	–	–	250	19th perc	$p>0.05$
ERPs — mean RT[1]	0.604		0.526		0.570		*X*
Variability in RT[1]	0.109		0.075		0.069		*X*
Stroop							
Mean RT[1]— total	5.263	<0.1 perc	4.871	<1st perc	4.443	<1st perc	*X*
Mean RT[1]— congruent	4.077	<1st perc	4.647	<1st perc	4.513	<1st perc	*X*
Mean RT[1]— incongruent	6.363	<1st perc	5.095	<1st perc	4.357	<1st perc	*X*
Number of errors	37	<1st perc	44	<1st perc	38	<1st perc	*X*
Rey/Taylor Complex Figure							
Copy: Rey scoring	18.5	<1st perc	–	–	21	<1st perc	$p>0.05$
Memory processes							
Working memory							
Spatial Span (WMS-III)	5	12th perc	–	–	11	42nd perc	$p<0.05$
Long-term memory							
Visual							
B.E.M. 144 — 24 figures	8.5	<3rd perc	–	–	10	44th perc	
Denman — faces	12	11 SS	–	–	13	12 SS	$p>0.05$
Rey/Taylor Complex Fig	6.5	<1st perc	–	–	10	24th perc	$p>0.05$
Verbal							
B.E.M. 144 — 24 sentences	7	<1st perc	–	–	9.5	34th perc	*X*
Linguistic functions							
Expression							
Boston Naming Test	24	<1st perc	–	–	32	<1st perc	$p<0.05$
Comprehension							
Peabody	159	93th perc	–	–	142	53th perc	$p<0.05$
Token Test	92	<6th perc	–	–	112	<6th perc	$p<0.05$
C–Cook Speed of Reading Test	1	<1st perc	–	–	3	<1st perc	$p>0.05$

RCI>1.96 represents the cutoff for clinical significance when $p=0.05$.

Verbal memory also improved following the second treatment series. In fact, recognition of the 24 sentences of the BEM-144 improved from below average at baseline to within the low average range after HBO_2 therapy (Baseline: <1st percentile; post-HBO_2: 34th percentile). Once again, due to unknown test–retest reliability, we could not identify whether these improvements on delayed recall for sentences were clinically significant.

4.2.2.4. Linguistic functions. With regard to expressive language, confrontational naming (Boston Naming Test) significantly improved by as much as 33% after HBO_2 therapy, although remaining severely impaired (baseline: <1st percentile; post-HBO_2: <1st percentile) (RCI=5.56; $p<0.05$). Receptive language, assessed with the Peabody Picture Vocabulary Test, was normal at baseline and remained near average following HBO_2 therapy (baseline: 93rd percentile; post-HBO_2: 53rd percentile). Post-test scores on the Token Test improved significantly when compared to baseline performance (RCI=9.96; $p<0.05$), although remaining well below the normal range (baseline: <6th percentile; post-HBO_2: <6th percentile). Similarly, speed of reading improved on the Chapman–Cook Speed of Reading Test while performance was still severely impaired (baseline: <1st percentile; post-HBO_2: <1st percentile). RCI did not disclose clinically significant improvement after HBO_2 therapy on the Chapman–Cook Speed of Reading Test (RCI=1.24; $p>0.05$).

