How and why hyperbaric oxygen therapy can bring new hope for children suffering from cerebral palsy – *An editorial perspective*

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Cerebral palsy (CP) is generally considered a non-progressive condition resulting from neurological injury in the antenatal or perinatal period. The increased survival rates of premature infants due to advances in neonatal intensive care has led to increased incidence of CP, which is now higher than three in 1,000 births. Perinatal hypoxic-ischemic (HI) events resulting in cellular necrosis, neuronal inactivation and cerebral white matter injury are the most common causes of severe neurological handicaps in children with CP.

The challenge

Physiologically, hypoxic-ischemic brain injury could be defined as acute oxygen and nutrient deprivation to the brain caused by faulty cerebral circulation, resulting in cellular bioenergetics failure and neurological dysfunction. As in stroke, traumatic brain injury (TBI) and age-related metabolic brain disorders, there is no effective treatment/metabolic intervention in routine clinical practice for children with CP. Intensive therapy and rehabilitation programs are valuable tools for improving the quality of life for these unfortunate children, but they offer, at best, only partial relief.

New results

In this current issue of *UHM*, Mukherjee *et al.* present convincing evidence that hyperbaric oxygen (HBO_2) therapy in combination with standard intensive rehabilitation (SIR) could be the coveted neurotherapeutic method for children suffering from neurological dysfunctions due to CP [1]. The idea that HBO_2 therapy can provide a valuable brain repair tool for CP is not new and has been investigated in several earlier clinical trials, but the results were conflicting [2-6]. What makes the current findings persuasive is the methodical, multifaceted comparison: The short-term and long-term outcomes of SIR in conjunction with normal air (21% oxygen) HBO_2 sessions at 1.3 atmospheres absolute (atm abs) were compared with those of SIR in conjunction with:

(a) 100% oxygen HBO_2 sessions at 1.5 atm abs and
(b) 100% oxygen HBO_2 sessions at 1.75 atm abs.

For long-term follow-up, patients were evaluated two and eight months after the beginning of treatment. Interestingly, significant long-term beneficial effects were observed for all combined treatments, including the case of normal oxygen at 1.3 atm abs, compared to SIR alone.

A call for consensus

While the findings support the idea that "low-dose" HBO_2 can provide new hope for children with cerebral palsy, additional, larger-scale clinical studies are needed to further confirm the findings and determine the most effective and personalized treatment protocols. Furthermore, before initiating future clinical trials, some issues associated with the optimal practice of HBO_2 therapy for children with CP should be explored:

- proper sham control;
- the optimal dose-response curve (oxygen and pressure levels);
- the optimal treatment duration/number of HBO_2 sessions; and
- the proper selection criteria of the study cohort.

Further below we reflect on the optimal HBO_2 therapy practice in light of the recent findings by Mukherjee *et al.* – of new understanding of the brain damage

associated with CP and of new understanding regarding the neurotherapeutic effects of hyperbaric oxygen. We hope that our reflections will ignite in-depth discussions within the hyperbaric medicine community, to help reach consensus on whether, why and how HBO_2 therapy can give hope to children with cerebral palsy.

Underlying repair mechanisms

It is now understood that the recently observed restoration of neuronal activity in the metabolically dysfunctional stunned areas following HBO_2 treatments is accomplished via an assortment of intricate mechanisms. The combined action of hyperoxia and hyperbaric pressure leads to significant improvement in tissue oxygenation and affects both oxygen-sensitive and pressure-sensitive genes. HBO_2 therapy can initiate vascular repair and improve cerebral vascular flow, induce regeneration of axonal white matter, stimulate axonal growth, promote blood-brain barrier integrity, and reduce inflammatory reactions as well as brain edema [7-12].

At the cellular level, HBO_2 can improve cellular metabolism, reduce apoptosis, alleviate oxidative stress and increase levels of neurotrophins and nitric oxide through enhancement of mitochondrial function in both neurons and glial cells, and may even promote neurogenesis of endogenous neural stem cells [7-13]. It is important to note that, as in stroke and TBI, the hypoxic-ischemic conditions following cerebral palsy engender depolarization of the mitochondria membrane and induction of mPTP (mitochondrial permeability transition pore), which reduces the efficiency of energy production and elevates the level of reactive oxygen species (ROS).

Tissue oxygenation via HBO_2 can inhibit mPTP and thus has the potential to reverse this abnormality [8]. However, it must be applied carefully to ensure that the increased tissue oxygen does not cause cellular toxicity due to overly high ROS levels.

