Hyperbaric oxygen therapy and preconditioning for ischemic and hemorrhagic stroke

Sheng-li Hu[1, 2, *], Hua Feng[2], Guo-hua Xi[1]

1 Department of Neurosurgery, University of Michigan, Ann Arbor, MI, USA
2 Department of Neurosurgery, Southwest Hospital, Third Military Medical University, Collaborative Innovation Center for Brain Science, Chongqing, China
*Correspondence to: Sheng-li Hu, M.D., husl1937@163.com.
orcid: 0000-0001-6438-6924

Abstract

To date, the therapeutic methods for ischemic and hemorrhagic stroke are still limited. The lack of oxygen supply is critical for brain injury following stroke. Hyperbaric oxygen (HBO), an approach through a process in which patients breathe in 100% pure oxygen at over 101 kPa, has been shown to facilitate oxygen delivery and increase oxygen supply. Hence, HBO possesses the potentials to produce beneficial effects on stroke. Actually, accumulated basic and clinical evidences have demonstrated that HBO therapy and preconditioning could induce neuroprotective functions *via* different mechanisms. Nevertheless, the lack of clinical translational study limits the application of HBO. More translational studies and clinical trials are needed in the future to develop effective HBO protocols.

Key words: hyperbaric oxygen; therapy; preconditioning; brain ischemia; hemorrhage; stroke; mechanism; clinical trial

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Introduction

Hyperbaric oxygen (HBO) therapy is a treatment *via* a procedure in which patients breathe in 100% pure oxygen at over 1.0 atmosphere absolute (ATA; 101 kPa). Typically, this therapy involves pressure between 1.5 and 3.0 ATA for 60 to 120 minutes, once or twice daily (Harch, 2015; Yan et al., 2015). It was initially developed at the 19th century for delivering HBO to caisson workers and deep-sea divers with decompression sickness. Until now, it has been widely used in patients with carbon monoxide poisoning, arterial gas embolism, hearing loss, gas gangrene, skin graft, radiation injury, and traumatic brain injury (Al-Waili et al., 2005; Davis et al., 2014; Wang et al., 2014; Hu et al., 2015a). It should be noted that HBO produces preventive and therapeutic effects on ischemic and hemorrhagic stroke (Sanchez, 2013; Stetler et al., 2014).

HBO therapy

To date, stroke is the major leading cause of death worldwide (Towfighi and Saver, 2011; Ding et al., 2014; Hafez et al., 2014; Seifert and Pennypacker, 2014; Hill et al., 2015; Xu et al., 2015). In the past 40 years, the stroke morbidity fell by 42% in developed countries, while rose in developing nations. Ischemic stroke occupies nearly 80% of stroke, which is a heavy burden of the patient's family and the society (Feigin et al., 2009). However, the treatments for stroke are still limited. Accumulated evidences demonstrate that the stability of oxygen saturation is critical for neuronal injury after stroke. Local hypoxia and anoxia result in cellular damage and ultimately complete stroke (Al-Waili et al., 2005). HBO has been shown to facilitate oxygen delivery, increase oxygen supply, ameliorate cerebral circulation, decrease cerebral edema, and reduce brain infarction and

utilized to treat cerebral ischemia (Sunami et al., 2000; Matchett et al., 2009; Sanchez, 2013; Ding et al., 2014). In animal models of brain ischemia, numerous studies show a neuroprotective role of HBO. HBO decreases infarct size and enhances survival after global and focal cerebral ischemia (Krakovsky et al., 1998; Yin et al., 2003; Schabitz et al., 2004). Other beneficial influences of HBO therapy on ischemic stroke include minimized apoptotic cell death (Yin et al., 2003; Veltkamp et al., 2006b), reduced blood-brain barrier breakdown (Veltkamp et al., 2006a), lessened brain edema (Huang et al., 2007), and improved neurological functions (Bennett et al., 2014). Interestingly, a recent study found that HBO therapy at 7 days after ischemic stroke promoted endogenous neurogenesis and enhanced neurological recovery *via* reactive oxygen species (ROS)/hypoxia-inducible factor-1alpha (HIF-1α)/β-catenin pathway. This implied HBO may be still effective for the stroke survivors (Hu et al., 2014).

