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Chapter 1

Introductory Chapter: Hyperbaric Oxygen Treatment: Old Treatment with New Understanding

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Additional information is available at the end of the chapter

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1. Introduction

Hyperbaric oxygen treatment (HBO_2) is a widely accepted adjuvant therapy in various health conditions that exhibit impaired tissue blood flow. The list of indications is widening as our knowledge and understanding on the mechanisms of HBO_2 action is getting larger. For example, in August 2013, the US Food and Drug Administration declared artery occlusion as one of the 13 specific indications for HBO therapy [1].

In April 2016, the Tenth European Consensus Conference on Hyperbaric Medicine was held, bringing consensus on accepted and non-accepted clinical indications and practice of hyperbaric oxygen treatment. Recommendations are listed in three levels of indications: from Type 1—strongly suggest that HBO_2 is to be accepted as primary treatment (example of accepted indications: carbon monoxide (CO) poisoning, mandibular osteonecrosis, gas embolism, anaerobic or mixed infections, decompression sickness, sudden deafness, etc.); Type 2—HBO_2 is suggested as it is supported by evidences (suggested indications: diabetic foot lesions, femoral head fracture, ischemic ulcers, etc.) and Type 3—where HBO_2 is optional, since it is not fully supported by evidences (e.g. brain injuries, radio-induced lesions, post-vascular procedure reperfusion syndrome, etc.). This consensus also provided negative recommendations, for example, where HBO_2 should not be used, such as autism spectrum disorders, placental insufficiency and cerebral palsy, to list some of them [2].

At high pressures, the delivery of the dissolved oxygen in plasma is enhanced, which contributes to better tissue oxygenation, cellular metabolism and, ultimately, healing. However, this is not the only potential mechanism for improved outcome of many diseases treated with HBO_2, since oxygen is highly reactive molecule and can induce upregulation of many various enzymatic systems in the cell, at cellular, genetic and molecular level. Particularly,

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vascular/endothelial function is affected by the HBO_2. Our understanding of these mechanisms of the HBO_2 effects is still emerging. There have been many controversies related to the HBO_2 protocols and indications. It is known that, as well as HBO_2 exhibit beneficiary effects on the tissue perfusion, it demonstrates high toxicity at higher pressures, due to increased oxidative stress and barotrauma. On the other hand, there is still a lack of the translation of the knowledge on the mechanisms of action of HBO_2 obtained from the experimental research to the clinical practice.

2. Effects of HBO_2 in brain injury

One interesting field of research of use of HBO_2 in treatment is brain injury, particularly traumatic brain injury and stroke in diabetes. In prospective, randomized controlled trial, in 79 diabetes patients suffering from acute intracerebral hemorrhagic stroke, both short-term and long-term neurological consequences were studied and compared in group on normobaric oxygen therapy and on HBO_2. At 1-month follow-up period, no distinct difference was observed between each group. However, after 6 months of follow-up, HBO_2 group exhibited better neurological consequences compared to control group (Barthel Index: 85.1 versus 65.6%, P = 0.080; mRS: 89.4 versus 68.8%, P = 0.045; Glasgow outcome scale: 83.0 versus 62.5%, P = 0.073; National Institute of Stroke Scale (NIHSS): 80.9 versus 56.2%, P = 0.035), supporting the hypothesis that HBO_2 is safe and effective therapy for the long-term neurological outcomes in diabetic patients with hemorrhagic stroke [3].

In traumatic brain injury (TBI) clinical study, 28 patients with persistent cognitive impairment caused by mild-to-moderate TBI were included and examined for the stem cell mobilization and recruitment to repair damaged neuronal tissue. HBO_2 treatment correlated with stem cell mobilization as well as increased cognitive performance. The limitation of the study was that peripheral blood sample was tested [4]. Similarly, 50 randomized subjects with TBI were examined for cognition and post-traumatic stress disorder symptoms. They completed a total of 30 HBO_2 exposures compared to sham-treated group. The symptoms improved in both groups and there were no statistically significant differences between groups. However, there was some improvement in the treatment group versus the control after subgroup analyses based on concussion history and individual test components [5]. In randomized controlled clinical trial, normobaric oxygen therapy was also employed in the treatment of 52 patients with either ischemic or hemorrhagic stroke in the first 12 h of accident. Normobaric oxygenation could improve long-time outcome of the patients based on the modified Rankin Scale neurology disability scoring system, but not on the Barthel results, 6 months after the discharge from hospital [6]. The retrospective observational trial demonstrated significant improvement in patients with acute neurological deficits due to ischemic stroke following cardiac surgery treated with HBO_2. However, the last study lacks control, which weakens the level of evidence of conclusions [7].

