Although oxygen has been known to be toxic for more than 200 years, the clinical importance of oxygen toxicity was not appreciated until an epidemic of retrolental fibroplasia occurred in the early 1950s. Oxygen at high partial pressures is toxic to the respiratory, cardiovascular, nervous, and gastrointestinal systems.

Toxicity results from the formation of oxygen-free radicals. These arise within mitochondria as oxygen is reduced to water, as byproducts of prostaglandin and thromboxane synthesis, and by the xanthine oxidase catalyzed reduction of xanthine or hypoxanthine. They are also produced by activated macrophages as part of the immune response. Superoxide anion is the radical most commonly produced. It dismutates to hydrogen peroxide, which is able to diffuse through lipid membranes. Hydrogen peroxide reacts with transition metals to produce the highly reactive hydroxyl radical which can initiate chain reactions of lipid peroxidation leading to cell rupture.

Oxygen radical scavengers such as superoxide dismutase and catalase protect the body against normal levels of oxygen-free radicals. Oxygen toxicity can result from either reperfusion of ischemic tissue or prolonged exposure to high concentrations of oxygen. Limiting hyperoxia to maintain arterial oxygen percent saturation ($S_aO_2$) ≥ 90% is recommended.

Introduction

The toxic properties of oxygen were first noted as early as 1782 when Scheele found that enriched oxygen atmospheres inhibited the growth of plants. In 1878, Paul Bert published *La Pression Barometrique* in which he described the universal nature of oxygen toxicity, the variation in sensitivity among species, and the involvement of the central nervous system in mammals suffering from such toxicity. Then, in 1912, Hill revealed its importance as a factor in decompression sickness. Most further study focused on the role of oxygen toxicity in hyperbaric environments, but in 1952 the clinical importance of oxygen toxicity achieved greater recognition when reports from England and Australia linked the incidence of retrolental fibroplasia (RLF) in premature infants to the duration of oxygen therapy. Additional studies between 1952 and 1954 finally confirmed oxygen as the causative factor in RLF. Since the late 1960s, oxygen toxicity has been found to play a role in many disease processes.

The toxic effects of oxygen are dependent on many factors including duration of exposure, barometric pressure of the inhaled gas mixture, composition of inhaled gases, $P_aO_2$, age, health and species of animal. About half the adult laboratory animals exposed to pure oxygen die after 72 hours. But in primates, death may be delayed up to 7 days. The earliest sign of oxygen toxicity in man is acute tracheobronchitis—an inflammation of the tracheobronchial tree characterized by impaired ciliary clearance, cough, chest pain and a decreased vital capacity. Onset occurs within 24 hours.
Studies with rats show morphological and functional changes in the alveolar septum, decreased chemotaxis and phagocytosis by alveolar macrophages, and endothelial swelling and bleb formation in 24 to 48 hours. Loss of capillary and alveolar epithelium, interstitial edema, decreased lung compliance and impaired gas exchange occur in 48 to 72 hours. Death is due to pulmonary edema and respiratory failure. Similar changes have been observed in premature infants who develop bronchopulmonary dysplasia secondary to prolonged ventilatory support.4

The central nervous system and hemoglobin are also affected by enriched oxygen mixtures. The central nervous system (CNS) effects of oxygen toxicity include convulsions indistinguishable from grand mal seizures. These convulsions are usually preceded by twitching around the eyes, mouth, and forehead. They produce no cumulative or residual harmful effects as long as the PaO2 is returned to normal levels. Retrolental fibroplasia is another CNS effect of oxygen toxicity. It is caused by vascular obliteration and fibroblastic infiltration in the retina of premature infants ventilated with 100% oxygen. Hemoglobin concentration decreases with prolonged exposure to high oxygen concentrations, reducing both oxygen-carrying capacity and the ability of the blood to buffer acids.5

Although the harmful effects of oxygen had been well established early in this century, the first clue to its mechanism of action did not come until 1954 when Gershman and associates noted the similarity in the toxic effects of hyperbaric oxygen and gamma radiation in mice. They also noted that the radical scavengers glutathione and beta-mercaptoethanol protected the mice from both hyperbaric oxygen and gamma radiation. They concluded that the injury produced in both cases was due to the formation of oxygen-free radicals.6 Subsequent research has provided abundant evidence that "... oxygen-free radicals may contribute to the development or exacerbation of ... cancer, heart attacks, stroke, and emphysema."7

