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Hyperbaric oxygen may induce angiogenesis in patients suffering from prolonged post-concussion syndrome due to traumatic brain injury

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Abstract.
Purpose: Recent clinical studies present convincing evidence that hyperbaric oxygen therapy (HBOT) may be the coveted neurotherapeutic method for brain repair. One of the most interesting ways in which HBOT can induce neuroplasticity is angiogenesis.

The objective in this study was to assess the neurotherapeutic effect of HBOT in post TBI patients using brain perfusion imaging and clinical cognitive functions.
Methods: Retrospective analysis of patients suffering from chronic neuro-cognitive impairment from TBI treated with HBOT. The HBOT protocol included 60 daily HBOT sessions, 5 days per week. All patients had pre and post HBOT objective computerized cognitive tests (NeuroTrax) and brain perfusion MRI.
Results: Ten post-TBI patients were treated with HBOT with mean of 10.3 ± 3.2 years after their injury. After HBOT, whole-brain perfusion analysis showed significantly increased cerebral blood flow and cerebral blood volume. Clinically, HBOT induced significant improvement in the global cognitive scores ($p = 0.007$). The most prominent improvements were seen in information processing speed, visual spatial processing and motor skills indices.
Conclusion: HBOT may induce cerebral angiogenesis, which improves perfusion to the chronic damage brain tissue even months to years after the injury.

Keywords: Hyperbaric oxygen, angiogenesis, MRI, perfusion, cognitive, TBI, post concussion

1. Introduction

The postconcussion syndrome (PCS) is a common sequelae of traumatic brain injury (TBI), and it is a symptom complex that includes headache, dizziness, neuropsychiatric symptoms, and cognitive impairment

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(Bazarian et al., 1999). PCS is most often described in the setting of mild TBI, but it may also occur after moderate and severe TBI. Thirty to 80 percent of patients with mild to moderate brain injury will experience some symptoms of PCS (McCauley et al., 2005). PCS can continue for weeks or months, and up to 25% of all patients experience prolonged PCS (PPCS) in which the symptoms last for over six months (Kashluba et al., 2004).

The most common pathological mechanism in TBI is diffuse shearing of the axonal pathways and small blood vessels, which is also known as diffuse axonal injury (Medana & Esiri, 2003). The secondary pathological mechanisms of TBI include ischemia, mild edema, and other biochemical and inflammatory processes culminating in impaired regenerative and/or healing processes resulting from increasing tissue hypoxia (Kochanek, 2007). Due to the diffuse nature of injury, cognitive impairments are usually the predominant symptoms localized in multiple brain areas (Kushner, 1998; Levin et al., 1987; Sohlberg & Mateer, 2001). The diffuse pathological damage in mild TBI injury cannot be easily visualized by typical neuroimaging methods such as CT or standard MRI and therefore diagnosis relies to a great extent on patients' subjective reports, in addition to cognitive and quality of life tests. However, other neuroimaging modalities such as brain SPECT, PET-CT, perfusion MRI and DTI can reveal structural and functional injury in patients suffering from post-concussion syndrome (Boussi-Gross et al., 2013; Efrati & Ben-Jacob, 2014; Eierud et al., 2014). For example, abnormal blood perfusion can be seen by perfusion MRI (Liu et al., 2013; Niogi et al., 2008).

Recent clinical studies in patients with chronic neurological impairments stemming from stroke, TBI and anoxic brain injury have shown that hyperbaric oxygen therapy (HBOT) may be the coveted neurotherapeutic method for brain repair (Boussi-Gross, et al., 2013; Boussi-Gross et al., 2014; Efrati & Ben-Jacob, 2014, 2014; Hadanny A & S, 2015; Peleg et al., 2013; Wolf et al., 2012). Several mechanisms have been suggested in pre-clinical studies for HBOT-induced neuroplasticity (Chen et al., 2010; Efrati & Ben-Jacob, 2014; Huang & Obenaus, 2011; Lin et al., 2012; Neubauer & James, 1998; Vlodavsky et al., 2006; Zhang et al., 2005). One of the most interesting mechanisms is angiogenesis, which has been tested in animal models (Duan et al., 2014; Lin, et al., 2012; Peng et al., 2014).

