Oxygen: An Anti-Inflammatory Drug

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Impaired tissue oxygenation and cellular hypoxia are major components in the pathophysiology of a large variety of clinical conditions, including acute and chronic ischemia, wounds and tissue trauma, infections, physical and chemical injuries, as well as inflammatory joint and connective tissue diseases [1]. Tissue hypoxia triggers an inflammatory response. Mechanisms of the intimate relationship between hypoxia and inflammation are gradually being elucidated and are expected to lead to the development of new treatment modalities to alleviate local destruction and also harness the systemic effects of exaggerated inflammatory response [1]. Evidently, the purpose of hypoxia-induced inflammation is to combat invasive microorganisms, clear tissue debris, and enhance tissue repair. However, too often the delicate balance between beneficial and potentially detrimental consequences of inflammation is impaired, causing local tissue damage and frequently culminating in a systemic inflammatory response that involves many organs and may lead to multiple organ dysfunction and failure [2].

In light of the key role of tissue hypoxia in the initiation and propagation of local and systemic inflammatory responses, evaluating the effects of treatment with oxygen at high ambient partial pressures in these conditions is called for.

Inhalation of oxygen increases oxygen delivery. A small addition to oxygen delivery is attained by an increase in hemoglobin saturation to 100%, and a significantly higher increment is achieved by physically dissolved oxygen in the plasma. The amount of dissolved oxygen increases in direct proportion to the ambient pressure. Altogether, this accounts for a rather modest (~10%) increase in arterial blood oxygen content during inhalation of 100% oxygen at normal atmospheric pressure, and a 30% increase during hyperbaric exposure to oxygen at 3 atmospheres [3,4]. The amount of physically dissolved oxygen in the plasma during exposure to 100% oxygen at 3 atmospheres (about 6 vol%) is sufficient to meet the average requirements of the tissues by means of dissolved oxygen alone. It should be emphasized, however, that the predominant change in oxygen availability to tissues during exposure to hyperoxia is not solely dependent upon the increase in oxygen content but is determined by the much more significant increase in arterial blood oxygen partial pressure. This increases from around 90 mmHg while breathing air at normal atmospheric pressure to values five to sevenfold higher while breathing 100% oxygen at normal atmospheric pressure, and may reach values higher than 2000 mmHg during hyperbaric exposure at 3 atmospheres. This rather dramatic increase in arterial blood oxygen pressures and the manifold increase in oxygen partial pressure gradient from the blood to the tissues account for the markedly facilitated diffusion of oxygen to tissues during hyperoxic exposures and to significantly improved tissue oxygenation [3,4].

The currently acknowledged roles of reactive oxygen species in tissue injury lead to a reluctant use of oxygen at high partial pressures (hyperoxia)

However, the advantage of exposure to hyperoxia in augmenting oxygen availability to tissues is challenged by the commonly accepted paradigm of tissue injury, which emphasizes the role of oxygen-derived free radicals formation in activating the inflammatory cascade by activating nuclear transcription factors, generating inflammatory mediators, up-regulating adhesion molecules, and consequently, increasing leukocyte-endothelial cell adhesion and microvascular barrier disruption [5,6]. Understanding the central role of reactive oxygen species in inflammation evoked concerns that the use of hyperoxia could exacerbate the process and its imminent deleterious consequences by adding extra oxygen to the system and thus increasing free radical formation [7,8].

The concern related to treatment modalities that may increase ROS generation and therefore to the use of hyperoxia in these conditions must be weighed against a steadily growing body of evidence on the beneficial effects of hyperoxia in diverse inflammatory conditions [9-13].

A major source of information on the effects of hyperoxia in inflammation originated from studies of ischemia and reperfusion [9]. On the one hand a large body of experimental data indicates that restoration of blood flow to ischemic tissues induces an acute burst of ROS formation that augments inflam-

ROS = reactive oxygen species

matory cascades, leading to increased leukocyte-endothelial cell adhesion, microvascular barrier disruption, and microvascular plugging (the "no reflow phenomenon") and, at least temporarily, aggravates tissue damage [5,6,14,15]. On the other hand, despite the established role of ROS in the pathophysiology of ischemia-reperfusion, the wish to abort the deleterious actions of tissue hypoxia triggered many studies on the use of hyperoxia in this condition. In this regard, definite beneficial effects of hyperoxia have been demonstrated in models of splanchnic IR – a potent generator of ROS production and a powerful inducer of local and systemic inflammatory responses. It has been shown that intraluminal perfusion of the gut with oxygenated saline during a period of regional intestinal hypotension eliminated the characteristic mucosal lesions [16]. In a study on the effects of hyperoxia in splanchnic IR in rats, we demonstrated a protective effect of hyperoxia on hemodynamic and metabolic parameters, as well as on survival [17]. In a follow-up study in the same model [18], we demonstrated that inhalation of 100% oxygen at normal atmospheric pressure attenuated the increase in mesenteric leukocyte rolling and adhesion and maintained mesenteric microvascular patency. Hyperoxia also improved the remote effects of splanchnic IR on pulmonary microhemodynamics, as well as on leukocyte sequestration and macromolecular leak in the lungs. These findings as well as data from another study on the effects of hyperoxia in severe splanchnic IR [19] support the protective microvascular anti-inflammatory effect of normobaric hyperoxia in intestinal IR.

