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Review article

The relation of hyperbaric oxygen with oxidative stress - reactive molecules in action

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ABSTRACT

It is obvious that hyperbaric oxygen (HBO) administrations result in increased levels of oxidation products and a wide array of studies exist in literature reporting significant lipid peroxidation and/or protein oxidation in blood and tissues of HBO-exposed organisms. Nevertheless, in cases not exceeding the universally approved limits of this precious therapeutic modality, effective endogenous antioxidant defense mechanisms are present hindering a real state of "oxidative stress." In early 2000s, hyperoxia achieved by HBO treatments has been reported to act in a double-faceted manner: (i) The hyperoxic effect which delivers oxygen to tissues with increased demand, and (ii) the reactive oxygen species (ROS)-mediated pathways known to be significantly elevated during HBO administrations. To date, ROS-signaling exhibits a great area in medical science opening new doors for researchers day by day. With regard to HBO, increased production of the superoxide radical followed by hydrogen peroxide seems to be the key point for its effects; the transcription factors nuclear factor erythroid 2-related factor 2 and hypoxia-inducible factor-1 alpha along with their main target protein heme oxygenase-1 are also involved in several mechanisms. This paper aims to briefly review some of the known interactions of HBO-triggered molecular details. By this way, we hope to attract more attention to this interesting research area in order to provide scientists a view for future projects.

KEY WORDS: Heme oxygenase, hydrogen peroxide, hyperbaric oxygen, reactive oxygen species, superoxide radical, transcription factors

INTRODUCTION

Hyperbaric oxygen (HBO) therapy is based on administering pure oxygen to the patient while undergoing increased ambient pressure. During the therapy session, the erythrocyte hemoglobin reaches 100% saturation and much more oxygen is dissolved in the blood plasma than regular; therefore high amounts of oxygen is delivered to almost all tissues that, in case of a number of well-defined pathologies, will benefit from this condition. Examples for pathologies which are known for beneficial effects of HBO therapy are problem wounds, necrotizing soft tissue infections, delayed radiation injury, refractory osteomyelitis, thermal burns, compromised skin grafts and flaps, crush injury, and compartment syndrome. Furthermore, the main health problem for which HBO is a life-saving treatment by enhancing blood and tissue oxygenation is, of course, carbon monoxide poisoning. Clostridial myositis or myonecrosis (gas gangrene) is also an important indication for HBO, which is due to the anaerobe characteristic of the pathogenic agent and can be cured by maintenance of the hyperoxic state [1]. On the other hand, a second mechanism of action of HBO treatment is the bubble reducing effect depending on the Boyle-Marriott law by increasing the ambient pressure. This mechanism comprises another group of life-saving indications for HBO: Decompression sickness and air/gas embolism. Pathologies such as central retinal artery occlusion [1,2] and idiopathic sudden sensorineural hearing loss [3] are also reported to benefit from HBO therapy and could be ordered, at least in part, to this pressure-dependent mechanism, but are also related with its hyperoxic effect.

Apart from cases representing the live-saving modality of HBO therapy where it is regularly the first choice for the physician, most other indications are based on inflammatory or infectious background for which HBO is mainly administered as an adjunctive or complementary method. In our institution, a number of experimental studies have been formerly conducted on the effects of HBO alone or in combination with other therapeutic approaches on inflammatory/infectious models which demonstrated beneficial effects for uveitis [4], myositis [5], cystitis [6-8], pancreatitis [9-11], colitis [12-17], mediastinitis [18], nephrotic syndrome [19,20], spinal cord injury [21,22], colonic anastomosis [23,24], osteomyelitis [25], and even for sepsis [26-28]. Another series of studies reflected good outcome with HBO in experimental ischemia/reperfusion [29-31] as an important model of inflammation, or cerebral ischemia [32-34]. Case reports and

series conducted on inflammatory [35,36] as well as other pathologic conditions [37,38] also represented profit when treated with HBO.