In the past few years, new perfusion MRI technique called dynamic susceptibility contrast (DSC) has been developed to measure cerebral blood flow (CBF) and cerebral blood volume (CBV). A direct histological evaluation showed that increased CBF and CBV correlated with brain angiogenesis (Jiang et al., 2005).

The aim of the current study was to evaluate the effects of HBOT on brain perfusion and cognitive functions in patients with chronic neurological deficiencies stemming from mild TBI.

2. Methods

A retrospective analysis of patients suffering from chronic neurocognitive damage due to mild TBI, treated at Sagol Center for Hyperbaric Medicine and Research at the Assaf Harofeh Medical Center, Israel between September 2013 and December 2014. The study was approved by the institutional review board of the hospital.

Inclusion criteria: patients who have completed two MRI brain imaging and were administered two neurocognitive tests, pre- and post- hyperbaric oxygen therapy (HBOT). All patients who agreed to go through the evaluation process signed an informed consent in addition to the informed consent signed for treatment. All patients applied for HBOT on their own interest.

2.1. Hyperbaric oxygen treatment

Patients were treated in a multiplace hyperbaric chamber (HAUX-Life-Support GmbH.) for 50–70 daily hyperbaric sessions, 5 days a week. Each session consisted of 60 minutes of exposure to 100% oxygen at 1.5 ATA. Acceptable compression and decompression rates of 0.8 meter per minute were used. Oxygen was supplied by tight masks.

2.2. MRI scan protocol

All patients underwent MRI scans 1-2 weeks prior to and after HBOT. Imaing was conducted using a 3 Tesla system (Skyra Siemens, Germany). The MRI protocol included the following sequences: T1 pre- and post- gadolinium injection T2, FLAIR, SWI and DSC. The MRI DSC sequence parameters are detailed in the supplementary S-I.

2.3. MRI analysis

MRI analysis was performed by WiseImage (Hod Hasharon, Israel, www.wise-image.com) using in-house software written in Matlab R2011 (Mathworks, Natick, MA). Images were corrected for motion using SPM software (version 8, UCL, London, UK).

DSC analysis was performed as described in previous studies (Ostergaard, Sorensen, et al., 1996; Ostergaard, Weisskoff, et al., 1996). A detailed description can be found in the supplementary material (S-I). In short, 3 types of analysis were performed: histogram analysis of the perfusion values, whole-brain perfusion maps and region of interest values.

2.4. Cognitive assessment

The patients' cognitive functions were assessed by NeuroTrax computerized cognitive tests (NeuroTrax Corp., TX) (Dwolatzky et al., 2003). Tests were administrated 1-2 weeks prior to and after HBOT. NeuroTrax tests evaluate various aspects of brain functions and include Verbal Memory (immediate and delayed recognition), Non-Verbal Memory (immediate and delayed recognition), Go-No-Go Response Inhibition, Problem Solving, Stroop Interference, Finger Tapping, Catch Game, Staged Information Processing Speed (single digit, two-digit and three-digit arithmetic), Verbal Function and Visual Spatial Processing. Cognitive index scores were computed from the normalized outcome parameters for memory, executive function, attention, information processing speed, visual spatial, verbal function and motor skills domains (Achiron et al., 2013; Thaler et al., 2012; Zur et al., 2014). A global cognitive score was computed as the average of all index scores for each individual.

After administration, the NeuroTrax data were uploaded to the NeuroTrax central server, and outcome parameters were automatically calculated using software blind to diagnosis or testing site. To account for the well-known effects of age and education on cognitive performance, each outcome parameter was normalized and fit to an IQ-like scale (mean = 100, S.D. = 15) according to the patient's age and education. The normative data used by NeuroTrax consist of test data from cognitively healthy individuals in controlled research studies at more than 10 sites (Doniger, 2014).

Specifically, the patients were given two different versions of the NeuroTrax test battery before and after HBOT, to allow repeated administrations with minimal learning effects. Test-retest reliability for these versions was evaluated and was found to be high, with no significant learning effect (Schweiger, et al., 2003; Melton, 2005).