4.2.2.5. Praxis. Assessment of ideational praxis revealed no disabilities before and after treatment, M.P. being able to

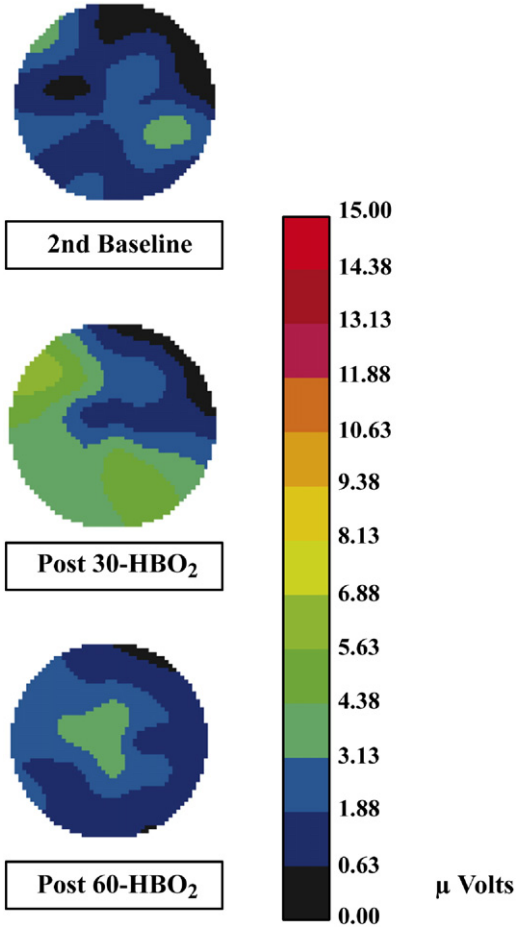

Fig. 2. Phase 2 — M.P.'s P300 amplitude distribution on the scalp, recorded at baseline, post-30 HBO_2 treatments and post-60 treatments in the visual oddball task. The frontal area of the scalp is represented on top and the occipital one, at the bottom.

adequately carry out complex movements. However, the execution of learned voluntary acts was significantly impaired and did not improve after treatment. In fact, based on categorization errors by Rothi and colleagues [36], M.P.'s pantomiming transitive gestures gave rise mostly to body part-as-tool errors (36–46%), in which the hand became the objects. In addition, perseverative gestures, errors in the movement direction (up–down, right–left) and the hand position were noted. Conventional communication gestures were also severely impaired. For instance, M.P. was unable to execute gestures like waving good-bye and the military salute, his series of movements being vague and disorganized.

4.2.3. SPECT neuroimaging

SPECT imaging was performed at three time points: before initiating the second treatment series, midway through the 60 HBO_2 treatments, and upon the completion of the entire treatment series. Results of the first session were not technically optimal, as M.P. was constantly moving throughout the entire procedure. However, data could still be analyzed after proper filtering was conducted. The three imaging sessions did not enable us to discriminate any improvement in oxygen uptake in the left fronto-parietal cortex, extending towards and affecting the left basal ganglia and the thalamus. The SPECT imaging also revealed a decreased oxygen uptake in the right cerebellar hemisphere, although this was much less severe than in the supratentorial area. Taken together, the imaging findings were compatible with a large infarction of the aforementioned areas of the left cerebral hemisphere accompanied by cerebellar diaschisis.

4.2.4. Electrophysiological measurements

Fig. 2 shows the P300 amplitude distribution in the visual oddball task at the three testing intervals: one year after the first treatment, after 30 new treatments and after the 60 HBO_2 treatments. As can be seen in Table 5, the initial increase in mean amplitudes recorded in the left hemisphere upon the completion of Phase 1 (post-20 HBO_2) was not maintained over time. In fact, a clinically significant decrease in P300 amplitude was observed between that recorded prior to initiating Phase 2 with recordings obtained one year earlier when M.P. had just received his last treatment session of Phase 1 (RCI=$p<0.01$). This significant attenuation in the amplitude of the P300 component one year post-Phase 1 was then followed by a significant recovery in the amplitude of the P300 waveform at midway

Table 5
Phase 2 — mean P300 amplitude and latency (±standard deviation) elicited by the rare stimulus in the visual oddball task

	Subregions	Post-20 HBO	Pre-60 HBO	Mid-60 HBO	Post-60 HBO	*p* value [a]	*p* value [b]
		Mean±SD	Mean±SD	Mean±SD	Mean±SD		
P3 amplitude (μV)	Central	4.3±2.0	2.6±0.5	4.1±1.3	4.0±1.3	NS	NS
	Right hemisphere	2.6±2.3	2.3±1.2	3.1±1.5	2.6±0.7	NS	NS
	Left hemisphere	4.6±1.1	2.4±0.8	4.2±1.1	3.2±0.8	*	*
P3 latency (m sec)	Central	450±40	431±65	464±20	451±73	NS	NS
	Right hemisphere	459±34	462±35	458±18	444±52	NS	NS
	Left hemisphere	465±40	444±62	388±45	429±70	NS	NS

