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The Three Components of Hyperoxia

The Good

Clearly, increasing inspired oxygen concentration can have beneficial effects during the perioperative period, including improved oxygen delivery to tissues and decreased incidence of wound infections associated with specific surgical procedures.[1] The work by Dr. Kotani *et al.*[2] published in this issue of ANESTHESIOLOGY shows that exposure to 100% oxygen during prolonged major procedures inhibits, but does not prevent, a decrease in antimicrobial function in alveolar macrophages (MØ) after surgery. In this study, there did not appear to be long-term pulmonary problems resulting from this therapy in otherwise healthy patients.

A greater increase in proinflammatory cytokines was observed in the group of patients administered 100% oxygen, compared with the group administered 30%. Increasing either tumor necrosis factor (TNF)-α or interferon (IFN)-γ improves antimicrobial pulmonary host defense in a number of animal models challenged with pathogenic bacteria. TNF-α is needed for neutrophil influx after intratracheal gram-negative challenge. Additionally, TNF-α and interleukin (IL)-1β are potent activators of neutrophils and MØ and are needed for transmigration of MØ and neutrophils to the site ofinfection. These proximal proinflammatory cytokines also enhance innate defenses by increasing phagocyte-induced killing of bacteria.

Chemokines that recruit and activate neutrophils (*e.g.*, IL-8) are also increased in the lungs after intratracheal instillation of *Escherichia coli* lipopolysaccharide or intact bacteria and increase neutrophil killing of *E. coli in vitro*. Additionally, inhibition of chemokine bioactivity in experimental *Klebsiella pneumonia* decreases neutrophil recruitment and bacterial clearance.[3] Finally, IL-12-induced IFN-γ release primes the MØ for enhanced TNF-α and IL-1β synthesis, thereby increasing MØ and neutrophil bactericidal activity. Therefore, hyperoxia-induced increases in proinflammatory cytokines are predicted to enhance antibacterial host defenses, as suggested by the authors.

However, increasing proinflammatory cytokines is a double-edged sword. For example, transient transgenic expression of TNF-α using defective adenovirus constructs protects against pulmonary *Klebsiella* challenge, but dosage is critical.[4] Higher expression of TNF-α is not beneficial. Furthermore, if the animals did not receive pulmonary bacterial challenge, a mild chronic inflammatory response could be detected in the lungs in response to the increased expression of TNF-α from the transfected respiratory epithelial cells.

The Bad

Increased ambient oxygen increases the rate of production of toxic reactive species. This occurs primarily

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as a result of generation of superoxide from the mitochondria and resultant increases in hydrogen peroxide and the hydroxyl radical through the oxidant cascade. There may also be a concomitant increase in antioxidant expression; however, the increased production of these tissue-protecting enzymes does not appear to be able to keep up with progressive oxidant generation.

In addition to the direct injury caused by the interaction of reactive species of oxygen with proteins, lipids, and nucleic acids, oxidants may also stimulate increased production of inflammatory cytokines, inducible NO synthase, and proteinases *via* intracellular signal transduction pathways. This may involve activation of transcription factors, such as nuclear factor κB.[5] Increased generation of proinflammatory cytokines leads to recruitment into the lung and activation in the lung of more inflammatory cells and to further release of chemical effectors and regulators of inflammation. In the later stages of hyperoxia, exposure to these mediators plays an increasingly important role in the pathogenesis of the lung injury.

The pulmonary surfactant system is also affected by hyperoxia, leading to the development of respiratory distress. Early leakage of protein into the alveoli as a result of hyperoxia can inactivate surfactant. Additionally, increased oxidant production injures alveolar type II cells, resulting in dysfunction of surfactant production. Although these changes generally occur later, subtle changes have been witnessed as early as 6 h after exposure to 100% ambient oxygen and clearly are demonstrable after 24 h of exposure.

The Ugly

Unfortunately, not everything we know about hyperoxia in healthy patients or experimental animals appears to apply in the presence of lung injury. Changes in the set point for oxygen toxicity have been demonstrated. Although there are no patient studies, there are a large number of animal experiments using several species that illustrate this point. Investigators have reported no difference, increased susceptibility to hyperoxia, or decreased susceptibility to increased ambient oxygen exposure, depending on the nature of the pulmonary inflammatory lesion. For example, during experimental sepsis, there is increased resistance to hyperoxic lung injury.[6] This is mediated by the expression of proinflammatory cytokines TNF-α, IL-1β, or IFN-γ. These mediators, individually or together synergistically, upregulate the mitochondrial antioxidant manganese superoxide dismutase. The increase in this antioxidant is believed to be an important mechanism in protecting the lungs against injury during exposure to 100% oxygen during sepsis.

Conversely, acid aspiration increases susceptibility of hyperoxic lung injury in a number of animal models. This injury decreases the time needed for 100% oxygen to produce demonstrable increases in lung injury and, more disturbingly, decreases the oxygen concentration at which pulmonary damage occurs.[7,8] Acid aspiration is neutrophil-dependent and necessitates several proinflammatory cytokines for complete expression of lung injury. Although the exact mechanism of enhanced pulmonary damage in response to hyperoxia is not known, there is evidence that increased generation of reactive species of oxygen and nitrogen, decreased antioxidant activity, and increased proteinases are involved.

Finally, particulate lung injury does not appear to change the set point for oxygen toxicity.[8] This occurs despite intense proinflammatory cytokine response and recruitment of large numbers of neutrophils and macrophages into the lung.[9] Differences in pulmonary oxygen sensitivity among sepsis, acid aspiration, and particulate inflammatory lung injury may reflect the different proinflammatory cytokine profiles generated in response to these insults.

Therefore, care must be taken when translating these findings to the general patient population. Too much importance must not be placed on the observation by Kotani *et al.*[2] that the host's antibacterial defense is improved as a result of hyperoxic therapy. Although that may be true in a modest sense, there is also concern that promoting an inflammatory response in the lung that is not detrimental to healthy patients could cause significant pulmonary problems in others. Furthermore, there is some discomfort in administering a therapy that these authors, as well as others, have shown to cause an increase in pulmonary dysfunction (a transient increase in atelectasis immediately after surgery). Clearly, risk-benefit must be better assessed in different patient populations. It would be a shame if, as a result of generalizing these findings in otherwise healthy individuals, other patients receive large concentrations of inspired oxygen inappropriately.

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