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Mini-Symposium: Oxygen and Infancy

Oxygen Toxicity

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EDUCATIONAL AIMS

- To understand the risks associated with supplemental oxygen.
- To summarise the common common clinical patterns of oxygen toxicity.
- To outline the biochemical mechanisms that lead to the toxic effects of oxygen.

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SUMMARY

Oxygen is one of the most widely available and used therapeutic agents in the world. However, it is all too easy forget that oxygen is a prescribable drug with specific biochemical and physiologic actions, a distinct range of effective doses and well-defined adverse effects at high doses. The human body is affected in different ways depending on the type of exposure. Short exposures to high partial pressures at greater than atmospheric pressure lead to central nervous system toxicity, most commonly seen in divers or in hyperbaric oxygen therapy. Pulmonary and ocular toxicity results from longer exposure to elevated oxygen levels at normal atmospheric pressure.

OXYGEN AND ITS HISTORY

Oxygen is a highly reactive non-metallic chemical element of atomic number 8 that readily forms compounds, particularly oxides, with most elements. After hydrogen and helium, oxygen is the third most abundant element in the Universe. On earth, oxygen normally exists in the atmosphere as a diatomic gas (O_2) that is colorless, odorless and tasteless.

Oxygen was discovered in the 1770s independently by Carl Wilhelm Scheele, in Sweden and Joseph Priestley in England in 1774; Priestley is often given priority because his work was published first. Antoine Lavoisier coined the name *Oxygen* in 1777. His experiments with oxygen helped to discredit the then-popular phlogiston theory of combustion and corrosion by proving that oxygen was the reactive constituent of air.

The detrimental effects of breathing elevated partial pressures of oxygen were first recognized in the late 19th century, Paul Bert being the first to describe the toxic effects of hyperbaric oxygen on the central nervous system [1] while Lorrain Smith was first to report the pulmonary effects [2].

OXYGEN AS A DRUG & OXYGEN DELIVERY SYSTEMS

Oxygen is one of the most widely available and used therapeutic agents in the world. Although often forgotten, it is important to remember that oxygen is a prescription drug with specific biochemical and physiologic actions, a distinct range of effective doses and well-defined adverse effects at high doses [3,4].

Oxygen is normally provided at atmospheric pressure (normobaric oxygen (NBO)) using a variety of masks that can provide inspired oxygen concentrations between 24%-90%. Masks with reservoirs, tightly fitting continuous positive airway pressure masks or mechanical ventilators can all deliver higher concentrations of oxygen. Oxygen at pressures higher than 1 atmosphere (hyperbaric oxygen HBO) requires a hyperbaric chamber, either filled with 100% oxygen and them compressed to the required pressure or a chamber filled with compressed air while the occupant breathes 100% oxygen at the same ambient pressure [3].

Delivery of oxygen to tissues depends on adequate ventilation, gas exchange and circulatory distribution. At atmospheric pressure, most of the oxygen is bound to hemoglobin and only a very small amount is dissolved in the plasma. On exposure to hyperoxia, hemoglobin becomes completely saturated with oxygen. While the amount of physically dissolved oxygen also increases, oxygen has a low solubility in blood and the amount of dissolved oxygen in blood during normobaric exposures to 100%

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oxygen can provide only a third of the resting tissue oxygen requirements [3]. On exposure to oxygen at a pressure of 3 atmospheres in a hyperbaric chamber, there is sufficient dissolved oxygen in the plasma to meet the average requirements of resting tissue by means of dissolved oxygen alone without contribution from oxygen bound to hemoglobin. This provides part of the rationale for the use of hyperoxia in situation in which the hemoglobin's oxygen carrying capacity has been impaired e.g. carbon monoxide poisoning [3]. However, the main improvement in cellular oxygenation results from an increase in the oxygen tension gradient consequent upon breathing oxygen and this drives the diffusion of oxygen from capillary blood into cells.

HYPEROXIA AND ITS CONSEQUENCES

By convention, normoxia is defined as the level of oxygen required for normal physiological process to occur [5]. At its simplest, hyperoxia is an excess of oxygen in body tissues, most commonly occurring in patients breathing supplemental oxygen to decrease tissue hypoxia.

Three types of risk occur in patients who receive supplemental oxygen [6]:

Physical effects

Pure oxygen is a dry gas. The respiratory tract normally warms humidifies and filters gases on inspiration but breathing dry supplemental oxygen at increased flow rates may overwhelm these systems. Subjective discomfort related to the drying of the respiratory mucosa as well as adverse affects on the respiratory mucous blanket and the activity of cilia may result. As a consequence supplemental oxygen is routinely humidified, although evidence to justify this is lacking [7]. More recently, there has been interest in use of high flow therapy that enables warmed, humidified oxygen to be given via nasal cannuale at high concentration without the adverse effects of drying and cooling of the airway [8].