2.5. Statistical analysis

In addition to the MRI analysis described above, continuous data were expressed as means $\pm$ standard errors. The normal distribution for all variables was tested using the Kolmogorov-Smirnov test. The mean differences between cognitive index scores before and after HBOT were analyzed using two tailed paired *t*-tests or a Wilcoxon signed-rank test. The alpha level was set to 0.05. Data were statistically analyzed using SPSS software (version 22.0).

3. Results

Ten patients suffering from chronic cognitive impairment stemming from TBI who were treated at the Sagol Center for Hyperbaric Medicine and Research between September 2013 and December 2014 fulfilled the inclusion criteria.

Patients' baseline characteristics are summarized in Table 1. The average age was 33.7 ± 3.4 years (13.5–48), and 6 out of the 10 patients (60%) were males. All patients had documented traumatic brain injury 6 months to 27 years (mean 10.3 ± 3.2 years) prior to HBOT. Six (60%) suffered from PCS after moderate to severe TBI and 4 (40%) suffered from PCS after mild TBI.

3.1. Neurocognitive evaluation

The effect of the hyperbaric oxygen treatment on the patients' cognitive functions, as assessed by the eight cognitive summary scores, is summarized in Table 2. HBOT induced a significant improvement in the global cognitive scores with a mean change of 6.8 ± 1.9 ($p = 0.007$). The most striking improvements were seen in the information processing speed (IPS), visual spatial processing (VSP) and motor skill indices, with mean changes of 9.6 ± 2.9 ($p = 0.005$), 10.1 ± 4.2 ($p = 0.0043$) and 9.5 ± 4.5 ($p = 0.013$) respectively. A statistically significant improvement was also found for the memory indices ($p = 0.015$). Executive functions and attention indices improved,

Table 1
Patients' baseline characteristics

Age (years)	33.7 ± 3.4
Sex	
Males	6 (60%)
Females	4 (40%)
Education	
None	1 (10%)
High School	7 (70%)
Academic degree	2 (20%)
Time from trauma (years)	10.3 ± 3.2
Severity of trauma	
Mild	4 (40%)
Moderate	2 (20%)
Severity	4 (40%)
Medications	
SSRI	3 (30%)
Benzodiapezines	1 (10%)
Opiates	1 (10%)
HBO sessions	62 ± 1.0
ATA	
1.5	4 (40%)
2	6 (60%)

Table 2
Cognitive indices at baseline, after Hyperbaric Oxygen Therapy (HBOT)

	Baseline	Post HBOT	Mean change	*P*-Value
General	84.±3.9	91.2 ± 4.2	6.8 ± 1.9	*__0.007__
Memory	78.2 ± 7.7	85.3 ± 8.4	7.0 ± 2.3	*__0.015__
Executive Functions	84.9 ± 3.0	90.2 ± 4.0	5.3 ± 2.9	__0.106__
Attention	88.6 ± 3.9	93.6 ± 3.3	4.9 ± 2.8	__0.113__
IPS	78.9 ± 5.2	88.5 ± 5.5	9.6 ± 2.9	*__0.005 (W)__
VSP	91.5 ± 5.1	101.6 ± 5.0	10.1 ± 4.2	*__0.043 (W)__
Verbal skills	77.9 ± 10.6	83.4 ± 5.5	5.5 ± 8.0	0.517
Motor skills	89.7 ± 6.4	99.2 ± 3.0	9.5 ± 4.5	*__0.013 (W)__

Data are expressed as means ± standard errors. IPS = Information processing speed, VSP = Visual spatial processing. W = Wilcoxon signed rank test.

but the pre-post difference did not reach significance (Table 2, Fig. 1).

3.2. Increased brain perfusion

DSC analysis was performed in 10 patients before and after HBOT. The average CBF, CBV and MTT whole brain maps are depicted in Fig. 2, and show the increase in CBF and CBV and the decrease in MTT. In addition, delta maps showed similar increased CBF, CBV and decreased MTT following HBOT.