Formation and chemistry of oxygen radicals

Radicals are atoms or molecules with one or more unpaired electrons, a feature which tends to make them very unstable. The sequential reduction of oxygen to water produces superoxide anion, hydrogen peroxide, and hydroxyl radical:

\[
\begin{align*}
O_2 & \xrightarrow{e^-} O_2^- \xrightarrow{e^-} \text{H}_2\text{O}_2 \xrightarrow{\text{OH}^-} \text{H}_2\text{O} \\
& \text{OH}^-
\end{align*}
\]

Superoxide anion (\(\cdot\text{O}_2^-\)) is produced both in and out of mitochondria. Within mitochondria, electrons are derived from the oxidation of carbohydrates, proteins, and lipids. In a series of energy conserving reactions, these electrons reduce oxygen to water with the concomitant production of adenosine triphosphate (ATP) (Figure 1). Between 96% and 99% of the oxygen consumed by mitochondria is reduced by cytochrome oxidase without the formation of intermediates. The remaining 1% to 4% of the oxygen is only partially reduced and forms the potentially toxic-free radicals.8 Ubiquinone is the major potential source of mitochondrial superoxide anion.

Endogenous non-mitochondrial sources of superoxide anion include activated neutrophils, prostaglandin synthesis and the reaction of xanthine oxidase with hypoxanthine or xanthine. Neutrophils, when activated by microbes or other foreign substances, quickly produce superoxide anion and hydrogen ions as part of their antimicrobial defense. The production of superoxide anion is accompanied by a large increase in oxygen consumption lasting 2 to 5 minutes called the "respiratory burst."

Prostaglandins are continuously synthesized from arachidonic acid derived from membrane phospholipids. Prostaglandin production increases after injury and plays a role in local inflammatory response. The conversion of prostaglandin \(G_2\) to prostaglandin \(H_2\) by peroxidase produces superoxide anion.8

Hearse and associates proposed that the action of xanthine oxidase is the primary source of oxygen radicals in reperfusion injury.9 During periods of ischemia, endothelial xanthine dehydrogenase is converted to xanthine oxidase and ATP is degraded to hypoxanthine. Xanthine oxidase then catalyzes the oxidation of hypoxanthine to uric acid, producing superoxide anion in the process. Recent evidence supports this proposed mechanism: bovine aortic endothelial cells subjected to 45 minutes of anoxia followed by reoxygenation became potent generators of superoxide anion and hydroxyl radical (\(\cdot\text{OH}\)). Generation of these radicals was completely abolished by superoxide dismutase (SOD) and catalase. Radical production was accompanied by cell death.10

Actions of oxygen-free radicals

Superoxide anion is the first radical produced in the reduction of oxygen to water, but it is slow to react with many possible target molecules.11-18 Much more reactive than superoxide anion is its conjugate acid, the hydroperoxy radical (\(\text{HO}_2^\cdot\)). This
radical reacts rapidly with polyunsaturated fatty acids and becomes more reactive as pH decreases. Because pH drops in the vicinity of membrane surfaces, the danger of HO₂⁻ induced lipid peroxidation increases. This danger would be amplified during periods of ischemia.

Nonetheless, the primary reaction of superoxide anion is its spontaneous dismutation to hydrogen peroxide (H₂O₂). This reaction occurs at least 1,000 times more quickly than the formation of HO₂⁻, and 100 times more quickly than the reaction of HO₂⁻ with polyunsaturated fatty acids. While not a free radical, H₂O₂ is nonetheless a powerful oxidant with cytotoxic properties. Like superoxide anion, H₂O₂ is produced by mitochondrial nicotinamide dehydrogenase (NADH) and ubiquinone. Generally, H₂O₂ is produced at about half the rate of superoxide anion.

Except for a few nucleophilic reactions, H₂O₂ reacts slowly, if at all, with organic molecules in the absence of heat, light, or transition metals to catalyze the cleavage of the oxygen-oxygen bond. One very important nucleophilic reaction is the formation of hypochlorous acid:

\[
\text{Myeloperoxidase} \\
H₂O₂ + HCl \rightarrow \text{HOCI} + \text{H₂O}
\]

Myeloperoxidase is a common ingredient in neutrophils and monocytes, and the formation of hypochlorous acid may contribute to their bactericidal ability. Hypochlorous acid oxidizes the α1 antiprotease which normally protects the cell against elastase and other proteases.