As demonstrated in other studies, hyperoxia appears to exert a simultaneous effect on a number of steps in pro-inflammatory cascades after IR, including interference with polymorphonuclear leukocyte adhesion, and attenuation of free radical production. Hyperbaric oxygen has been shown to decrease rolling and adhesion of PMNL in the microcirculation and to ameliorate the systemic inflammatory response following IR of skeletal muscle [20-22], small bowel [17-19], heart [23], skin flaps [24], and liver [25], as well as after carbon monoxide poisoning [26]. Further studies demonstrated that HBO may affect PMNL-endothelial cell adhesion through modification of CD18 and thus down-regulate CD11/18 function [9,27]. Hyperbaric oxygen also reduces the expression of the endothelial adhesion molecules E-selectin [28] and intracellular adhesion molecule-1 [10]. Furthermore, hyperoxia is known to enhance the production of nitric oxide mostly by inducing eNOS protein production [10]. Increased nitric oxide levels may inhibit PMNL adhesion by inhibition of CD18 function and down-regulation of endothelial adhesion molecule synthesis [10,29]. Moreover, it has been shown in ischemic skin flaps treated with HBO that hyperoxia increases local endothelial surface superoxide dismutase activity [24]. This action of hyperoxia may diminish the more distal pro-inflammatory events initiated by ROS after tissue injury; indeed, hyperbaric oxygen has been shown to decrease lipid peroxidation (a typical free radical reaction) in a number of IR models [25,26,30].

Beneficial actions of hyperoxia are not limited to IR and have been demonstrated in various other inflammatory conditions. Hyperbaric hyperoxia has been demonstrated to exert beneficial anti-inflammatory actions in experimental colitis [12], Crohn's disease [31], carrageenan-induced paw edema [13], traumatic brain injury [32], and zymosan-induced generalized inflammation [11,33]. Anti-inflammatory actions of hyperoxia have also been demonstrated in sepsis and endotoxemia [34-36].

The available experimental data are sufficient to support a suggestion that hyperoxia exerts beneficial anti-inflammatory effects in models of tissue hypoxia. Furthermore, some of the data also indicate that hyperoxic therapy does not increase, and in many cases may even attenuate the overall oxidative stress in these conditions. It is not yet possible to distinguish the direct effects of hyperoxia on different stages of the pro-inflammatory cascade from the effects of improved tissue oxygenation that may abort or call off the entire process.

A steadily growing body of data indicates that hyperoxia exerts beneficial anti-inflammatory actions that should be explored in the clinical arena

The main limitations of hyperoxic therapy are its potential toxic effects. Within the normobaric pressure range (up to 1 atmosphere) the most prominent toxic effect of oxygen is a pulmonary inflammatory response that may develop upon prolonged exposures to oxygen at partial pressures above 0.6 atmospheres (above 60% oxygen at normal atmospheric pressure). Pulmonary oxygen toxicity involves the airways and lung parenchyma, causes tracheobronchitis, and may culminate in a full-blown histological and clinical picture of acute respiratory distress syndrome. When used at higher pressures in a hyperbaric chamber, the chief additional toxic manifestation of oxygen is a reversible grand mal-like seizure that may appear above a threshold oxygen pressure of around 3 atmospheres [37].

Owing to possible pro-inflammatory effects of high dose oxygen therapy, it is mandatory to use it in clinically effective, yet non-toxic, doses. Selection of oxygen dosage is far from being trivial, since its effects are determined by the combination of its partial pressure and the duration of the exposure. Well-established clinically effective HBO regimens are available for a list of currently approved clinical indications. Presently used HBO treatment protocols are restricted to oxygen pressures below the threshold for cerebral toxicity (up to 3 atmospheres) and for treatment sessions shorter than the latent period for lung and brain toxicity. However, since advocates of HBO therapy seldom control their observations with an appropriate normobaric group, significantly less data are available on the clinical effects of normobaric hyperoxia. In principle, exposures to 100% oxygen

IR = ischemia-reperfusion
PMNL = polymorphonuclear leukocytes
HBO = hyperbaric oxygen

for less than 6–8 hours are well below the threshold for any clinically significant pathology [37].

Overall, the steadily growing body of observations on anti-inflammatory effects of hyperoxia justifies appropriately controlled laboratory and clinical studies of oxygen therapy at doses that will maximize its potential beneficial effects within a non-toxic range of pressure/duration combinations. The widespread availability, ease of application and low cost of normobaric hyperoxia justify well-controlled laboratory and clinical studies that will compare its effects to the effects of HBO and determine its role as a potential therapeutic tool in acute and chronic human hyper-inflammatory conditions.

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