Clinical trials regarding the effects of HBO on cerebral ischemia have also been performed in the past decades. Until now, there have already been 11 randomized controlled trials (Bennett et al., 2014). Li et al. (1998) reported that electroencephalogram (EEG), cerebral blood flow, and serum superoxide dismutase were improved in the HBO treated group compared with the control group. Another group enrolled 112 patients with acute stroke that were divided into two parts. The results showed that HBO therapy significantly reduced the serum levels of soluble intercellular adhesion molecule, soluble vascular cell adhesion molecule, soluble E-selectin, and matrix metalloproteinase-9 compared to the routine treatment group (Zhao et al., 2008). A study enrolled 33 participants admitted to the emergency department within 24 hours of stroke onset. But the results suggested there was no notable benefit on neurological assessment at 24 hours after HBO treatment (Rusyniak et al., 2003). A systematic review of 7 of the 11 randomized trials showed no significant difference was observed in the mortality at 6 months in the HBO treated group compared with the control group (Bennett et al., 2014). However, 4 of 14 disability and neurological function scale scores were improved with HBO therapy. For example, the mean Orgogozo Scale score was higher and the mean Trouillas Disability Scale score lower following HBO treatment than that of the control group (Bennett et al., 2014). The authors concluded that, although current evidences are not enough to offer explicit guideline for clinical medicine, the possible value of HBO in clinical practice are not excluded (Bennett et al., 2014). The possible reasons for these results of the above trials include inappropriate sample sizes, relaxed patients selection, unsuitable HBO protocols such as timing, oxygen dose, and inappropriate outcome measures (Bennett et al., 2014).

Intracerebral hemorrhage (ICH), a particularly devastating form of stroke, always leads to severe disability and mortality (Keep et al., 2012; Mendelow et al., 2013). Diverse mechanisms, including primary brain tissue damage, early hematoma expansion, mass effect, toxicity of blood component, and inflammation, cause brain injury following ICH (Xi et al., 2006, 2014; Xiong et al., 2014; Schlunk and Greenberg, 2015; Selim and Sheth, 2015; Xiong and Yang, 2015). To date, therapy strategies toward ICH injury mechanism such as neurosurgical interventions demonstrate limited effects. Multimodality treatments may be more effective for improving ICH outcome (Pandey and Xi, 2014). Hyperbaric oxygenation has shown beneficial influences on hemorrhagic stroke in experimental models and clinical practice. Laboratory data suggested that HBO therapy could ameliorate early brain injury, reduce brain edema, and decrease neurological deficit induced by ICH through a mechanism involving the improvement of cerebral oxygenation and metabolism (Zhu et al., 2015). Another study found that HBO treatment reduced early perihematomal brain edema in a rat whole blood injection model (Qin et al., 2008a). Additionally, Peng et al. (2014) reported that HBO may promote intracephalic angiogenesis following ICH. Two recent clinical studies revealed that HBO therapy could minimize depression symptoms induced by ICH and facilitate memory recovery after stroke (Cao et al., 2013; Boussi-Gross et al., 2015). Unfortunately, there are only a few clinical trials worldwide today. It is urgent to perform translational research and clinical trials in the field of HBO treatment on ICH.