The control group dilemma

There are inherent ethical and logistic difficulties in handling the sham-control in HBO_2 therapy trials. The standard requirement for proper sham-control is: *"Medically ineffectual treatment for medical conditions intended to deceive the recipient from knowing which treatment is given."*

Hyperbaric oxygen therapy includes two active ingredients: pressure and oxygen. The pressure is being utilized for increasing plasma oxygen, but the pressure change by itself may have significant effects on the cellular level. The pressure effect may be of greater significance in human tissues that are under tight autoregulation pressure control, such as the brain and kidneys [14-18]. The intracranial pressure, the pressure within the skull and thus in the brain tissue and cerebrospinal fluid (CSF), is normally 0.0092-0.0197 atm (7–15 mm Hg). Any increase in cranial pressure may have a significant effect on neurons, glial cells and the function of endothelial cells [14,15, 18].

A classical example that highlights the significance of small changes in pressure is acute mountain sickness (AMS) and high-altitude cerebral edema (HACE). In AMS and HACE, even a small increase in ambient air pressure – less than a sixth of an atmosphere – may reverse the pathology [19]. Put together, the observations imply that any increase in pressure, even with reduced oxygen percentage, cannot serve as a placebo since it exerts at least one of the two active ingredients of HBO_2 therapy.

Elevated pressure with low oxygen can be an effectual treatment

To generate the sensation of pressure, the chamber pressure must be 1.3 atm abs or higher. However, breathing normal air, even at 1.3 atm abs, cannot serve as a proper sham-control since it is not an *"ineffectual treatment,"* as required by the placebo definition; it leads to significant physiological effects resulting from the elevated pressure and the tissue oxygenation. Therefore, as we discuss below, such doses should be regarded as a dose-comparison study, as was correctly done by Mukherjee *et al.*, who demonstrated that it is effective in the treatment of children with CP [1]. Other clinical trials also found that patients treated with low oxygen showed improvements similar to patients treated with higher dosages [2,4,20,21]. However, in those trials, the low-dose treatments were mistakenly regarded as sham-control, leading to incorrect conclusions. In studies 4, 20 and 22, room (21% oxygen) air at 1.3 atm abs was used as a sham-control to test the HBO_2 effect on CP and patients with mild TBI (mTBI) treated with 100% oxygen at 2.4 atm abs. Another study used lower-than-normal (14% oxygen) air at 1.5 atm abs to test the effect of hyperbaric

oxygen on children with cerebral palsy who were treated with 100% air at 1.5 atm abs [2]. In all of those studies, the treated group and the low-oxygen group, which the authors mistakenly considered to be sham-control, show similar improvements [2,4, 20,21]. Consequently, the authors in both studies concluded that the observed improvements were merely placebo effects and therefore that HBO_2 therapy had no neurotherapeutic effects on mTBI and CP.

Their conclusions are clearly challenged by the findings of Mukherjee *et al.* published in this volume and by recent clinical trials testing the effect of HBO_2 on post-stroke and mTBI patients [1,23,24]. Changes in brain activity that were assessed by SPECT imaging, as described next, further support this understanding [23,24].

HBO_2 therapy can activate neuroplasticity and revitalize brain functions: New trials provide convincing evidence that hyperbaric oxygen can induce neuroplasticity, leading to repair of chronically impaired brain functions and improved quality of life in post-stroke and mTBI patients with prolonged post-concusssion syndrome, even years after the brain insult [23,24].

These trials adopted the crossover approach in order to overcome the inherent sham-control constraints of HBO_2 therapy. In this approach, the participants are randomly divided into two groups. One, the trial group, receives two months of HBO_2 treatment while the other, the control group, goes without treatment during that time. The latter are then given the same treatment two months later. The advantage of the crossover approach is the option for a triple comparison:

- between treatments of two groups,
- between treatment and non-treatment periods of the same group, and
- between treatment and non-treatment periods in different groups.

The study endpoint included blinded detailed computerized clinical evaluations that were blindly compared for all patients, with single-photon emission computed tomography (SPECT) scans. HBO_2 sessions led to similar significant improvements in tests of cognitive function and quality of life in both groups. No significant improvements occurred by the end of the non-treatment period in the control group. What made the results particularly persuasive was that the results of SPECT imaging were well correlated with clinical improvements and revealed restored activity mostly in metabolically dysfunctional stunned areas. Those observations indicate hyperbaric oxygen as a potent means of delivering to the brain sufficient oxygen to activate neuroplasticty and restore impaired functions that are accomplished via an assortment of intricate mechanisms, some of which were mentioned earlier.