Whole brain histogram analysis of CBF and CBV was performed and the maximum peak height was calculated before and after HBOT. The patients' average histograms are shown in Fig. 3A (CBF) and Fig. 3B (CBV), which depict an increase in peak height ($p = 0.005$ and $p = 0.002$ respectively).

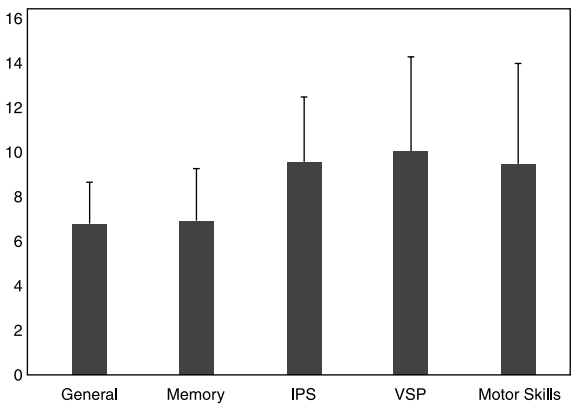

Fig. 1. Improvements in Cognitive function, ADL and quality of life (EQ-5D, EQ-VAS). A. Mean changes of the corresponding cognitive indices at baseline and after HBO2.

3.3. Regional changes in blood perfusion and volume

Most of the anatomic structures that presented a significant increase in CBF also exhibited an increase in CBV. Changes were found in grey matter as well as white matter structures (supplamentary SI: Table S).

Increases in CBF and CBV were found in regions related to visual functions (cuneus, occipitofrontal fasciculus, lingual gyrus) sensory-motor function (centrum semiovale, cerebellum, postcentral gyrus, precentral gyrus, and striatum) memory and attention (temporal structures, cingulum) as well as the frontal and parietal regions.

4. Discussion

The present study shows for the first time that HBOT induced neuroplasticity can be mediated by enhanced brain angiogenesis in post TBI patients. This was evidenced by increases in CBF and CBV, along with significant cognitive improvement, following HBOT. Furthermore, HBOT may induce angiogenesis even in the late chronic phase (10.3 ± 3.2 years after the acute insult).

In standard healthy conditions, the brain utilizes almost all of the oxygen/energy supplied to it. The

