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Review

Mechanisms of pulmonary oxygen toxicity

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Abstract. Increasing use of oxygen in clinical practice has provided new impetus for determining mechanisms of acute pulmonary oxygen toxicity. The pathophysiology of lungs exposed to oxygen in vivo and in vitro suggests a direct toxic effect of hyperoxia upon lung cells, with variation in sensitivity to injury among cell types. The currently accepted primary mechanism for oxygen-induced cellular injury is enhanced oxygen-derived free radical generation with subsequent oxidative attack upon basic cell constituents. The major intracellular sources of increased free radicals are undetermined, but there is sufficient evidence that the extracellular contribution, specifically from PMN leukocyte influx into lungs is not critical to lethal pulmonary oxygen toxicity. Cellular protection is provided by intracellular enzymatic and nonenzymatic antioxidant defenses, which can be manipulated by experimental treatments to alter survival in O_2 . Our increasing knowledge of the mechanisms of oxidant toxicity may lead to improved strategies for early detection of lung damage and for the prevention or treatment of injury.

Key words: Free-radical – Hyperoxia – Oxygen toxicity – Polymorphonuclear leukocyte (PMN).

The toxicity of oxygen was realized shortly after the discovery of this gas approximately 200 years ago. About 100 years ago, Bert described the central nervous system effects of oxygen at hyperbaric pressures of 2 atmospheres absolute (ata) and above while Lorrain-Smith described the pulmonary damage that results from exposure at 1 ata O_2 [1]. During most of the past century, the toxicity of oxygen remained a medical curiosity of interest mainly to divers or others exposed to elevated barometric pressure. However, the advent of efficient systems for delivery of high concentrations of oxygen in a hospital setting has markedly increased the population at risk for oxygen toxicity and has led to recent intensification of efforts to understand the mechanism and pathophysiology of this disorder. This brief review will focus on pulmonary toxicity which is the major manifestation of oxygen poisoning in the hospitalized patient.

It is now appreciated that the pathophysiologic alterations of pulmonary oxygen toxicity correspond to those of the adult respiratory distress syndrome [5, 17]. Damage to the cells of the alveolar septum, predominantly the capillary endothelium but also the membranous (Type I) epithelium, results in interstitial and then alveolar edema. Organization of the protein rich alveolar edema fluid results in "hyaline membranes" which were formerly accorded a prominent place in pathologic descriptions of the oxygen toxic lung. Acute oxygen exposure also causes a tracheobronchitis which accounts for many of the early symptoms of poisoning. Sublethal injury to the lung can result in a subacute or chronic injury associated with reparative processes characterized by cell proliferation, infiltration with inflammatory cells, fibrosis, and areas of emphysema. During experimental continuous exposure to oxygen at 1 ata, tracheo-bronchitis develops during the initial 12 h, alterations of alveolar septal cellular function develop in approximately 24 h, evidence of interstitial edema is seen at approximately 48 h, and death occurs in approximately 72 h. This time course may vary slightly depending on species or relative tolerance of individual animals. Indications are that the course of toxicity is similar in patients, although the amount of reliable data is limited [5].

The mechanisms that lead to the acute lung damage with oxygen exposure have been intensively investigated and many possibilities have been proposed. It is important to recognize that, although lung damage is the predominant manifestation of O_2 poisoning, the effects of systemic hyperoxia may influence pulmonary toxicity. Furthermore, the relatively slow rate of development of lethal pulmonary damage raises the possibility for multiple secondary effects on the lung which in themselves may influence the rate of pulmonary damage. These considerations may account for the indirect or secondary phenomena which at one time or another have been thought to be the primary mechanism for lung toxicity. Some of the secondary or indirect factors that may modify the course of pulmonary damage include:

1) Lung infection due to altered tracheo-bronchial clearance and alveolar macrophage function

2) Pulmonary hypertension and increased capillary permeability related to release of mediators from adrenal glands, central nervous system or other systemic sources

3) Atelectasis due to absence of an inert fraction in alveolar gas

4) Alteration of surfactant function related to its inactivation by edema fluid or depression of granular pneumocyte (type II cell) function

5) Lung damage from products secreted or released from inflamatory cells. This possibility will be discussed more fully below.

Although these modifying factors may alter the course of lung damage, they do not account for the primary effects of O_2 on lung cells.