Electrodes values were pooled in subregions.
*Level of significance: $p<0.017$.
[a] Comparison post-20 HBO_2 treatments from Phase 1 and pre-60 treatments from Phase 2.
[b] Comparisons pre-, mid- and post-60 HBO_2 treatments in Phase 2.

through the second series of HBO_2 treatments ($p<0.01$), which was followed by a trend toward further gains when M.P. had completed Phase 2 ($p>0.08$) (refer to Table 5). Moreover, the P300 latency recorded at pooled electrodes over the damaged (left) hemisphere was significantly shortened at mid-testing ($p<0.01$) when compared to pre-Phase 2 recordings, but returned to pre-Phase 2 levels later on with the remaining 30 HBO_2 treatments, in such a way that the P300 latency obtained at baseline was not significantly different from that obtained post-Phase 2 ($p>0.58$) (refer to Table 5).

As for recordings taken at pooled central electrodes sites and those located in the right hemisphere, we found no P300 amplitude or latency difference between that taken prior to the onset of the second treatment series with that recorded either at midway or following the completion of the second treatment series ($p>0.02$) (refer to Table 5).

5. Discussion

There were three main objectives to the present study: 1) to investigate the therapeutic value of repeated exposures to HBO_2 therapy following neurological stabilization; 2) to assess whether improvements (electrophysiological and sensorimotor) made following a series of 20 HBO_2 treatments would still be observed one year later; and 3) to evaluate whether functional improvements resulting from the first series of 20 HBO_2 treatments could be enhanced one year later as M.P. would receive a second, more extensive series of 60 HBO_2 treatments. The main finding obtained in the initial phase of this single-case study was that the mere exposure to a series of 20 HBO_2 treatment sessions received during the chronic post-ischemic stage was sufficient to exert sensorimotor gains and a significant enhancement in P300 amplitude over pooled electrodes from the damaged hemisphere when performing a classical visual oddball paradigm. The latter result has previously been associated with improvements in the allocation of attentional resources and to the constant updating of the content manipulated in working memory [37].

Our results also showed that the beneficial effects of HBO_2 therapy observed after the initial series of 20 HBO_2 treatments were found to be greatly attenuated, if not completely vanished, one year later, as revealed by a significant decrease of the P300 amplitude recorded in the damaged hemisphere before initiating Phase 2. However, ERP recordings taken at midway through the second series of HBO_2 treatments showed that the observed beneficial effects of HBO_2 therapy on cognitive functioning could be reinstated by the administration of 30 daily exposures to HBO_2 therapy. In fact, we found that the amplitude of the P300 component in a visual oddball paradigm was significantly greater following 30 consecutive HBO_2 treatments when contrasted with that obtained prior to initiating Phase 2. Moreover, in this second treatment phase, our results nearly confirm that being exposed to a more extensive series of HBO_2 treatment sessions would yield even greater beneficial effects, as a trend toward significance was obtained when we contrasted the amplitude of the P300 waveform collected at midway through the second treatment series with that exerted after having completed the entire series of 60 HBO_2 treatments.

The second series of 60 HBO_2 treatments yielded clinically significant improvements on various cognitive functions. The most notable changes were observed on working memory, information processing speed and language (expression and comprehension) abilities. These cognitive improvements coincided with the aforementioned enhancement in P300 amplitude for pooled electrodes located over the damaged hemisphere found after Phase 2. These findings suggest that M.P. greatly benefited from receiving the second series of 60 HBO_2 treatments as overt clinical improvements on various neuropsychological tests were observed post-Phase 2.

With regard to sensorimotor functions, M.P.'s gait velocity and balance improved significantly after each series of HBO_2 treatments. An actual improvement of 17% in gait velocity is somewhat similar to gains obtained in chronic stroke patients following various physical intervention programs [38–42]. The gains in equilibrium were, however, no longer demonstrable after one year, but reappeared after an additional series of treatments. The degree of improvement in sensitivity is more difficult to interpret. After the first series of treatments, we and the patient observed a positive response to tactile stimulation in several areas of the right hemibody, which had been unresponsive to touch at baseline testing. After the second series of exposures to HBO_2, only an increase in the forehead sensitivity was observed, albeit not consistently. The discrepancy between the initial and the later findings may be related to the use of a more objective test (Semmes–Weinstein filaments) in the second phase of our study, an observation that stresses the importance of relying on objective measurements when investigating the effects of HBO_2 therapy.

