Hyperbaric oxygen pretreatment and preconditioning

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ABSTRACT

Exposure to hyperbaric oxygen (HBO_2) before a crucial event, with the plan to create a preventing therapeutic situation, has been defined "preconditioning" and is emerging as a useful adjunct both in diving medicine as well before ischemic or inflammatory events. Oxygen pre-breathing before diving has been extensively documented in recreational, technical, commercial and military diving for tissue denitrogenation, resulting in reduced post-diving bubble loads, reduced decompression requirements and more rapid return to normal platelet function after a decompression. Preoxygenation at high atmospheric pressure has also been used in patients before exposure to clinical situations with beneficial effects, but the mechanisms of action have not yet been ascertained. During the reperfusion of ischemic tissue, oxygenated blood increases numbers and activities of oxidants generated in tissues. Previous reports showed that HBO_2 preconditioning caused the activation of antioxidative enzymes and related genes in the central nervous system, including catalase (CAT), superoxide dismutase and heme oxygenase-1. Despite the increasing number of basic science publications on this issue, studies describing HBO_2 preconditioning in the clinical practice remain scarce. To date, only a few studies have investigated the preconditioning effects of HBO_2 in relation to the human brain and myocardium with robust and promising results.

RATIONALE

Preoxygenation by breathing elevated concentrations of oxygen (O_2) before an event has been documented to induce various effects that mirror the physiologic and therapeutic applications demonstrated both in extreme environments and in selected clinical applications. In the most trivial form, 100% oxygen prebreathing has been used to extend useful apnea time during breath-hold diving and to denitrogenate the lungs and other tissues before flights at very high altitudes or even before extravehicular activities (EVA) in space at reduced ambient pressure. A clinical counterpart is a recommended safety maneuver to extend safe intubation time after rapid induction of anesthesia and muscle paralysis, allowing prolonged laryngoscopy exposure time for tracheal intubation, especially in patients at risk of rapid desaturation following apnea such as pregnant women, small children and the obese.

Diving medicine applications

It has been exhaustively documented that oxygen exposure can be successfully utilized for recreational, technical, commercial [1] and military diving [2]. Among the clinical conditions that can be treated with oxygen therapy, decompression sickness (DCS) is one of the most common complications [3].

HBO_2 and normobaric oxygen (NBO_2) prebreathing maneuvers have been shown to be beneficial in preventing or reducing air bubble formation and platelet activation after a given dive profile, thus reducing the development of DCS [4,5]. Bosco and colleagues demonstrated that in-water O_2 prebreathing at a depth of 6 or 12 msw led to lower bubble scores than prebreathing O_2 at the surface in open-water sea divers after a set dive exposure [5]. The HBO_2 preconditioning procedure for denucleation may have a potential application in decreasing the DCS risk in humans. In addition, the authors showed that pre-

breathing HBO_2 constitutes an overall more efficient treatment than NBO_2 for reducing decompression-induced bubble formation and platelet activation [5].

The in-water prebreathing treatment has also been tested at higher depth (30 msw) for short exposure times, and the oxidative status and intracellular calcium ($[Ca^{2+}]_i$) of peripheral blood lymphocytes have been analyzed [6]. Results from this work showed additionally that prebreathing oxygen may enhance lymphocyte antioxidant activity and reduce ROS levels. Prebreathing oxygen in water may also preserve calcium homeostasis, suggesting a protective role in the physiological lymphocyte cell functions. Notably, the authors found augmented catalase enzyme activity as well as increases in catalase, superoxide dismutase and gluthatione peroxidase mRNA gene expression, which were interpreted as an enhanced antioxidant defense. In addition, no $[Ca^{2+}]_i$ increase was observed, thus suggesting supplementary evidence of a decreased oxidative stress [6].

In 2006, Landolfi and colleagues demonstrated that the partial pressure of dissolved nitrogen in fast tissues at 4 atmospheres absolute (atm abs) (405.30 kPa) after compression was similar between the groups of tissues that received previous hyperbaric oxygen and those that did not receive preoxygenation, thus suggesting that the N_2 washout effect by oxygen at ground level is quickly neutralized at depth [7]. The authors also reported a reduction of post-decompression bubble formation from 4 atm abs (405.30 kPa) after pretreatment with oxygen at 1.6 atm abs (162.12 kPa). This finding is consistent with the mechanism of gas nuclei elimination by oxygen pretreatment [8]. Indeed, previous experimental studies have shown that the delay for regeneration of a depleted gas nuclei population may be of the order of a few hours up to 100 hours [9].

In the same vein, an elegant 2009 study from Castagna and collaborators showed that breathing NBO_2 for 30 minutes before an open water air dive provided significant reduction in decompression-induced bubble formation, observed after the evaluation of venous gas emboli (VGE), Doppler ultrasound and bubble formation score [2]. VGE production is higher for repetitive dives than for a single dive [10], with a more significant risk of developing DCS following multiday repetitive dives [11]. Castagna [2] addresses three different hypotheses to explain how reduction of VGE can be dependent upon oxygen prebreathing: Denitrogenation, gas nuclei removal and hemodynamic effects. Notably in denitrogenation, inert gases accumulated in tissues diffuse more easily toward the bloodstream after a hyperoxic exposure that causes arterial O_2 pressure increase. This process reduces tissue N_2 supersaturation, thus preventing bubble production [12]. In addition, it has been reported that further protection against the onset of DCS is provided by exercise because increased metabolic levels improve ventilation, perfusion and diffusion during preoxygenation before altitude decompression [13]. In gas nuclei removal, O_2 has the potential of replacing N_2 in the nucleus by diffusion, thus eliminating pre-existing gas micronuclei prior to the bubble formation process [7,14,15]. Moreover, it has been shown that O_2 is responsible for the removal of protein-coated bubbles by the lymphatic bed [16], suggesting a reduction of gas nuclei in both venous and lymphatic systems [2]. However, it was demonstrated that this preoxygenation procedure causes a reduction in bubble size but not density [8]. Regarding hemodynamic effects, a significant heart rate and cardiac output decrease in parallel with a vascular resistance increase were found to follow a hyperoxic preconditioning at sea level for one hour in healthy subjects [17]. These adaptations persisted for more than an hour after restoring the environmental 21% O_2 [18].