OXYGEN TOXICITY AND HBO

Oxygen is essential for life; in other words, for human being life without oxygen is impossible. Furthermore, it is also well known that the production of free radicals, particularly reactive oxygen species (ROS), is inevitable in aerobic life. Due to its atomic structure, oxygen itself owns a biradical nature and has also the ability to trigger ROS production in higher amounts. Exposure to supranormal levels of oxygen is therefore a case which has to be handled with care even in normobaric conditions [39]. Starting with the report of Lorrain Smith in 1899 [40], a huge number of articles regarding the details of oxygen toxicity are apparent in the medical literature, mainly describing a relation with ROS [41-46]. Due to this relation and known fact that oxidative stress is a consequence of enhanced ROS production, HBO has been used as a good model for inducing oxidative stress in experimental conditions; between the mid 80s and mid 90s a research team from the University of Texas [47-51], and others [52,53] concentrated on preventing the lung and or brain against HBO-induced toxicity by supporting the endogen antioxidant system, mainly glutathione (GSH) and superoxide dismutase (SOD). However, it has to be noted that such studies [47-53] used generally extremely high pressure/duration ranges, i.e. higher than 4 atmospheres and longer than 2 h, which cannot be adapted to the regular use of HBO for therapeutic reasons. According to the Undersea and Hyperbaric Medical Societies' guidelines, the maximal pressure and duration of HBO administration is set to be 3 atmospheres and 2 h [54]; this range is proven to be safe and potential side-effects are very rarely reported.

To elucidate the relation between HBO treatments within the safe therapeutic limits, i.e. at the maximal 3 atmosphere/2 h range, and its potential oxidative effect in living organisms, a research group lead by the Department of Physiology of our institution conducted a series of experimental studies in rats. In those studies, the lung, since being the first encountering site of hyperbaric hyperoxia, blood/erythrocytes, since building a bridge between the lung and all other tissues during delivering the huge amounts of oxygen, and the brain, because of its highest vulnerability to hyperoxic conditions compared to other organs, were chosen as the ideal targets for evaluating the effects of HBO. At the preliminary stage, a clear relation with HBO oxidative stress markers and indices of the endogenous antioxidant system were seen [55,56], for which the potential interaction of the pressurized ambient air was eliminated and the effect seem mainly to depend on pure oxygen exposure [57,58]. One step forward, the increasing effect of HBO on oxidant/antioxidant biomarkers was defined to be pressure-related in a nearly linear manner [58,59]. Then, a similar linear relation with the exposure time was also observed [60,61], leading to the conclusion that the hyperbaric hyperoxic oxidative effect is both pressure- and duration-dependent [62].

After the definition of the exposure pressure/duration-related action of HBO on the organism's oxidant/antioxidant systems [58-62], we concentrated on how long the increased levels of oxidation products or antioxidants persist after a single exposure to the maximal HBO-administration limit at 3 atmospheres for 2 h: As a result, all alterations turned to normal range at last in 90 min in the lung and erythrocytes [63], as well as in the brain cortex tissue [64]. Interestingly, the reversal of oxidation products occurred approximately half an hour earlier than those of the antioxidant enzymes' activities [63,64], which was interpreted to prove the safety of HBO administrations at therapeutic ranges. Another interesting note from these studies was the fact that in the brain cortex tissue [64] the drop of oxidation products was earlier apparent than in the lung and erythrocytes [63]. This finding reflected that, although being categorized as a highly vulnerable target for hyperoxia, the brain tissue owns relatively good endogenous defense mechanisms against hyperbaric hyperoxic stress, at least in part at the used maximal pressure/duration range of the above-mentioned experiments. Supportively, in another study, one of these potential defense mechanisms was asserted to be asymmetric dimethylarginine [65], an endogenous inhibitor of nitric oxide synthase.