Contrary to this beneficiary results, recent Cochrane database systemic review included 11 randomized clinical trials (RCTs) involving 705 participants to examine the effect of HBO_2

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on clinical outcomes of ischemic stroke. Fatality rate at 6 months was not significantly different in those receiving HBO_2 compared with the control group. However, HBO_2 significantly improved 4 of 14 scale measures of disability and functional performance, for example, the mean Orgogozo Scale score was higher (MD 27.9 points, 95% CI 4.0–51.8, P value 0.02) and Trouillas Disability Scale score was lower with HBO_2 (mean difference (MD) 2.2 point reduction with HBOT, 95% CI 0.15–4.3, P value 0.04). The limiting factor of this meta-analysis was variable quality of the methodology of the evaluated trials; thus, it is not conclusive on clear clinical benefit as well as on exclusion of it [8].

Analyses of several trials, such as the Department of Defense/Veterans Administration (DoD/VA) sponsored trials, previous published reports on the use of HBO_2 therapy on stroke and moderate chronic traumatic brain injury (mTBI) and preliminary reports from the HOPPS Army trial, suggest the approval of HBO_2 for neurological indications, especially for mTBI and post-concussion syndrome (PCS), as a safe and viable treatment for recovery in the post-acute phase [9]. In the context of the preparation of impending National Institute of Neurologic Disorders and Stroke-funded, multi-center, randomized, adaptive Phase II clinical trial—the Hyperbaric Oxygen Brain Injury Treatment (HOBIT) trial, 30 studies (8 clinical and 22 pre-clinical) that administered HBO_2 within 30 days of a TBI were analyzed. The pre-clinical studies consistently reported positive treatment effects across a variety of outcome measures with almost no safety concerns. Of the eight clinical studies reviewed, four were based on the senior author's (GR) investigation of HBO_2 as a treatment for acute severe TBI [10].

The mechanisms by which HBO_2 induces brain neuroplasticity can be demonstrated by highly sensitive MRI techniques of dynamic susceptibility contrast-enhanced (DSC) and diffusion tensor imaging (DTI). Fifteen patients afflicted with prolonged post-concussion syndrome were treated with 60 daily HBO_2 sessions. The cerebral blood flow and volume significantly increased after HBO_2. There was significant improvement in the memory, information processing speed, executive functions and global cognitive scores (evaluated by NeuroTrax) after HBO_2. Fractional anisotropy values were significantly increased and mean diffusivity was significantly decreased in both white and gray matter structures after HBO_2 [11].

Hyperbaric oxygen in combination with thrombolysis shows neuroprotection in acute ischemic stroke in rats by reducing infarct volume and improving functional outcome in the early post-stroke period [12]. HBO_2 can induce cerebral angiogenesis and improve both white and gray microstructures indicating regeneration of nerve fibers which correlates with the neurocognitive improvements [11]. Potential metabolic effects in the mechanisms of HBO_2-induced improved neurostructural and neurofunctional outcomes were also examined in diabetic female rats. Particular emphasis was given to the role of cyp450 enzymes' metabolites of arachidonic acid. Cortical infarct size and total infarct size were equally and significantly reduced in HBO_2- and HET0016 (inhibitor of 20-HETE production)-treated diabetic female rats. Cyp2J3 mRNA was significantly increased in all study groups, and Cyp2C11 mRNA was significantly increased in the group receiving HET0016 treatment followed by HBO_2 exposure and in the multiple HBO_2 group compared to the control group. Endothelial nitric oxide synthase (eNOS) enzyme's expression was significantly increased after HBO_2 treatments, and

expression of epoxide hydrolase 2 was increased in all groups compared to the control group. All together, these results suggested that cytochrome P450 metabolites and the NO pathway are involved in the observed therapeutic effects of HBO_2 and HET0016 in diabetic female Sprague-Dawley rats. Furthermore, HBO_2 and HET0016 are very effective treatments of stroke [13]. Similarly, HBO_2 treatment on rats with experimental traumatic spinal cord injury was performed 1, 6 and 24 h after brain trauma. HBO_2 improved the results of the inclined plane level tests and motor strength test. Early HBO_2 treatment resulted in higher recovery rates, particularly when treatment started in the first hour. In traumatized rats, nitrite levels in spinal cord increased compared to control group; however, they diminished after HBO_2 treatments. As earlier the HBO_2 treatment was conducted, the greater decrease in nitrite levels was observed [14].