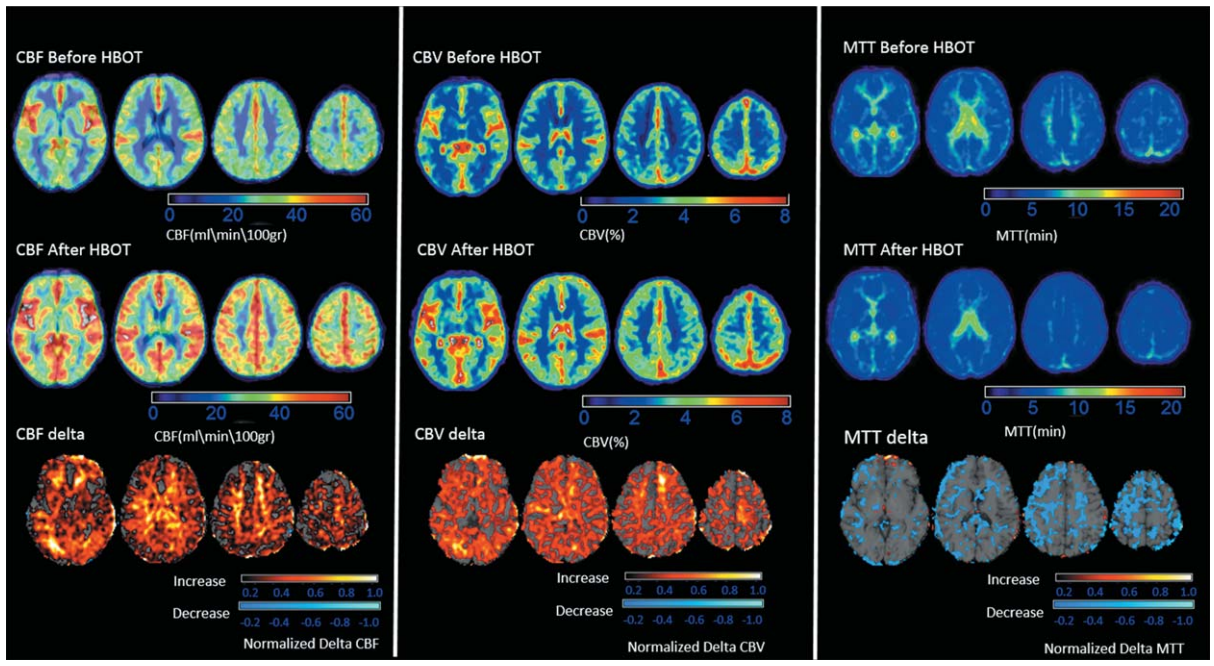

Fig. 2. Average DSC maps pre and post HBOT and DSC normalized delta maps. Top row: CBF, CBV and MTT pre-HBOT. Middle row: CBF, CBV and MTT maps post-HBOT. Bottom row: normalized delta maps, showing increases in CBF and CBV and a decrease in MTT post-HBOT.

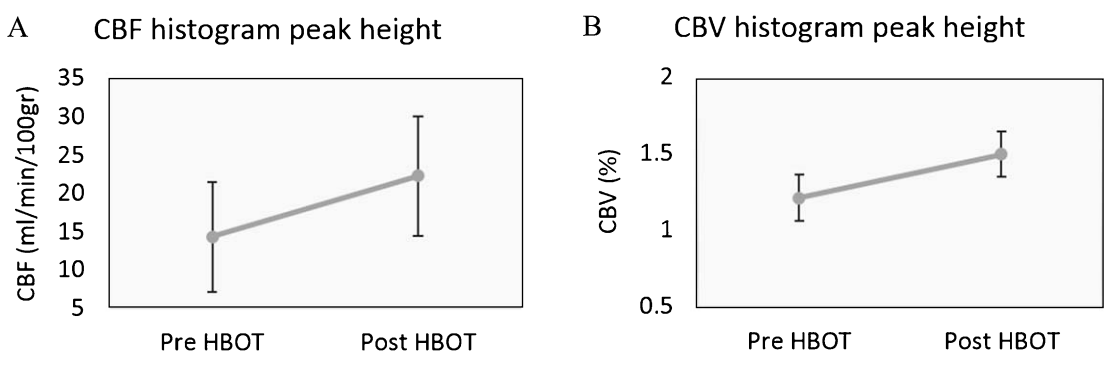

Fig. 3. Global increases in CBF and CBV maps after HBOT. (A) A graph of average histogram peak heights of CBF maps before and after HBOT ($p = 0.005$). (B) A graph of average histogram peak heights of CBV maps before and after HBOT ($p = 0.002$).

global brain hypoperfusion detected in post TBI patients serves as a rate- limiting factor for any regenerative process (Graham & Adams, 1971; Graham et al., 1978; Kim et al., 2010; Ostergaard et al., 2014; Stein et al., 2004). The disproportionate CBF reductions seen in the posterior cingulate cortices, the thalami, and many locations in the frontal cortices suggest widespread but non-uniform hypoperfusion, beyond the hypoperfusion seen in areas of focal cortical injury, which represent the local effects of focal loss of tissue and its associated perfusion (Kim, et al., 2010). HBOT, by increasing the oxygen level in the blood and body tissues, can supply the energy needed for different brain repair mechanisms (Efrati & Ben-Jacob, 2014). However, in order to maximize the regenerative process of neurons and glia cells, a new, non-hypoxic environment needs to be generated. Various stroke models have strongly suggested that angiogenesis, by delivering the oxygen support, can catalyze brain plasticity, enhance neurogenesis and synaptogenesis and