Nearly all of the above studies tested the oxidative potential of HBO when administered in a single-session modality. However, in clinic conditions, HBO is generally planned for at least 5 and sometimes up to 40 or, in troublesome cases, more sessions near 100. Therefore, in another set of experiments the potential cumulative oxidative effect of HBO was tested in rats exposed to 5, 10, 15, 20, 30, and 40 daily consecutive 90 min sessions at 2.8 atmospheres [66-68]. The main result of these studies reflected evidence for an accumulation of oxidation products with prolonged exposure periods in the lung [66] and erythrocytes [67], but not in brain tissue [68]. The good news, however, was that the level of antioxidant enzymes activities accompanied the increase of oxidative stress markers; so, a real "oxidative stress" [69] was not apparent which -one more time- supports the safety of HBO within its approved therapeutic limits. On the other hand, with regard to the results of the brain study [68], a better defense mechanism in the cerebral cortex, white matter, and cerebellum [65] was present again.

ADDITIONAL MECHANISMS OF ACTION FOR HBO

For a long time, the efficacy of HBO was simply explained by the above explained two mechanisms, i.e. the pressure-dependent bubble-reducing action and the maximal saturation-dependent hyperoxygenation of tissues. With beginning of the 2000s, the molecular interactions of the hyperoxic effect started to be argued widely. Many physiologic roles of free radicals and reactive species in cellular function and signaling were defined [70,71] with particular importance referred to the superoxide anion hydrogen peroxide cascade [71-73]; these two versatile endogenously produced reactive intermediates were also brought forward to be responsible for - at least in part - the beneficial effects of HBO [74].

There is no doubt that, in case of hyperbaric hyperoxia, e.g. HBO, the production of ROS is enhanced, and the superoxide radical along with hydrogen peroxide possess the

supreme fraction among them. The hyperoxic oxidative effect is inevitable during HBO exposures and, by this way, not only the delivery of supra-physiologic oxygen levels but also the triggering action of hyperoxia on several molecular pathways is responsible for the benefits of this therapeutic modality [75]. The first molecule which is reported to be a mediator for the beneficial actions of HBO, particularly by supporting the tolerance of the organism against oxidative damage, was heme oxygenase-1 (HO-1) [76], also called heat shock protein (HSP)32, an ubiquitously expressed multitask enzyme with the main job of heme degradation but also known for its important roles in the regulation of cell proliferation, differentiation, oxidant/antioxidant systems, and apoptosis, thereby affecting inflammatory processes and immune response [77]. In this context, the neuroprotective action of HO-1 [78] could also explain the better outcome in the oxidative status of the "brain" studies [64,68] mentioned above.

With a connection to HO-1, the nuclear factor erythroid 2-related factor 2 (Nrf2), an important component of the cellular defense, presents also a relation with HBO as a mediator of its effects [79]. Nrf2 is a redox-sensitive transcription factor and HO-1 is defined to be its principal target protein [80]. With this regard, involvement of the Nrf2/HO-1 axis looks very important, particularly in the use of HBO for pretreatment/preconditioning reasons [81-83]. Apart from HSP32 (HO-1), taking a look on other members of the HSP family, which are proteins that are produced by cells in response to exposure to stressful conditions, increased values of HSP70 [84-86] but not HSP72 [87,88] were reported with HBO exposure.