In this context, the present findings showing a modulation of the P300 component amplitude subsequent to HBO_2 therapy are quite robust, as previous electrophysiological studies using similar visual oddball paradigms to elicit P300 waveform components are thought to remain unaffected by practice/habituation effects despite frequent retesting [43,44]. Moreover, with respect to the ERP findings, the contribution of factors other than the HBO_2 intervention influencing brain activity, such as biological and environmental factors [45] or placebo effects [23,36], can be ruled out in the present study. Cortical reactivation was limited to the damaged left hemisphere, as no change was noted in the unaffected right hemisphere despite the equivalent influence of aforementioned factors on both cerebral hemispheres. These findings support previous evidence showing that the ERP technique may constitute a reliable approach to monitor clinical recovery [46].

However, the present single-case study comes with important limitations. Although spontaneous recovery could not

have accounted for the significant improvements in the electrophysiological and neuropsychological measures as M. P. was considered to be in a chronic post-ischemic stage, practice/habituation effects on some of the neuropsychological tasks at retest cannot be excluded even though alternative versions were used for some of them. However, familiarity with the test procedure and/or variation in time of the measures could not entirely account for the overall improvements in cognitive functioning. In fact, a recent study of chronic brain-injured patient has shown that speed of information processing, assessed by simple RT, as well as verbal/visual recognition memory and working memory are not subject to significant practice effects across testing sessions [46].

Despite these limitations, the improvements observed in the present single-case study provide preliminary evidence suggesting that HBO_2 treatments may have beneficial therapeutic effects on brain functioning. In line with previous case and clinical studies [18–20,47], our findings suggest that some chronic disabilities following brain insult can benefit from HBO_2 therapy by improving brain oxygenation. However, these beneficial effects seem to exert rather transient gains as those observed following the initial 20 treatments series were found to be greatly attenuated one year later. In fact, the administration of an additional series of HBO_2 treatments was necessary to reinstate the improvements in brain functions observed following the completion of the initial treatment series.

Taken together, this study suggests that 20 HBO_2 sessions were insufficient to consolidate permanent neuronal changes induced by the treatment, although specifications on the optimal therapeutic window (dosage and number of treatments) remain to be systematically explored. Thus, further longitudinal investigations should attempt to verify whether the administration of a more extensive series of HBO_2 sessions, such as that performed in the second phase of this study, would lead to longer-lasting improvements of cognitive functioning with TBI patients in the chronic post-ischemic stage. Thus, studies are required to investigate the possibility that a weekly HBO_2 treatment following an extensive rehabilitative program such as that provided to M.P. be sufficient to maintain the overall improvement in idling neuron's physiological activation that led to improved brain functioning. One could also examine whether a combination of more traditional therapeutic alternatives (physical, occupational and speech therapies) with HBO_2 treatments would lead to longer-lasting improvements.

Finally, there is an interesting element in our findings that does not fit in clinical results of an increased cerebral blood flow in formerly hypoactive areas, resulting from as little as a single one-hour exposure to HBO_2 therapy. In fact, despite improvements in cognitive functions, the SPECT images obtained in our study failed to reveal any change in oxygen uptake after 60 HBO_2 treatments and continued to show severe circulatory disturbances in the left fronto-parietal cortex, extending towards and affecting the left basal ganglia and the thalamus. On the one hand, this may support the contention of a time limit within which the cerebral ischemic penumbra is reversible. On the other hand, it could be that less severely affected neurons have significantly benefited from HBO_2 therapy, as it has been previously suggested that benefits of HBO_2 therapy are limited by the severity of the neuronal damage caused by the insult [48]. Therefore, electrophysiological measurements may be more sensitive than SPECT scanning to detect improvements in brain functioning resulting from HBO_2 therapy.

6. Conclusion

HBO_2 therapy seems to have some therapeutic potential in the management of acquired brain injury in the chronic stage. The present single-case study provides preliminary evidence of neuropsychological and electrophysiological improvements after series of 20 and 60 treatments, although the first dosage appeared to be insufficient to produce permanent benefits. Further studies using different treatment parameters are thus required before we can objectively measure the effectiveness of this treatment alternative.

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