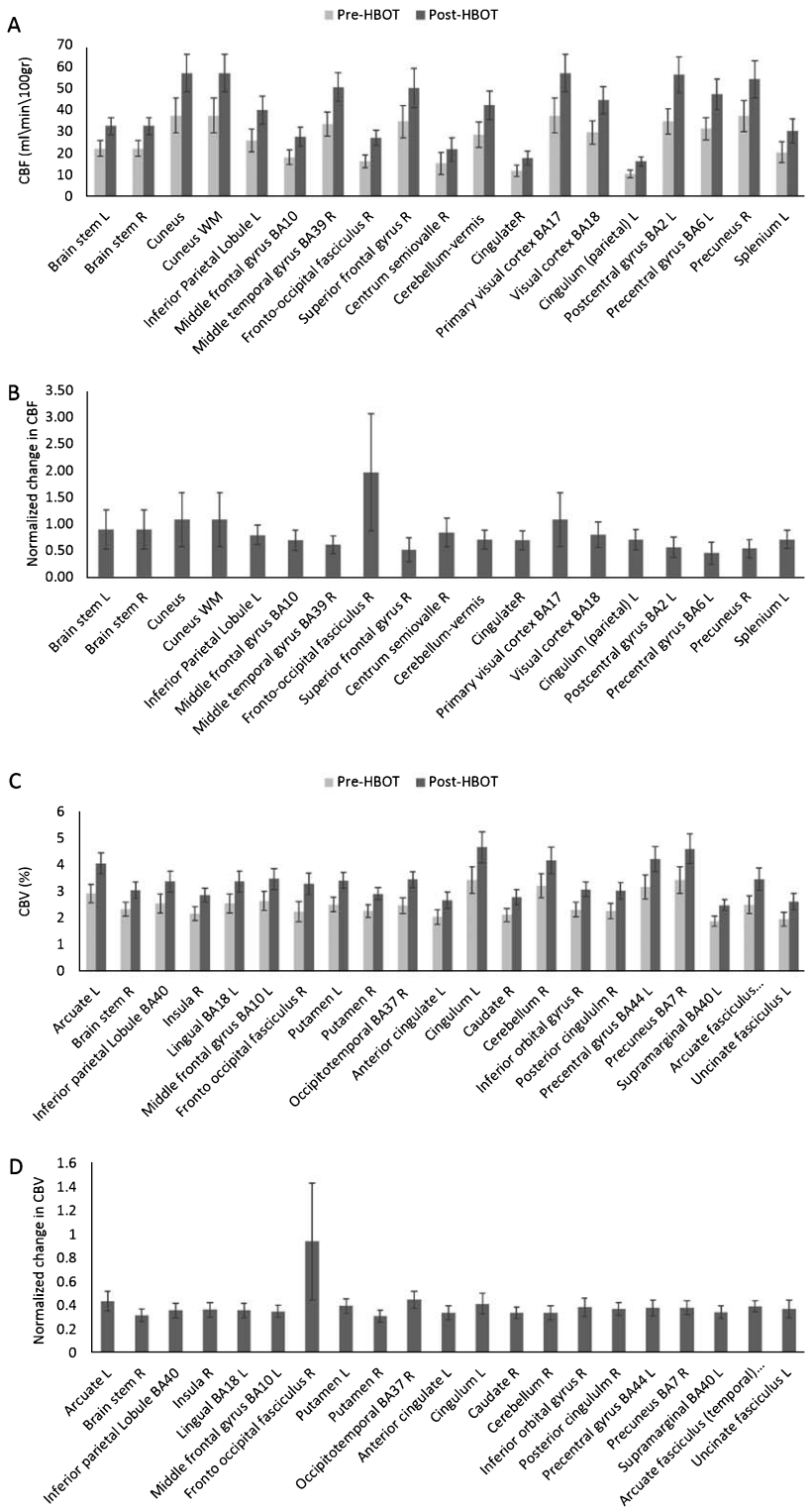

Fig. 4. Graphs of CBF and CBV averages and standard error in significant clusters. (A) Averages of CBF before and after HBOT. (B) Normalized delta of CBF maps. (C) Averages of CBV before and after HBOT. (D) Normalized delta of CBV maps.

foster functional recovery (Chen et al., 2003; Jiang, et al., 2005).