Probably the most important reaction contributing to the toxic effect of H₂O₂ is its reduction to hydroxyl radical in the presence of ferrous iron.
(Fe\(^{+2}\)). This may occur by way of a metal catalyzed Fenton reaction:

\[
\begin{align*}
\cdot O_2 + Fe^{+3} & \longrightarrow Fe^{+2} + O_2 \\
H_2O_2 + Fe^{+2} & \longrightarrow Fe^{+3} + \cdot OH + OH^- \\
or H_2O_2 + Cu^+ & \longrightarrow Cu^{+2} + \cdot OH + OH^- 
\end{align*}
\]

Another possible mechanism of \(*OH\) formation is the reaction of \(H_2O_2\) with complexed superoxide anion. Superoxide anion can form relatively stable complexes with simple cations and with cytochrome \(p450\). Such complexes may be common in biological systems whenever metalloproteins are present.

Of the three intermediates formed by partial reduction of oxygen, only \(*OH\) seems reactive enough to pose the direct threat of cytotoxicity. But reduction of oxygen, only \(*OH\) seems reactive enough to pose the direct threat of cytotoxicity. But the formation of \(*OH\) requires catalysis of \(H_2O_2\) by transition metals which are usually bound to ligands within the cell, not in free solution. Yet superoxide anion and \(H_2O_2\) produced outside the cell have been implicated in causing intracellular damage. How can this be?

**Action at a distance**

Superoxide anion is poorly reactive with biomolecules and rapidly dismutates to \(H_2O_2\). Hydrogen peroxide is also poorly reactive, but it can readily diffuse through aqueous solutions or lipid membranes. Once in contact with a transition metal it can quickly form \(*OH\). Once formed, \(*OH\) will only travel a few Angstroms before it reacts with another molecule. By these means, superoxide anion can cause damage at distant sites.

Another mechanism for action at a distance involves the formation of highly reactive intermediate radicals which migrate through the lipid membrane. This is the basis for a lipid peroxidation chain reaction in which \(*OH\) reacts with a membrane lipid to form an intermediate lipid peroxy radical (LOO\(*\)):

1. \(LH + \cdot OH \longrightarrow LOO\(* + 2H^+\)
2. \(LOO\(* + L'H \longrightarrow LOOH + L'\)
3. \(LOOH + Fe^{+2} \longrightarrow LO\(* + Fe^{+3} + OH^-\)
4. \(LOOH + Fe^{+3} \longrightarrow LOO\(* + Fe^{+2} + H^+\)

The second propagation step requires a period of hours at \(37^\circ C\). Since lipids in the membrane are constantly migrating, the slowness of this propagation step allows the chain of lipid peroxidation to spread outward from the initiation site. Lipid peroxides formed during the second propagation step are fairly stable, but they rapidly decompose to other radicals in the presence of reduced metals like \(Fe^{+2}\) or \(Cu^+\). These new radicals can further perpetuate the lipid peroxidation chain by abstracting \(H^+\) from polyunsaturated fatty acids. The result of such peroxidation is decreased fluidity, increased permeability, and eventual rupture of membranes.

**Oxygen radical scavengers**

What mechanisms protect us from oxygen derived radicals? The primary defenses are the superoxide dismutases, catalase and glutathione peroxidase (Figure 2). Manganese SOD is found in mitochondria where it protects cells from oxidation by catalyzing the dismutation of superoxide anion to hydrogen peroxide. Likewise, catalase and glutathione hasten the reduction of hydrogen peroxide to water. (GSH is reduced glutathione and GSSG is oxidized glutathione.) Hydroxyl radicals formed from hydrogen peroxide in the presence of ferrous iron may be scavenged by a number of substances including mannitol and allopurinol.