The safety of more advanced attempts to deliver increased oxygen levels to hypoxic or ischemic tissues, such as with hyperbaric oxygen therapy, is also being questioned [15]. There are substantial number of evidence that HBO_2 significantly improves physiologic measures without causing cerebral or pulmonary toxicity and can potentially improve clinical outcome [10]. In contrast to chronic, intermittent HBO_2 treatments which do not increase oxidative stress and restore the mechanisms of vascular relaxation in diabetic rats [16, 17], acute HBO_2 can increase oxidative stress and transiently impair the endothelium-dependent vasorelaxation, even in healthy rats [18]. In study on isolated aortic rings in healthy male Sprague-Dawley rats, acetylcholine-induced relaxation and hypoxia-induced relaxation which were impaired after acute HBO_2 due to increased serum oxidative stress and superoxide production were restored by superoxide scavenger TEMPOL. The mRNA expression of iNOS was decreased in the acute HBO_2 and 24 h after HBO_2 while gene expression of superoxide dismutase SOD1 and SOD3 and NADPH oxidase was increased in the intermittent HBO_2 group. The expression and activity of catalase and glutathione peroxidase were increased in the intermittent HBO_2 group as well. Vasorelaxation was restored and oxidative stress was normalized 24 h after the treatment [18].

In attempt to evaluate possibility to use HBO_2 in other neurological diseases, such as Alzheimer's disease (AD), the studies were performed in the triple transgenic model of AD in old mice. HBO_2 reduced hypoxia, amyloid burden and tau phosphorylation in 3xTg mice and ameliorated their behavioral deficits. HBO_2 attenuated neuroinflammatory processes by reducing astrogliosis, microgliosis and the secretion of proinflammatory cytokines (IL-1β and TNFα) and increasing expression of scavenger receptor A, arginase1 and anti-inflammatory cytokines (IL-4 and IL-10) [19]. The beneficial effect of HBO_2 for neurological outcome after stroke has been illustrated in many studies, and meanwhile, many underlying mechanisms associated with neuroprotection have been demonstrated, such as cerebral oxygenation promotion and metabolic improvement, decreased oxidative stress and apoptosis, blood-brain barrier protection, anti-inflammation and decrease in cerebral edema, intracranial pressure modulation and increased vascular and neural regeneration [20]. However, as noted previously, studies performed in human stroke patients lack controls. Thus, data are not

sufficiently evidence-based, although promising. In human stroke, there is an urgent need for the randomized double-blind controlled clinical trials to have undoubted evidence on the HBO_2 effects in stroke. In the future, this type of studies will lead to uniform criteria on the dose, number of sessions and oxygenation levels in different types of stroke.

3. Potential HBO_2 use in inflammatory bowel diseases

Another interesting and controversial field of potential HBO_2 application is inflammatory bowel diseases and radiation-induced chronic gastrointestinal symptoms. Again, some studies presented beneficiary effects of HBO_2 in the model of ulcerative colitis, by stimulating colonic stem cells to promote healing. However, this study lack control group [21]. On the other hand, well-controlled study in mice model of DSS-induced colitis demonstrated that HBO_2 significantly reduces colitis severity. Gene expression and activity of antioxidative enzymes were changed by the HBO_2, as well as the inflammatory microenvironment in the gut mucosa. This was manifested by the clinical features of colitis (e.g. bleeding, frequency of stool) and by histological assessment of the gut tissue and reversal of IL-1β, IL-2 and IL-6 gene expression. Also, the immune cell expansion and mobilization were impaired. HIF-1α mRNA level strongly correlated to GPx1, SOD1 and IL-6 mRNA expression, suggesting that HIF-1α is involved in the transcriptional regulation of these genes during colonic inflammation and HBO_2 [22]. On the other hand, a prospective randomized study failed to demonstrate that HBO_2 can improve the effects of standardized treatment in a severe attack of ulcerative colitis [23]. Additionally, no evidence that patients with radiation-induced chronic gastrointestinal symptoms, including those patients with rectal bleeding, benefit from hyperbaric oxygen therapy in HOT2 study (a double-blind, sham-controlled, phase 3 randomized study of patients (≥18 years) with chronic gastrointestinal symptoms for 12 months or more after radiotherapy) [24]. Obviously, there is a discrepancy of the data from experimental study and clinical observational studies, which need to be resolved by well-controlled randomized clinical trials and well-settled experimental studies.

4. Conclusion

HBO_2 is an established therapeutic approach in many acute, life-threatening conditions and also has been submitted to scrutinizing evaluation for new indications. Not only there is a wide field of potential application of HBO_2 in experimental research and clinical therapy, but also there is a need for improved understanding of the mechanisms of action of HBO_2. Mechanisms of HBO_2-induced beneficiary effects are under intense investigation and their understanding promise HBO_2 with low unwanted side effects when utilized in well-designed controlled fashion.

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