HBOT induced angiogenesis has been amply confirmed in pre-clinical models and can be deduced from brain SPECTs of post stroke and TBI patients even years after the acute insult (Boussi-Gross, et al., 2013; Duan, et al., 2014; Efrati et al., 2013; Lin, et al., 2012; Peng, Yang, & Yang, 2014). In the current study, for the first time in humans, perfusion MRI showed HBOT can induce significant increases CBF and CBV in the injured brain regions (Table 2). The increased perfusion to the malfunctioning tissue, alongside the significant cognitive improvement suggest that impaired tissue perfusion may indeed serve as a rate limiting factor for regeneration and neuroplasticity even years after the acute insult.

Increase in CBF and CBV was found to be correlated with improvement in cognitive functions. Significant increases in cognitive performance were found for visual spatial ability, information processing speed and motor function. Both CBF and CBV increased in the occipital cortex and the occipito-frontal fasciculus which are known to be related to visual processing (Purves, 2012; Urbanski et al., 2008); in parietal regions, including the precuneus and inferior parietal lobule which are known to be related to calculation; (Simon et al., 2002, 2004) and brain regions known to be involved in motor skills such as the Corona Radiata, Striatum, and Cerebellum (Kim & Pope, 2005; Parent & Hazrati, 1995; Timmann et al., 2010). These findings strengthen our conclusion that the neural plasticity, reflected by the cognitive improvement, is induced by the angiogenesis, manifested by the increase in blood flow and volume.

This study, as well as previous studies, was performed on patients with chronic neurocognitive impairment, challenges the hypothetical time limit for possible neuroplasticity after brain injury (Boussi-Gross, et al., 2013, 2014; Efrati & Ben-Jacob, 2014, 2014; Hadanny A & S, 2015; Peleg, et al., 2013; Wolf, et al., 2012). The mean time from the acute insult to initiation of HBOT was 10.3 ± 3.2 years; i.e., when spontaneous improvement is not expected. This demonstrates that appropriate biological trigger can induce neuroplasticity months to years after the acute injury.

Numerous mechanisms of initiation of cellular and vascular repair by HBOT have been suggested in addition to angiogenesis and improved cerebral vascular flow. These include improved mitochondrial function and cellular metabolism, improved BBB and inflammatory reactions, reduced apoptosis, alleviation of oxidative stress, increased levels of neurotrophins and nitric oxide, and up-regulation of axonal guidance agents (Efrati & Ben-Jacob, 2014; Efrati, et al., 2013). Moreover, the effects of HBOT on neurons can be mediated indirectly by glial cells. HBOT may also promote neurogenesis of endogenous neural stem cells (Efrati & Ben-Jacob, 2014; Efrati, et al., 2013). The common denominator underlying all these mechanisms is the fact that they are oxygen-dependent. HBOT may enable the metabolic change simply by supplying the missing energy/oxygen needed for these regeneration processes (Efrati & Ben-Jacob, 2014; Efrati, et al., 2013). The induction of angiogenesis, as demonstrated in this study, may serve as infrastructure that enables the regenerative process and the preservation of newly generated metabolic functioning (Chen, et al., 2003; Jiang, et al., 2005).

Our study has several limitations. The major limitation is the relatively small number of patients, which raises the question regarding the applicability of the findings to larger cohort of post concussion patients. However, the findings seen in perfusion MRI in all the patients are consistent with findings in animal models and provide an important tool for further large scale studies. In addition, the MRI method used in our study– DSC –produced the absolute values of CBF and CBV. These values are expected to be stable between 2 examinations during the chronic stage and no change is expected, within a time period of 3 months, without any significant potent intervention. The cognitive improvement seen here is in line with our earlier randomized controlled trial on mild TBI patients (Boussi-Gross, et al., 2013).

Second, our study lacks an appropriate control group. Nevertheless, one should not expect any "sudden" significant change in absolute CBV, CBF values or significant neurocognitive improvement years after the acute insult.

In addition, previous randomized controlled trial have shown that during 3 months of no intervention, the control group cognitive scores and brain perfusion using SPECT did not change significantly. (Boussi-Gross, et al., 2013).

5. Conclusion

HBOT may induce cerebral angiogenesis in patients suffering from post-concussion syndrome stem-

ming from mild TBI. Angiogenesis which improves perfusion to the areas with chronic injury goes side by side with beneficial effect on cognitive impairments, even months to years after the injury.

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