![Figure 2: Oxygen-free radical scavengers](image)

**Figure 2**

Oxygen-free radical scavengers

<table>
<thead>
<tr>
<th>GSSG + 2H(_2)O</th>
<th>2GSH</th>
</tr>
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Superoxide dismutases (SOD) speed up the dismutation of superoxide anion to hydrogen peroxide. Likewise, catalase and glutathione hasten the reduction of hydrogen peroxide to water. (GSH is reduced glutathione and GSSG is oxidized glutathione.) Hydroxyl radicals formed from hydrogen peroxide in the presence of ferrous iron may be scavenged by a number of substances including mannitol and allopurinol.
E (α-tocopherol) is especially important because it can interrupt the lipid peroxidation chain reaction and because it may be bound to cell membranes where it is in position to intercept radicals before they can initiate peroxidation of lipid membranes. Allopurinol is also of special interest because it rapidly scavenges hydroxyl radicals.

As we have seen, oxygen radicals occur naturally, and the body has evolved a variety of defense mechanisms to protect us from oxygen toxicity. But these protective mechanisms can be overwhelmed when oxygen radicals are formed quickly and in large quantity. As anesthetists, two types of oxygen toxicity are of special interest: reperfusion injury and pulmonary oxygen toxicity.

**Reperfusion injury**

One of the phenomena which helped uncover the role of oxygen-derived radicals in oxygen toxicity was the "oxygen paradox." In this phenomenon, reoxygenation of an isolated rat heart after a period of hypoxic perfusion led to increased myocardial damage, as measured by creatinine phosphokinase (CPK) concentration, myofibrillar disruption, loss of basement and plasma membranes, mitochondrial swelling, distention of T-tubules, and an increase in lipid peroxidation products. Reperfusion injury has subsequently been demonstrated in a variety of organs including intact hearts in vivo, intestine, cremasteric muscle, and brain tissue.

Oxygen radical scavengers such as SOD, catalase, and allopurinol reduce the extent of damage caused by reperfusion in these organs. Coronary artery flow in isolated rat hearts decreased from 13.5 ml/min in untreated hearts to 5.5 ml/min after 60 minutes of hypoxic perfusion. That flow decreased further to 3.8 ml/min after 10 minutes of reoxygenation. Coronary flow after reoxygenation increased to 7.6 ml/min in the SOD-treated group and to 6.3 ml/min in the group treated with glutathione.

In another experiment, infarct size in intact dog hearts reperfused for 5 hours after 1 hour of left anterior artery occlusion was 89% of the area at risk. Treatment with SOD and catalase reduced infarct size to 63% of the area at risk. Also, the use of SOD, catalase, mannitol or desferoxamine (an iron chelator) reduced the incidence of ventricular fibrillation and tachycardia during reperfusion.

**Pulmonary oxygen toxicity**

In an extensive review of pulmonary oxygen toxicity published in 1972, Winter and Smith concluded:

- Oxygen toxicity did not occur when the partial pressure of oxygen was less than 0.5 atmospheres absolute (ATA), even with prolonged exposure.
- Less than 24 hours' exposure to 1.0 ATA oxygen \( (\frac{F1O2}{2} = 1.0 \text{ when atmospheric pressure } = 760 \text{ torr}) \) caused no problems.
- No evidence exists suggesting that patients with preexisting pulmonary disease are more susceptible to the toxic effects of hyperoxia.

These conclusions were largely based on two prospective human clinical studies. The first found no difference in \( VD/VT \), \( QS/QT \), or \( C_L \) in patients ventilated mechanically for 21 to 24 hours after bypass surgery with inspired oxygen at 1.0 ATA or \( \leq .42 \text{ ATA} \). The second study involved two groups of patients with irreversible head injuries. One group received 1.0 ATA oxygen, the other room air (.21 ATA). Thirty hours of hyperoxia caused a significant increase in \( VD/VT \) while 40 hours' hyperoxia caused a significant increase in \( QS/QT \). All patients were receiving steroids, compounds that accelerate the onset of pulmonary toxicity.

Other studies cited by Smith and White were conducted in human volunteers. Five studies involving 67 subjects exposed to hyperoxia for 24 to 110 hours found significantly decreased vital capacity when inspired oxygen was .75-.98 ATA. Four other studies involving 13 subjects found that 6-12 hours of exposure to 1.99 ATA oxygen decreased vital capacity. However, one subject showed no decrease after 11 hours. Finally, hundreds of hours of exposure to 0.3 ATA oxygen in manned spacecraft failed to produce measurable changes in pulmonary function.