HBO PRECONDITIONING

Preconditioning is a potential method to reduce illness severity which means a prior exposure to a stress/stimulus inducing tolerance to the subsequent fatal stimulus (Keep et al., 2014). Recently, HBO preconditioning has been extensively investigated in ischemic/hypoxic heart (Yogaratnam et al., 2006), liver (Losada et al., 2014), kidney (He et al., 2011) injury and traumatic brain and spinal cord injury (Hu et al., 2008, 2010; Lu et al., 2012) and displays positive results. Besides, the clinical studies of HBO preconditioning on cardiac surgery have suggested that HBO pretreatment could reduce neuropsychometric dysfunction, modulate the inflammatory response, improve left ventricular stroke work, and lessen postoperative complications after cardiopulmonary bypass (Alex et al., 2005; Yogaratnam et al., 2010). Very recently, a prospective, randomized clinical trial demonstrated repeated HBO could downregulate the release of cerebral and myocardial biochemical markers and reduce

the length of intensive care unit and hospital stay (Li et al., 2011). All of these data indicate the strong implications of HBO preconditioning in ischemic and hemorrhagic brain injury. HBO preconditioning was first used in a gerbil brain ischemia model (Wada et al., 1996). Since then, a wide range of documents explored the neuroprotective role and underlying mechanism of HBO preconditioning on ischemic and hemorrhagic stroke (Qin et al., 2007, 2008b; Yan et al., 2013; Hu et al., 2015b; Yang et al., 2015). Most of the investigations found that pretreatment with HBO was beneficial and useful in different animal models despite some negative results (Wada et al., 1996; Prass et al., 2000; Qin et al., 2007, 2008a). Nevertheless, the lack of clinical translational studies limits the application of HBO preconditioning to reduce ischemic and hemorrhagic brain damage.

Mechanisms of HBO therapy and preconditioning

Multiple mechanisms are involved in HBO therapy and preconditioning. Directly, HBO therapy increases oxygen tension in brain tissue. For instance, brain tissue partial pressure of oxygen could elevate from a baseline 20–40 mmHg to 420 mmHg with 2.5 ATA HBO therapy through which HBO may improve the local tissue metabolism (Matchett et al., 2009). HBO therapy also inhibits oxidative stress, which is considered to be one of the most important factors contributing to cerebral ischemic and hemorrhagic injury (Matchett et al., 2009; Ding et al., 2014). Besides, HBO may produce neuroprotective role *via* the suppression of inflammation. Microglia/macrophage polarization is a common phenomenon after stroke. M1 type microglia/macrophages are proinflammatory and M2 type anti-inflammatory (Zhao et al., 2015). So HBO therapy may promote the M2 transformation of microglia/macrophages in stroked brain. In addition, a variety of proteins such as cyclooxygenase-2 (Cheng et al., 2011), matrix metalloproteinase-9 (Hu et al., 2008), osteopontin (Hu et al., 2015b), SirT1 (Yan et al., 2013), heat shock protein 72 (Wada et al., 1996), ribosomal protein S6 kinase (Qin et al., 2008b) are involved in the effects of HBO preconditioning.

Limitations

Although increasing evidences have provided promising results of HBO therapy for stroke, it should be noted that some issues need to be addressed. For example, the optimal protocols, including pressures, doses, and time windows, should be validated. A past study indicated 5 sessions rather than 2 or 3 sessions of preconditioning with HBO could exert reduction of brain edema (Qin et al., 2007). Three clinical trials also suggested HBO failed to induce neuroprotection against brain ischemia (Anderson et al., 1991; Nighoghossian et al., 1995; Rusyniak et al., 2003). These results may be related to the time point of starting treatment and pressure used in HBO therapy (Michalski et al., 2011). Animal studies have revealed early HBO therapy may be more effective (Badr et al., 2001; Lou et al., 2004). Hence, more randomized clinical trials are needed to validate optimal protocols for stroke patients.

Conclusion

HBO therapy or preconditioning may provide beneficial effects on ischemic and hemorrhagic brain injury. To develop effective HBO protocols for ischemic and hemorrhagic stroke, more translational studies and clinical trials are needed.

Author contributions

SLH searched the literature, analyzed the data, designed and wrote this paper. GHX and HF designed and revised it.

Conflicts of interest

There is no conflict of interest to declare.

Plagiarism check

This paper was screened twice using CrossCheck to verify originality before publication.

Peer review

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