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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.

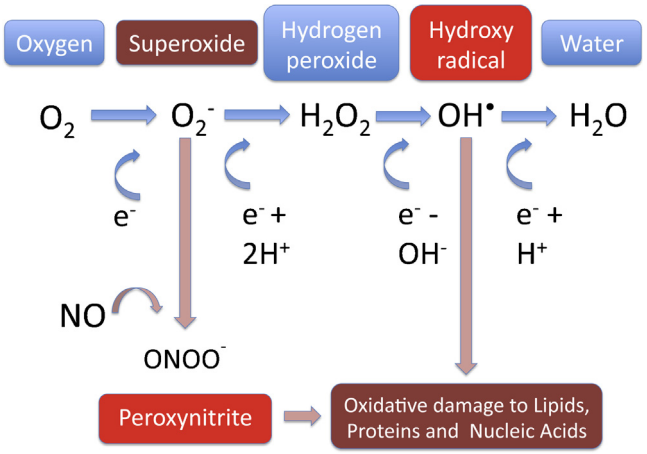

Figure 1. The figure illustrates the production of reactive oxygen species by the stepwise reduction of oxygen to water. The Hydroxy radical and perxoynitrite are the most reactive species in the process.

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.

PULMONARY

Pulmonary oxygen toxicity is the result of persistent exposure of the lungs to elevated oxygen levels at normal atmospheric pressure. As the respiratory system is exposed to the highest concentration of oxygen in the body it is the first organ to show signs of toxicity.

The rate at which oxygen toxicity develops is directly related to the partial pressure of inspired oxygen. Oxygen toxicity does not usually occur when the concentration of oxygen is less than 50% (an oxygen fraction of 50% at normal atmospheric pressure corresponds to exposure to oxygen at 50kpa) [14]. This data, however, is obtained from young, healthy subjects. It should also be noted that hyperventilation of air at atmospheric pressures does not cause oxygen toxicity, because sea-level air has a partial pressure of oxygen of 21kpa and the lower limit for toxicity is more than 30kpa

Pulmonary oxygen toxicity is characterised by an initial period in which no overt clinical manifestations of toxicity can be detected. The duration of this latent period is inversely proportional to the level of inspired oxygen [14]. This varies from 4 to 22 hours at greater than 95% oxygen [3]. At partial pressures of 200 to 300 kPa, 100% oxygen at 2 to 3 times atmospheric pressure, symptoms may begin as early as 3 hours after exposure to oxygen.

The first manifestation of pulmonary toxicity is tracheobronchial irritation. Clinically, this presents as prominent substernal pain or pleuritic pain. Comroe et al reported this to occur after about 14 hours of 100% oxygen inhalation [15]. Later studies showed that similar substernal pain was associated with cough and progressive dyspnoea in men exposed to 98% oxygen for 30 to 74 hours [16].

A decrease in activity of cilia may be the first indicator of oxygen induced tracheobronchial inflammation, being significantly decreased in ten normal volunteers after only 3 hours of breathing 90-95% oxygen [17]. The most widely applied index of oxygen toxicity in humans has been decreases in vital capacity, followed by progressive abnormalities in the carbon monoxide diffusing capacity [16]. Evidence of decline in lung function can occur after 24 hours of continuous exposure to 100% oxygen [3]. Breathing 100% oxygen also eventually leads to collapse of alveoli (atelectasis), an effect that breathing oxygen at the same partial pressure of oxygen but in the presence of inert gases such as nitrogen will prevent.

Longer exposures to oxygen may induce diffuse alveolar damage. The clinical symptoms as well as the laboratory, imaging and pathological findings of oxygen induced alveolar damage are not significantly different from those of acute respiratory distress syndrome (ARDS) from other causes [18]. Prolonged exposure to sublethal concentrations of oxygen may result in chronic pulmonary fibrosis and emphysema with tachypnoea and progressive hypoxaemia. It is difficult, however, to partition the relative contributions of the hyperoxia, the underlying clinical condition and mechanical ventilation to the ensuing clinical picture.