Rethinking the HBO_2 dose-response curve

The aforementioned recent trials provide convincing evidence that HBO_2 can repair brain damage in post-stroke and mTBI patients. These results, and in particular the remarkable agreement between clinical improvements and SPECT imaging, imply that the observed improvements following HBO_2 therapy in the earlier studies on mTBI patients and children with CP were due to the neurotherapeutic effect of hyperbaric oxygen rather than being a placebo effect.

By the same token, the observed improvements following either normal air at 1.3 atm abs (on patients with mTBI) or 14% air at 1.5 atm abs (on children with CP) imply that HBO_2 sessions can have significant neurotherapeutic effects even at low dosage, provided there is pressure elevation. Therefore, as we mentioned earlier, such doses should be considered as dose-comparison studies rather than sham-control, as was correctly done by Mukherjee *et al.*, who demonstrated normal air at 1.3 atm abs to be an effective treatment for children with CP rather than a placebo effect [1]. These results are also in agreement with the earlier findings by Collet *et al.* [4] that were perceived as puzzling for more than a decade. Yet, as stated by Collet *et al.* (Collet *et al.* 2001): *"The improvement seen in both groups for all dimensions tested deserves further consideration."* The results by Mukherjee *et al.* clearly responded to this suggestion by considering room air at 1.3 atm abs as dose-comparison. Their findings could have been even more persuasive had they included metabolic imaging as part of their evaluations. Since they did not, this issue should be further addressed in future studies.

Clearly, large-scale, well-controlled, pressure dose-response studies are required to determine the optimal HBO_2 therapy protocol for different conditions. Until such information is available, any treatment involving change in the environmental pressure should be considered as a dose-comparison rather than a sham-control study. Moreover, since at a young age, brain protection is stronger (reflected by high ROS levels associated with CP) and neuroplasticity is more potent, it is reasonable to expect that optimal efficacy will be achieved by lower

tissue oxygenation. Along such line of reasoning, the previously described trials used 2.0 atm abs for post-stroke patients and 1.5 atm abs for patient with mTBI with an intact macrovascular bed [23,24]. Due to the high diversity in the manifestation of cerebral palsy and in its severity, future efforts should also be directed towards a personalized dose-response curve. For example, it is likely that higher tissue oxygenation will be the practice of choice for children with a high expression of ApoE4, which is an inhibitor of mitochondrial respiration.

Treatment duration and monitoring protocols:

Treatment duration is another elusive issue that needs to be resolved by future studies. It is quite clear that weeks to months would be necessary for brain tissue r egeneration and angiogenesis, but the upper time limit from which no further improvements are expected remains unknown. The first clinical evaluation (not metabolic/physiological evaluation) should be done after a sufficient number of HBO_2 sessions and should expect sizable changes. One must bear in mind that children with CP suffer neurological deficiency since birth, so it will take time for the brain repair to become clinically apparent. For example, it is not reasonable to administer 20 daily HBO_2 sessions to children with pervasive developmental disorders (PDD) and expect to see significant clinical progress within a time frame of less than a month [25].

On the other hand, it is important to perform frequent metabolic/physiological evaluations, which may provide valuable information for adjusting the dose-response curve. More studies are needed to determine the minimal effective dosage and the treatment duration for specific brain injuries. Non-invasive, in-chamber measurements that are currently being developed, specifically EEG and DTI, may shed some light on this important question.

It is also crucial to perform long-term post-treatment evaluation, as done by Mukherjee *et al.*, who performed evaluations after two and eight months [1]. Especially, when children are concerned, one expects that HBO_2 therapy will ignite the brain's innate repair system so that improvements will continue long after the treatment. As Mukherjee *et al.* have found, different doses may generate similar short-term improvements but can lead to different long-term post-treatment effects. In other words, dose-response curves should be assessed based on long-term effects. Clearly, there is an urgent need for larger-scale, prospective studies with long-term follow-up.