There are also risks from oxygen's combustibility and the potential for fire when supplemental oxygen is being used, a particular issue in adult patients who smoke.

Physiological effects

Oxygen may induce physiological changes. These include vasodilatation of the pulmonary vasculature and vasoconstriction of the systemic circulation.

There are also important links between oxygen levels and inflammatory responses. High oxygen concentrations may indirectly ameliorate the inflammatory response by reducing the level of tissue hypoxia and as a consequence the levels of hypoxic inducible factor-1a (HIF-1a), a key regulatory molecule of both hypoxia and the inflammatory response [9].

By far the most important and potentially lethal physiological consequence continues to be seen in acutely ill patients with chronic obstructive pulmonary disease. If these patients are given uncontrolled oxygen therapy, they may develop worsening hypercapnic (type II) respiratory failure, potentially leading to severe respiratory acidosis [10] and coma [11]. Such situations are uncommon in childhood but may occur in children with severe neuromuscular disease who have chronic respiratory failure.

Biochemical and Cellular effects

Oxygen toxicity is the condition that results from the harmful effects of breathing molecular oxygen (O_2) at elevated partial pressures. Severe cases can result in cell damage and death with the most obvious effects seen in the central nervous system, lungs and eyes although other systems can be affected.

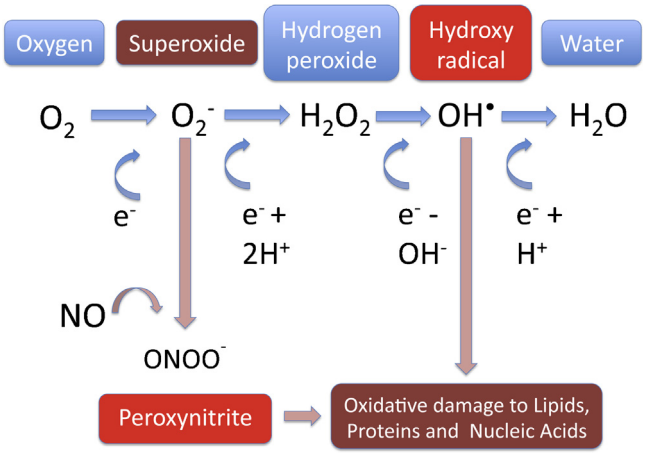

Figure 1. The figure illustrates the production of reactive oxygen species by the stepwise reduction of oxygen to water. The Hydroxy radical and perxoynitrite are the most reactive species in the process.

MECHANISMS OF OXYGEN TOXICITY

The biochemical basis for the effects of hyperoxia is the formation of oxygen-free radicals (Figure 1). These have one or more unpaired electrons, a combination that makes them very unstable. The most biologically significant of these reactive oxidant species are the hydroxyl ion and peroxynitrite. Peroxynitrite, the product of the reaction between superoxide and nitric oxide, in particular, interacts with lipids, DNA, and proteins via direct oxidative reactions or via indirect, radical-mediated mechanisms [12]. These reactions trigger cellular responses ranging from subtle modulations of cell signaling to overwhelming oxidative injury, committing cells to necrosis or apoptosis. The understanding of the molecular mechanisms underpinning both hyperoxia and hypoxia is still emerging [9,10,12,13].

Although the body has many antioxidant systems these are eventually overwhelmed at very high concentrations of free oxygen when the rate of oxidative damage overwhelms the capacity of the systems that prevent or repair it. Cell damage and death result.

CLINICAL CONSEQUENCES OF OXYGEN TOXICITY

While oxygen therapy is a cornerstone of modern medical practice, the recognition of oxygen toxicity as an important clinical problem is relatively recent. Reports in the early 50s linked oxygen therapy and retrolental fibroplasia in premature infants. It was reported in the early 1970s that breathing 50-100% oxygen at one atmosphere was potentially toxic to the lungs. There has since been recognition of the toxic effects on other systems of the body including the eyes, red cells, liver, heart, kidneys and endocrine systems as well as general damage to cells.

The body is affected in different ways depending on the type of exposure. Short exposures to high partial pressures at greater than atmospheric pressure lead to central nervous system toxicity most commonly seen in divers or in hyperbaric oxygen therapy. Pulmonary and ocular toxicity results from longer exposure to elevated oxygen levels at normal atmospheric pressure.

In general, those most at risk of oxygen toxicity are patients on high concentrations of supplemental oxygen (particularly premature infants), underwater divers and those undergoing hyperbaric oxygen therapy.