Optimization of intermittent oxygen/air exposure protocols prolongs the safe use of hyperoxia

Haim Bitterman

Clalit Health Services, Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, Israel

A steadily growing body of data indicates that hyperoxia (the use of oxygen at pressures that are higher than its normal atmospheric partial pressure) exerts an extensive profile of physiologic and pharmacologic effects that improve tissue oxygenation, exert anti-inflammatory and antibacterial effects, and augment tissue repair mechanisms [1]. Such data establish the rational for the use of normobaric and hyperbaric hyperoxia in a list of clinical conditions characterized by tissue hypoxia, inflammation, infection, and impaired tissue healing. The major limitation confronting the clinical use of hyperoxia is its potential toxicity and the relatively narrow margin of safety that exists between its effective and toxic doses. The most obvious toxic manifestations of oxygen are those exerted on the respiratory and central nervous systems [2]. At pressures higher than 0.6 ATA (atmospheres absolute), (e.g. 60% oxygen at normal atmospheric pressure), and up to 2.8 ATA the most important toxic effect of hyperoxia is a pulmonary inflammatory response that may culminate to a full blown ARDS (Acute Respiratory Distress Syndrome). At pressures higher than 2.8 ATA the most prominent toxic effect of hyperoxia is on the brain, usually manifesting as tonic-clonic grand-mal type convulsions.

Currently employed hyperoxic treatment protocols or exposures to oxygen in recreational and military diving are safe because they are restricted to durations that are significantly shorter than the latent period required for development of toxic effects. Another currently employed approach to effective safe use of hyperoxia is that of intermittent exposures to oxygen with intervening air breaks during which subjects are exposed to air at the same ambient pressure. Presently used intermittent exposure protocols in humans are based on theoretical considerations, practical experience, and a limited number of observations that support a significant extension of oxygen tolerance in man by intermittent oxygen exposures. However, the basic mechanisms by which intermittent exposures convey protection against oxygen toxicity, and enable prolongation of the total exposure time to oxygen are largely unknown.

The study of Chavko and colleagues published in this issue of the ‘Journal of Experimental and Integrative Medicine’ [3] compared in rats two regimens of intermittent exposures to hyperbaric oxygen at 2.8 ATA on pulmonary oxygen toxicity. They quantified lung tissue mRNA of the pro-inflammatory cytokines TNF-α, IL-1, and IL-6, as well as that of HSP70 (Heat shock protein 70), and followed respiratory frequency and tidal volumes as markers of respiratory function. In this study intermittent hyperbaric oxygen (HBO) exposures (broken by 10 min hyperbaric air intervals) attenuated lung tissue expression of pro-inflammatory cytokines and changes in respiratory frequency and tidal volume. Rats exposed to an intermittent protocol that started with three longer (60 min) intermittent exposures followed by six shorter (30 min) exposures fared better than those exposed to a mirror image protocol (six 30 min exposures followed by three 60 min exposures). HSP70 mRNA was significantly higher in the continuous exposure (control) group and in the intermittent group of initial longer oxygen duration followed by shorter duration exposures. The authors mark the better protective effects of the intermittent protocol with initial longer hyperoxic sessions and suggest that a more robust exposure may be needed to provoke protective mechanisms. They also suggest that beneficial effects of intermittent exposure to hyperbaric oxygen upon pulmonary oxygen toxicity may be partially related to induction of HSP70 expression and its alleged protective effects against the pulmonary inflammatory response to hyperoxic stress.

The attractive possibility to diminish toxic effects of hyperoxia and to prolong safe total duration of exposures to oxygen by protocols that introduce intermittent isobaric air breaks (at the same ambient pressure) has previously been studied both by modeling data from animal experiments [4-6] as

www.jeim.org
well as by rather empirical studies in healthy humans [7, 8]. Unfortunately, theoretical modeling has not yielded further sufficient validation of safe human protocols for the clinical and diving arenas. Most intermittent hyperoxic protocols that are currently in use for clinical indications and for treatment of diving accidents have been modified throughout the years largely based on rather limited experimental observations in humans and on empirical experience.

The present study follows two previous studies of the same group. In one study they assessed the effect of intermittent air breaks on brain tolerance to HBO at 6 ATA. Using two different intermittent protocols, performed within what was found to be an optimal time window, they found a 2.4 fold increase in the duration of total O2 time to seizures compared to a continued HBO exposure control group [9]. In another extensive study they examined the effects of various intermittent hyperbaric oxygen/air protocols at 2.8 ATA on tolerance to pulmonary oxygen toxicity and on lung tissue expression of antioxidant enzymes, iNOS (inducible nitric oxide synthase), inflammatory cytokines, and lung tissue nitration [10]. It was found that all intermittent exposure schedules prolonged cumulative O2 time before death up to a maximal plateau level (~10 hours). It was also found that some of the intermittent protocols caused a markedly diminished expression of inflammatory cytokines and that this effect may be mediated by the anti oxidative and anti-apoptotic effects of the inducible form of heme oxygenase, HO-1 (Heme oxygenase-1).

In this regard, hyperbaric oxygen preconditioning should also be taken into consideration while contemplating on possible mechanisms of the protection conveyed by intermittent exposure to hyperoxia. In fact, HBO preconditioning has been found to up-regulate antioxidant enzymes [11], attenuate early apoptosis [12], and to induce tolerance against ischemic spinal cord injury [11, 12] and brain ischemia-reperfusion injury [13]. Yet, currently available data indicate that although induction of "classical" anti-oxidant enzymes may be important in protection conveyed by HBO preconditioning, the thus far demonstrated time frame of the phenomenon is long and may not be relevant for explaining rapid tolerance conveyed by intermittent oxygen/air exposures.

Intermittent exposure to oxygen represents an attractive way to enable prolonged use of hyperoxia. In this regard, the present study of Chavko and colleagues [3] adds important information on mechanisms of the protective effects of intermittent hyperoxia as well as a hint on a possible superiority of intermittent exposure protocols that start with a more robust exposure for enhanced triggering of protective mechanisms. Further studies are needed for elucidation of mechanisms by which intermittent oxygen/air exposures induce tolerance against toxic effects of hyperoxia. Such studies will form a direly needed pre-clinical data base for better construction of treatment protocols that could be tested in the clinical arena. It should be remembered that the available information on the subject originates from studies on healthy animals and healthy human volunteers. Application of inferences drawn from such studies to clinical conditions that by themselves are characterized by different combinations of tissue hypoxia, acute and chronic inflammatory responses, vascular derangements, and sometimes also infection, will require specific laboratory and clinical testing. Few experimental examples that highlight superiority of intermittent hypoxic protocols in animal models of human diseases characterized by enhanced systemic and pulmonary inflammatory responses already exist [14]. Yet, we are still far from having substantiated clues to the design of validated appropriate intermittent hypoxic protocols that will favor tissue repair by correcting hypoxia and diminishing local tissue inflammatory responses whilst preventing or restraining potential toxic pro-inflammatory effects of oxygen.

References


**Key words:**
Hyperbaric oxygen; Hyperoxia; Inflammation; Oxygen; Oxygen toxicity

**Correspondence:**
H. Bitterman
Department of Internal Medicine, Carmel Medical Center, 7 Michal Street, Haifa 34632, Israel.
haimb@tx.technion.ac.il

Received: August 19, 2012
Accepted: August 28, 2012
Published online: September 7, 2012

DOI:10.5455/jeim.070912.ed.015

©2012 GESDAV.
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided that the work is properly cited.