The currently accepted primary mechanism for oxygen toxicity is the "free-radical" theory which ascribes tissue damage to the increased generation of oxygen-derived radicals during exposure to elevated oxygen tensions [6, 13, 15]. These oxygen derived radicals include superoxide anion ($O_2^{\cdot-}$) and its protonated form ($HO_2\cdot$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($HO\cdot$). These radicals are

characterized by an increased reactivity compared with molecular oxygen towards biomolecules. (It should be noted that ground state molecular oxygen is a bi-radical although its reactivity towards biomolecules is limited because of the spin state of electrons in its outer orbitals). The free-radical theory of oxygen toxicity further states that an increased rate of generation of these reactive products results in oxidative attack upon cell constituents including proteins (particularly SH groups), lipids, and nucleic acids. Damage to cell or organelle membranes or alterations of key intracellular enzymes results in cell death which culminates in organ failure. Cell damage depends not only on the rate of generation of toxic radicals but also on anti-oxidant defenses and on co-existing reparative processes [8]. Considering this, it is remarkable that the course and manifestations of toxicity are similar amongst individuals and species but also understandable that relatively small changes in either the rate of radical generation or activity of defense mechanisms could markedly alter the external manifestations of toxicity. For example, the reported relative resistance of some primates to 1 ata O_2 [19] may represent a relatively small change in tolerance, since a modest 10 to 20% increase in the dose of O_2 (i.e., to 1.1 or 1.2 ata O_2) could result in the fulminant toxicity seen with most other species.

What is the metabolic source of increased oxygen radicals during hyperoxic exposure? During normoxia, oxygen radicals are produced in the cell as a by-product of electron transport in mitochondria and endoplasmic reticulum, from auto-oxidation of quinols, flavins, catechols, and other organic compounds, and by peroxisomes, phagolysosomes and perhaps other organelles [2, 12, 14, 31, 32]. Some of these processes show an increased rate of oxygen radical generation as external PO_2 is increased as required for the "free-radical" theory of O_2 toxicity. However, the precise source for the increased generation of oxygen derived radicals during hyperoxia remains unresolved.

Recently, it has been postulated that the source of oxygen-derived radicals associated with oxygen toxicity may be the polymorphonuclear leukocyte (PMN) [10]. This hypothesis gained adherents because PMN accumulate in the lungs during the latter stages of oxygen poisoning of normal animals at 1 ata and because these cells could, if stimulated, release oxygen radicals into the external milieu where antioxidant defenses are relatively deficient. Models of lung injury have demonstrated (not surprisingly) that inflammation of the lung can interact with hyperoxic injury to potentiate lung damage [28]. In addition, toxic products from PMN or non-cellular systems (e.g., xanthine plus xanthine oxidase) in high concentration can damage lung cells [18, 27]. Evidence to support the PMN hypothesis is the relatively decreased sensitivity to oxygen toxicity associated with systemic depletion of PMN [25], although it should be noted that this observation could not be confirmed [23].

On the other hand, considerable evidence suggests that PMN do not play a major role in the pathogenesis of pulmonary damage during hyperoxia. First, studies with in vitro systems have indicated that hyperoxia can damage lung tissue in the absence of PMN [21]. Second, although PMN do increase as a percent of the cells obtained by lung lavage, the increase in the number of PMN in the lung with O_2 toxicity is small compared with that seen in pneumonia and other acute inflammatory conditions (indeed, Lorrain-Smith [20] in his initial morphologic ob-

servations of oxygen toxicity commented on the paucity of inflammatory cells). Parenthetically, phagocytes from O_2 exposed lungs are not known to have an increased rate of oxygen radical generation (which could render them more potent compared to cell from pneumonic lungs) and in fact the respiratory burst (i.e., stimulated O_2^- production) of the alveolar macrophage and PMN is depressed by O_2 exposure [2, 9, 24]. Third, the presence of pre-existing lung damage with accumulation of PMN is generally associated with decreased rather than increased sensitivity to oxygen toxicity. Examples are the recently demonstrated increase of O_2 tolerance in animals following pre-exposure to sublethal doses of oxygen [4] or pretreatment with BCG [7], endotoxin [11, 29], oleic acid [26], phosgene [22], or alphanaphthylthiourea (ANTU) [30]. Fourth, experimental alteration of oxygen sensitivity has revealed a poor correlation between lung damage and the presence of PMN. We have recently shown that the accelerated mortality of rats exposed to 2 ata O_2 or pretreated with disulfiram and exposed to 1 ata O_2 occurs without influx of PMN into the lung [16]. This evidence has led us to conclude that PMN influx during oxygen toxicity represents a temporal response to tissue damage from intracellularly generated oxygen-derived free-radicals and that phagocytic cells play a relatively minor role in the amplification of the acute lung response. Their role in the chronic resolving phase of sublethal oxygen toxicity remains to be determined.

In conclusion, the last 25 years have seen major progress in our understanding of the mechanisms and patho-physiology of pulmonary oxygen toxicity and, in particular, with the elucidation of the "free-radical" theory. Important remaining problems are the subcellular site(s) for oxygen radical generation, the methods for the detection of radicals and their secondary products, approaches for the early detection of damage to bio-molecules, and the means to augment anti-oxidant defenses. With solution of these problems, it should be possible to expand significantly the value and indications for the therapeutic use of oxygen.

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