Optimal candidates for HBO_2 therapy

Brain insults may result in a variety of brain injuries. The most severe is necrosis, which cannot be reversed. However, as was mentioned earlier, necrotic foci are often surrounded by metabolically dysfunctional, stunned areas, which manifest as regions of high anatomy-physiology mismatch. Current imaging technologies reveal that the stunned brain areas may persist for months and years after an acute brain event [24, 26-28] and this is where metabolic intervention can be most effective [23,24]. For this reason, the optimal candidate for hyperbaric oxygen is a patient with unrecovered brain injury where tissue hypoxia is the limiting factor for the regeneration processes. In this patient, HBO2 may induce neuroplasticity in the stunned regions where there is a brain anatomy/physiology (e.g., SPECT/CT) mismatch [23, 24]. Unfortunately, in many – if not most – clinical studies done with hyperbaric oxygen on brain-injured patients, including those with cerebral palsy, the stunned areas have not been assessed by imaging. The anatomical/physiological imaging should be incorporated as an essential part of the basic evaluation of every candidate for hyperbaric oxygen therapy. In a similar manner, transcutaneous oximetry at the ulcer bed serves as a basic evaluation for patients suffering from peripheral non-healing wounds [29,30}.

An urgent call

In conclusion, we call on the hyperbaric community to rethink the neurotherapeutic effects of HBO_2 therapy and to agree on common and scientifically sound guidelines to best conduct prospective, controlled HBO_2 clinical trials. Reaching a consensus on the way to handle the control group, dose *vs.* efficacy, selection criteria of the study cohort and duration of treatment will pave the way for future studies that will explore the full potential of neurotherapeutic HBO_2.

We envision future studies that will demonstrate the effectiveness of HBO_2 therspy for a wide spectrum of syndromes that currently have partial or no solutions, such as central sensitization (fibromyalgia), radiation damage, vascular dementia and other metabolic aging effects.

The authors report that no conflict of interest exists with this submission.

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REFERENCES

1. Mukherjee A, Raison M, Sahni T, Arya A, Lambert J, Marois P, et al. Intensive rehabilitation combined with hyperbaric treatment in children with cerebral palsy: A controlled longitudinal study Undersea Hyperb Med. 2014.

2. Lacey DJ, Stolfi A, Pilati LE. Effects of hyperbaric oxygen on motor function in children with cerebral palsy. Ann Neurol. 2012; 72(5): 695-703.

3. Hardy P, Collet JP, Goldberg J, Ducruet T, Vanasse M, Lambert J, et al. Neuropsychological effects of hyperbaric oxygen therapy in cerebral palsy. Dev Med Child Neurol. 2002; 44(7): 436-46.

4. Collet JP, Vanasse M, Marois P, Amar M, Goldberg J, Lambert J, et al. Hyperbaric oxygen for children with cerebral palsy: a randomised multicentre trial. HBO-CP Research Group. Lancet. 2001; 357(9256): 582-6.

5. Montgomery D, Goldberg J, Amar M, Lacroix V, Lecomte J, Lambert J, et al. Effects of hyperbaric oxygen therapy on children with spastic diplegic cerebral palsy: a pilot project. Undersea Hyperb Med. 1999; 26(4): 235-42.

6. James PB. Hyperbaric oxygenation for cerebral palsy. Lancet. 2001; 357(9273): 2052-3.

7. Chen Z, Ni P, Lin Y, Xiao H, Chen J, Qian G, et al. Visual pathway lesion and its development during hyperbaric oxygen treatment: a bold- fMRI and DTI study. J Magn Reson Imaging. 2010; 31(5): 1054-60.

8. Huang L, Obenaus A. Hyperbaric oxygen therapy for traumatic brain injury. Med Gas Res. 2011; 1(1): 21.

9. Neubauer RA, James P. Cerebral oxygenation and the recoverable brain. Neurol Res. 1998; 20 Suppl 1: S33-6.

10. Vlodavsky E, Palzur E, Soustiel JF. Hyperbaric oxygen therapy reduces neuroinflammation and expression of matrix metalloproteinase-9 in the rat model of traumatic brain injury. Neuropathol Appl Neurobiol. 2006; 32(1): 40-50.

11. Lin KC, Niu KC, Tsai KJ, Kuo JR, Wang LC, Chio CC, et al. Attenuating inflammation but stimulating both angiogenesis and neurogenesis using hyperbaric oxygen in rats with traumatic brain injury. J Trauma Acute Care Surg. 2012; 72(3): 650-9.

12. Zhang JH, Lo T, Mychaskiw G, Colohan A. Mechanisms of hyperbaric oxygen and neuroprotection in stroke. Pathophysiology. 2005; 12(1): 63-77.

