Intensive Care Med (2005) 31:1150–1152
DOI 10.1007/s00134-005-2700-7

EDITORIAL

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Hyperbaric oxygen and sepsis: time to recognize

Received: 31 May 2005
Accepted: 29 June 2005
Published online: 21 July 2005

This editorial refers to the article available at http://dx.doi.org/10.1007/s00134-005-2701-6

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For many critical care physicians the indications for hyperbaric oxygen (HBO) therapy are still a matter of debate, and it is therefore often referred to as a "therapy in search of diseases" [1]. While accepted as the primary treatment of severe decompression illness [2] and other forms of cerebral gas embolism [3], other proposed indications still are controversial. Nevertheless, there are several indications for which evidence exists that HBO therapy alone or as an adjunct has beneficial effects [4, 5]. Most of these indications affect intensive care medicine or even belong primarily to this specialty. A major problem in understanding the underlying mechanisms of HBO, however, has been the view that it is technically rather complex and demanding means to improve tissue O_2 delivery or, in other words, to compensate for a lack of O_2 transport capacity. Newer findings, however, clearly suggest that this is only one aspect of its action, since it is now well-established that O_2 administered at supranormal pressures may also act as a signal transducer [6, 7], which results in the enhanced expression of antioxidative enzymes as well as in modulation of the expression of growth factors and cytokines. These properties of pure O_2 breathing at supra-atmospheric pressures have allowed researchers to explain the beneficial effects of HBO for carbon monoxide poisoning or reperfusion injury and opened new windows to encourage the research on its qualities during systemic inflammation.

In *Intensive Care Medicine* Oter et al. [8] now report on the effect of HBO, alone or in combination with the antibiotic cefepime, on liver function and morphology in rats rendered septic by intraperitoneal injection of an *Escherichia coli* suspension. The main findings of this study are that: (a) sepsis per se results in a marked increase in markers of tissue oxidative stress, which increases while the activities of the antioxidant enzymes decreased, associated with (b) a rise in blood transaminase activity documenting hepatocyte injury and (c) marked neutrophil infiltration and cell "degeneration" in the liver. Antibiotic treatment and HBO alone resulted in both reduced plasma transaminase activities and attenuated tissue oxidative stress, but combining HBO and antibiotics was most efficient. Furthermore, the combined treatment provided only rather normal histological findings. Finally, the HBO-treated animals even presented with increased antioxidant enzyme activities in the liver. The authors concluded that HBO may be a useful adjuvant for improving the efficacy of the treatment of sepsis.

That HBO exposure may have beneficial effects in experimental models of systemic inflammation is by no means new, and Oter et al. confirm previous findings in rodents by other authors. Several studies have reported that HBO exposure blunts the vascular derangements and organ failure in a zymosan-induced shock model in rats, ultimately resulting in improved survival [9, 10, 11], and in endotoxic rats HBO attenuated LPS-induced acute lung injury [12]. Although both interventions led to a highly reproducible, generalized systemic inflammation, which

is consistent with consensus definitions of the host inflammatory response, neither endotoxic nor zymosan-induced shock mirror all aspects of human bacterial sepsis. Thus they may be referred to as artificial and not similar enough to any clinically observed insult. The study by Oter et al. has the merit of investigating an animal model of systemic bacterial sepsis as a result of localized infection, which, furthermore, integrates standard clinical care using antibiotics. In this context, the crucial role of HBO-induced improvement in host defense may have assumed particular importance for the authors' findings: it is well-established in humans that HBO exposure increases both the respiratory burst and phagocytic capacity while, interestingly, chemotaxis is reduced [13]. Several further mechanisms established in models of ischemia-reperfusion injury may help to explain the data reported by Oter et al. HBO has been shown both to decrease the rolling and adhesion of polymorphonuclear leukocytes via inhibition of neutrophil β_2-integrins [14, 15, 16] and to reduce leukocyte-endothelium interaction via downregulation of cell adhesion molecules [17, 18]. The well-established improvement in microvascular perfusion that results from these effects [19, 20] most likely is partially related to an HBO-induced stimulation of NO synthesis [12, 21]. Finally, Oter et al. even demonstrated that HBO beneficially affected oxidative stress in their model. Although previously reported by other authors [11] particularly in the context of CO intoxication [22, 23], at first glance this observation seems paradoxical since the enhanced formation of oxygen free radicals is directly related to the O_2 partial pressure [24]. It is well-known that exposure to HBO promotes oxidative stress [25, 26], for example, to the DNA [27]. It is noteworthy, however, that HBO is associated with increased local endothelial surface superoxide dismutase activity [27, 28], and that HBO-induced DNA strand breaks are not only rapidly repaired but, furthermore, induce efficient adaptive protective mechanisms resulting in complete protection against subsequent oxidative stress, at least in healthy volunteers [28].

What is the clinical impact of the study by Oter et al.? Clearly the inherent risks of HBO therapy [29] as well as its technical complexity will preclude a wide-range use for the treatment of sepsis and septic shock, particularly in the context of today's budget limitations. Nevertheless, the findings of this study provide another step in understanding the pathophysiology of sepsis and the exciting biochemical effects of hyperbaric oxygen. More than this, similar to hemorrhagic and ischemia reperfusion-induced shock [30, 31], the door for investigating the "smaller little (?) brother" of hyperbaric oxygen, normobaric hyperoxia, i.e., pure O_2 breathing under normobaric conditions, in such a clinical state has become a little more open.

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