Another target molecule which is known to be involved in the action mechanism(s) of HBO is the hypoxia-inducible factor-1 alpha (HIF-1α) [75]. HIFs are transcription factors that respond to changes of oxygen availability in the cellular environment, generally by increased expression in response to hypoxia [89]. Logically, due to providing hyperoxia but not hypoxia, the HBO-mediated activation of HIF-1α-related pathways looks somewhat ironic. This could be explained by the rapid fall of tissular oxygen levels after the hyperoxic state, i.e. imitating hypoxia. It is reported that continuous hypoxia induces only HIF-1α, whereas intermittent hypoxia induces both HIF-1α and Nrf2 [90]. Concordantly, the hyperoxia-normoxia-hyperoxia cycle between HBO sessions can be adapted to normoxia-hypoxia-normoxia loops, i.e. simulating intermittent hypoxia; as a result, both HIF-1α and Nrf2 are stimulated by HBO. The interactions of transcription factors and their target proteins have already a lot of secrets to be elucidated; as an interesting report for the HBO-related molecules defined yet, it was stated that HIF-1α normally down-regulates HO-1 induction, but in case of Nrf2 over-expression the inhibitory effect of HIF-1α gets reversed and by this way, both Nrf2 and HIF-1α contribute to the HO-1-mediated action [91]. Therapeutic effects of HBO which depend on HIF-1α-related pathways are mainly concentrated on increasing the ischemic tolerance [92-94] and wound healing [95,96]. But controversially, the inhibitory action of HBO on HIF-1α expression due to its hyperoxic state while undergoing the therapy session has also been reported for mediating beneficial effect [97].

HBO AND THE ENDOGENOUS ANTIOXIDANT SYSTEM

In the above listed experiments proving a pressure [58,59] and exposure time-dependent [60,61] relation of HBO on oxidant and antioxidant markers, generally elevated activities of the main antioxidant enzymes such as SOD, catalase, and GSH peroxidase were detected [62]. The high levels of enzyme activities persisted longer than those of oxidation products' lifetime [63,64]. Earlier studies which aimed to test preventive strategies against oxygen toxicity by administration of extreme higher pressure/duration procedures resulted in the exhaustion of antioxidant sources [47-51]. A continuing study of our institutional team presented the ability of HBO on increasing copper/zinc (Cu/Zn)-SOD expression at its mRNA level [98]. Interestingly, melatonin, a versatile molecule with strong antioxidant action [99], lowered the Cu/Zn-SOD mRNA expression rate of HBO; however, when administered alone, melatonin itself caused nearly the same Cu/Zn-SOD expression level as HBO [100], indicating an interaction between melatonin, and HBO which has to be thoroughly defined. Indeed, reports of our team [101-103] and others [104-106] designated melatonin as an ideal supportive agent for HBO therapy which will not disturb and could possibly contribute to the healing effects by protecting potential uncontrolled oxidative reactions.

Taking a nearer look on our studies regarding the melatonin-HBO interactions on oxidant/antioxidant status of the organism; melatonin was able to reduce the increased level of oxidation products in both lung [101] and brain [102] tissue, whereas the HBO-induced increase of antioxidant enzymes activities were only slightly affected by melatonin administration. Results of the single-session studies [101,102] were also supported by similar outcome later, shown in a consecutively administered 10 days HBO experiment [103]. Interestingly, all three works reflected a higher efficacy for endogenously secreted melatonin than the exogenously administered option at pharmacologic doses.

The increasing effect of melatonin on antioxidant enzymes gene expression has been known for a relatively long time [107]. To date, it is also clear that HBO has the ability to induce antioxidant gene expression [98,108]. However, the details of molecular interactions between melatonin and HBO-triggered pathways still need to be elucidated and warrant promising results for the scientific background of hyperbaric medicine.

CONCLUDING REMARKS

As extensively reviewed by Prof. Stephen R. Thom, pioneer of hyperbaric medicine research, "oxidative stress is fundamental to HBO therapy" [75]; however, the oxidative level caused by HBO within its usual therapeutic limits could be characterized as a "controlled oxidative stress", since the rise of oxidation products are generally accompanied by significantly increased levels of antioxidants. On the other hand, controlled levels of oxidative stress which do not overcome the antioxidant capacity of the organism can trigger a number of molecular pathways by using the reactive intermediates as signaling agents.

Taken together, the hyperoxic state as a rule of HBO administrations, can beneficially act via both the hyperoxygenation of tissues and the ROS-induced actions triggering several bioactive molecules including Nrf2, HIF-1α, and HO-1. Of course, the molecular interactions of HBO and HBO-induced mechanisms are not limited to these 3 examples and more studies are needed in order to enlighten the exact mechanisms of action in detail.

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