13. Gunther A, Kuppers-Tiedt L, Schneider PM, Kunert I, Berrouschot J, Schneider D, et al. Reduced infarct volume and differential effects on glial cell activation after hyperbaric oxygen treatment in rat permanent focal cerebral ischaemia. Eur J Neurosci. 2005; 21(11): 3189-94.

14. Etzion Y, Grossman Y. Pressure-induced depression of synaptic transmission in the cerebellar parallel fibre synapse involves suppression of presynaptic N-type Ca2+ channels. Eur J Neurosci. 2000; 12(11): 4007-16.

15. Hanlo PW, Gooskens RJ, van Schooneveld M, Tulleken CA, van der Knaap MS, Faber JA, et al. The effect of intracranial pressure on myelination and the relationship with neurodevelopment in infantile hydrocephalus. Dev Med Child Neurol. 1997; 39(5): 286-91.

16. Berman S, Abu Hamad R, Efrati S. Mesangial cells are responsible for orchestrating the renal podocytes injury in the context of malignant hypertension. Nephrology (Carlton). 2013; 18(4): 292-8.

17. Efrati S, Berman S, Goldfinger N, Erez N, Averbukh Z, Golik A, et al. Enhanced angiotensin II production by renal mesangium is responsible for apoptosis/proliferation of endothelial and epithelial cells in a model of malignant hypertension. J Hypertens. 2007; 25(5): 1041-52.

18. Johnson W, Nguyen ML, Patel R. Hypertension crisis in the emergency department. Cardiol Clin. 2012; 30(4): 533-43.

19. Markovic D, Kovacevic H. Recompression therapy of mountain sickness. Arh Hig Rada Toksikol. 2002; 53(1): 3-6.

20. Harch PG. Hyperbaric oxygen therapy for post-concussion syndrome: contradictory conclusions from a study mischaracterized as sham-controlled. J Neurotrauma. 2013; 30(23): 1995-9.

21. Wolf G, Cifu D, Baugh L, Carne W, Profenna L. The effect of hyperbaric oxygen on symptoms after mild traumatic brain injury. J Neurotrauma. 2012; 29(17): 2606-12.

22. Wolf EG, Prye J, Michaelson R, Brower G, Profenna L, Boneta O. Hyperbaric side effects in a traumatic brain injury randomized clinical trial. Undersea Hyperb Med. 2012; 39(6): 1075-82.

23. Boussi-Gross R, Golan H, Fishlev G, Bechor Y, Volkov O, Bergan J, et al. Hyperbaric oxygen therapy can improve post concussion syndrome years after mild traumatic brain injury - randomized prospective trial. PLoS One. 2013; 8(11): e79995.

24. Efrati S, Fishlev G, Bechor Y, Volkov O, Bergan J, Kliakhandler K, et al. Hyperbaric oxygen induces late neuroplasticity in post stroke patients--randomized, prospective trial. PLoS One. 2013; 8(1): e53716.

25. Sampanthavivat M, Singkhwa W, Chaiyakul T, Karoonyawanich S, Ajpru H. Hyperbaric oxygen in the treatment of childhood autism: a randomised controlled trial. Diving Hyperb Med. 2012; 42(3): 128-33.

26. Fernandez-Bouzas A, Harmony T, Fernandez T, Silva-Pereyra J, Valdes P, Bosch J, et al. Sources of abnormal EEG activity in brain infarctions. Clin Electroencephalogr. 2000; 31(4): 165-9.

27. Siddique MS, Fernandes HM, Wooldridge TD, Fenwick JD, Slomka P, Mendelow AD. Reversible ischemia around intracerebral hemorrhage: a single-photon emission computerized tomography study. J Neurosurg. 2002; 96(4): 736-41.

28. Neubauer RA, James P. Cerebral oxygenation and the recoverable brain. Neurol Res. 1998; 20 Suppl 1: S33-6.

29. Niinikoski JH. Clinical hyperbaric oxygen therapy, wound perfusion, and transcutaneous oximetry. World J Surg. 2004; 28(3): 307-11.

30. Efrati S, Gall N, Bergan J, Fishlev G, Bass A, Berman S, et al. Hyperbaric oxygen, oxidative stress, NO bioavailability and ulcer oxygenation in diabetic patients. Undersea Hyperb Med. 2009; 36(1): 1-12.

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