There are various pharmacological agents that can alter the rate of development and severity of oxygen toxicity [14,19]. Dexamethasone treatment in rats exposed to hyperoxia results in both greater oxygen induced lung injury and lower activities of the lungs antioxidant enzymes [20]. This is of potential clinical importance in the treatment of sepsis, ARDS and premature babies who may be treated with high doses of steroids while being ventilated on high concentration oxygen. Other agents, which increase cell metabolism including epinephrine, oestrogen, amphetamines and thyroid hormones, have similar effects on the severity of pulmonary oxygen toxicity. Bleomycin, which is metabolised with the production of free radical intermediates, may worsen oxygen induced lung injury. In animal models, the toxic effects of hyperoxia and bleomycin are synergistic, resulting in more extensive lung injury and fibrosis [21]

CENTRAL NERVOUS SYSTEM

Central nervous system (CNS) toxicity usually results from short exposure to high concentrations of oxygen at greater than atmospheric pressure. Exposure to partial pressure of 160 kPa, about eight times the atmospheric concentration, for minutes to hours is usually associated with CNS toxicity [22,23]. These conditions are only met in certain situations such as diving or during hyperbaric oxygen treatment. CNS toxicity does not occur during normobaric exposures.

Clinical signs of CNS toxicity start with visual changes such as tunnel vision, tinnitus, nausea, facial twitching, dizziness and confusion. The time for the appearance of symptoms is inversely related to the oxygen pressure and may be as short as 10 minutes at pressures of 4-5 atmospheres absolute [3]. This may be followed by tonic clonic seizures and subsequent unconsciousness. However, there appears to be no consistent pattern in the appearance of minor signs before the development of seizures.

Seizures are the most dramatic and dangerous sign of oxygen toxicity but are reversible without residual neurological damage if the inspired oxygen partial pressure is reduced. The onset of seizures is dependent on the partial pressure of oxygen and the exposure duration. However, exposure time before onset is unpredictable amongst individuals and even in the same individual day-to-day [24,25]. Many external factors such as underwater action, exposure to cold and exercise will decrease the time to CNS symptoms [26]. Decreased performance is also closely related to the retention of carbon dioxide [27]. Oxygen toxicity is particularly hazardous during diving because of the risks of drowning following a seizure.

Diagnosis of CNS toxicity in divers is difficult prior to the development of seizure activity because the early symptoms are non-specific and do not follow a typical sequence, being potentially related to many factors common to the underwater environment such as narcosis, congestion and coldness. Early symptoms may be more useful in diagnosis in those undergoing hyperbaric oxygen therapy.

Oxygen toxicity in divers is preventable. Protocols have been developed since the Second World War to limit exposure and partial pressure of oxygen inspired. In some diver training courses, divers are taught to plan and monitor what is called the oxygen clock of their dives. This is a notional alarm clock, which ticks more quickly at increased partial pressure of oxygen, and is set to activate at the maximum single exposure limit recommended in the National Oceanic and Atmospheric Diving Manual [28]. Diving below 60metres on air would expose the diver to increasing danger of oxygen toxicity as the partial pressure of oxygen exceeds 140 kPa so a gas mixture such as heliox (helium and oxygen) must be used which contains the less than 21% oxygen. Recreational divers commonly breathe nitrox up to 40% oxygen and technical divers also use pure oxygen or nitrox containing up to 80% oxygen. Divers who breathe oxygen fractions greater than air need to be trained in the dangers of oxygen toxicity and how to prevent them

There are also schedules used for hyperbaric oxygen treatment that allow periods of breathing air rather than 100% oxygen to reduce the chance of seizure or lung damage [29]. Sessions are restricted to less than two hours each and a pressure below the threshold for CNS toxicity.

OCULAR TOXICITY

Ocular toxicity, like pulmonary toxicity is usually caused by longer exposure to elevated oxygen levels at normal atmospheric pressure.

Prolonged exposure to high, inspired fractions of oxygen damages the retina. In preterm infants, the developing retina is not fully vascularized and supplemental oxygen is a risk factor, although not the main risk factor, for the development of retinopathy of prematurity [30,31]. In retinopathy of prematurity the development of the retinal vessels is first arrested and then proceeds abnormally with the associated growth of fibrous tissue. Restricting oxygen use does not necessarily reduce the rate of retinopathy of prematurity and may raise the risk of hypoxic-related complications.

In adult divers under hyperbaric conditions, eye damage has also been noted. Here the mechanism of damage is different to the damage to the developing eye in premature infants.

In some divers with prolonged exposures and frequently in those undergoing hyperbaric oxygen therapy, hyperoxic myopia has occurred. The myopia is attributed to an increase in the refractive power of the lens and is usually reversible with time [32].

OTHER ORGANS

Oxidative damage may occur in any cell in the body and has been implicated in red cell destruction [33], myocardial [34], endocrine (adrenal, gonads and thyroid) [35–37] and renal damage [38].

RESEARCH DIRECTIONS

- More detailed understanding of the molecular signalling pathways involved in the response to hyperoxia.
- The potential clinical role of hyperoxia in the management of clinical conditions with impaired oxygen delivery.

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