Hyperbaric medicine applications

Preoxygenation at high atmospheric pressure has been used in patients before exposure to clinical situations with beneficial effects, but the mechanisms of action have not yet been ascertained. During the reperfusion of ischemic tissue, oxygenated blood increases numbers and activities of oxidants generated in tissues. Reperfusion increases the hazardous effects of early ischemic injury by release of cytokines and reactive oxygen species such as hydroxyl radical (•OH), superoxide radical (O_{2^-}), and hydrogen peroxide (H_2O_2) and by the activation of a complement system. This phenomenon has been broadly named ischemia-reperfusion (I/R) injury. All tissues can be involved in I/R, and animal models demonstrating the tolerance and vulnerability of different organs have been presented. There are many studies investigating I/R injury in different tissues such as kidney, liver, lung, testis, brain, heart muscle and skeletal muscle in the literature [19]. I/R injury in skeletal muscles and in bone may occur with vascular problems, including atherosclerotic occlusive disease, arterial thrombosis, or arterial

embolism, and after organ transplantation, cardiovascular surgery and vascular trauma [20]. In addition, limb ischemia-reperfusion occurs often in surgical procedures, such as when using a tourniquet to provide a bloodless surgical field [21].

In fact, despite improvements in surgical techniques and in anesthetic management, I/R injury remains an inevitable event of cardiac surgery, resulting in significant postoperative complications and multiple-organ dysfunction. Ischemia-reperfusion injury during cardiopulmonary bypass (CPB) also leads to myocardial stunning, necrosis or apoptosis that manifests clinically either acutely as low cardiac output or chronically as heart failure [22]. To date, brain injury after CPB for cardiac surgery has been well documented. Sequelae can be as mild as postoperative cognitive dysfunction and postoperative delirium and as severe as stroke [23].The etiology of cerebral injuries is probably multifactorial, from an interaction among cerebral microemboli, global cerebral hypoperfusion, inflammation, cerebral temperature modulation and genetic susceptibility [24].

Preconditioning is defined as the application of an intervention to activate endogenous protective mechanisms to potentially lessen the morphologic and functional sequelae of a subsequent ischemia insult. The phenomenon of ischemic preconditioning was first described in a canine myocardium ischemia-reperfusion injury model [25] and subsequently was shown in the brain [26]. Since then, intense research in the field of pharmacology has progressed to identify agents such as volatile anesthetic agents and ischemic preconditioning [27-29] that could duplicate the protective effects of preconditioning for cardiac surgery.

Previous reports showed that HBO_2 preconditioning caused the activation of antioxidative enzymes and related genes in the central nervous system including catalase (CAT), superoxide dismutase and heme oxygenase-1 [30–32]. Despite the increasing number of basic science publications on this issue, studies describing HBO_2 preconditioning in the clinical practice of cardiac surgery remain scarce. To date, only a few studies have investigated the preconditioning effects of HBO_2 in relation to the human brain and myocardium.

In 2004, Sharifi, *et al.* [33] described the successful use of HBO_2 to inhibit restenosis after percutaneous transluminal coronary intervention (PTCI) in acute myocardial infarction. In 2005, Alex, *et al.* [34] observed that repetitive pretreatment with three sessions of HBO_2 at 2.4 atm abs (243.18 kPa) before on-pump coronary artery bypass graft (CABG) surgery reduced neuropsychometric dysfunction and modulated favor-ably the inflammatory response after CPB. More recently, Yogaratnam, *et al.* [35] reported that preconditioning with a single session of HBO_2 at 2.5 atm abs (253.32 kPa) for 90 minutes before on-pump CABG surgery improved left ventricular stroke work post-CABG surgery while reducing intraoperative blood loss, ICU length of stay, and postoperative complications.

Additionally, Li, *et al.* [36] aimed to determine whether HBO_2 preconditioning could decrease the release of cerebral and myocardial biochemical markers such as S100B protein, neuron-specific enolase (NSE), and troponin I (cTnI) in the peri- and post-CABG surgery period. The primary end point of this last extensive study was to show that repeated HBO_2 preconditioning sessions significantly decreased release of S100B and NSE. A secondary end point of this study was to assess the effects of HBO_2 preconditioning on serum troponin I, inotrope usage, ventilator hours, length of ICU stay, postoperative duration of hospital stay, hemodynamic parameters and serum CAT activity. This study demonstrated positive results on the cardiac and neurologic functions of repeated HBO_2 preconditioning in on-pump surgery patients, but not for off-pump CABG surgery patients. The authors interpret these data as an indication that more ischemic events were happening during cardiopulmonary bypass and were prevented by preoxygenation.

A recent experimental paper has identified an important mechanism involved in triggering the beneficial effect of HBO_2 preconditioning, as the intracellular induction of heme-oxygenase-1 in hepatic IR injury [37]. Whether the various preconditioning protocol factors such as pressure, frequency or lag time before surgery contributes to the different results should be investigated in further studies and applied to diverse surgical procedures, especially major surgeries leading to postoperative ICU admission.

Conflict of interest

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

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