Research since 1972 has generally upheld the conclusion that 0.5 ATA oxygen is harmless in healthy adults. However, exposure to more than 0.9 ATA oxygen does cause harmful changes in less than 24 hours. Sackner and associates showed that 3 hours' exposure to 0.9 ATA oxygen significantly slows treacheal mucous velocity, although it has no effect on vital capacity. Also, Konradova and associates found that 2 hours' exposure to 0.9 ATA reduced the density of cilia in rabbit treacheal epithelium from 9.7 cilia/\( \mu \text{m}^{2} \) to 2.6 cilia/\( \mu \text{m}^{2} \) and caused more than 90% of the goblet cells to discharge their mucus. Since mucous clearing is a necessary defense mechanism, its impairment could render an individual more susceptible to infection.

Pulmonary edema and fibrosis are late and end stage processes in pulmonary oxygen toxicity. The onset of these processes, however, begins within 24 hours of exposure to 1.0 ATA oxygen. Davis and associates conducted bronchoalveolar lavages of healthy volunteers and found that 16 hours of .95...
ATA oxygen caused increased concentrations of fibronectin and alveolar-macrophage derived growth factor for fibroblasts. They also found increased levels of albumin and transferrin in the lavage fluid indicating increased alveolar-capillary leakage.  

Does preexisting pulmonary disease make patients more susceptible to oxygen toxicity? One study showed that there was no difference in the response of baboons with induced lung damage to 0.4 or 1.0 ATA oxygen. But there is some evidence that hyperoxia may impair pulmonary function and induce hypoxemia in human subjects under stress.

Register and associates compared the effects of oxygen at 0.3 ATA and 0.5 ATA during postoperative ventilation of patients recovering from coronary artery bypass surgery and found that oxygen carrying capacity was impaired at the higher oxygen concentration. Those patients ventilated with 0.5 ATA oxygen had a mean PaO\(_2\) of 60.1 torr 15 minutes after extubation, while those ventilated with 0.3 ATA oxygen had a mean PaO\(_2\) of 66.4. Hyperoxia-induced hypoxemia was also observed in 10 baboons exposed to 108 hours of 0.9 ATA oxygen. PaO\(_2\) decreased from 90 ± 4 to 46 ± 5 torr and Qs/Qt rose to 30 ± 2% when the animals were returned to a normoxic environment. VD/VT, PaCO\(_2\) and pH were not altered by exposure to hyperoxia.  

**Summary and conclusions**

Oxygen toxicity is a well-established phenomenon capable of causing reperfusion injury and pulmonary toxicity. Toxic effects are dependent on oxygen tension rather than concentration, and oxygen tensions below 0.5 ATA appear to be benign in adult humans. The earliest symptom of oxygen toxicity in adult volunteers is substernal pain and typically occurs within 12 to 16 hours of breathing oxygen at 1.0 ATA. Decreases in VC had been thought to be the most sensitive indication of oxygen toxicity, however, decreases in ciliary density and mucous velocity can be seen within 2 hours of exposure to 0.9 ATA oxygen. Impairment of an important host defense mechanism may increase the risk of bacterial infection in patients ventilated with pure oxygen for long periods. This possibility deserves further research.

A major factor complicating clinical research is the great variability in susceptibility to oxygen toxicity between and even within species. Studies with U.S. Navy divers have found that individual susceptibility may vary greatly. What implications does this have for the treatment of patients with preexisting systemic disease? The vast majority of the research on oxygen toxicity and radicals has been conducted in healthy laboratory animals. How far can those results be extrapolated to human patients in varying states of health undergoing a wide spectrum of surgical insults? Does chronic obstructive pulmonary disease (COPD) increase the likelihood that a patient will develop a toxic reaction to oxygen? If so, how quickly will damage occur? Will patients with coronary artery disease who have intraoperative ischemia experience reperfusion injury? Will they benefit from SOD therapy? Since we know exposure to pure oxygen is potentially harmful, it may be unethical to subject patients to 100% oxygen for the sake of a controlled prospective study. And yet we need to know how preexisting systemic disease affects susceptibility to oxygen toxicity. This area poses a great challenge for research.

Should the possibility of oxygen toxicity affect our practice of anesthesia? Too little is known about oxygen toxicity to be dogmatic. Yet we can minimize the risk of oxygen toxicity by balancing the risks of hyperoxia against those posed by hypoxia, i.e., inadequate tissue oxygenation. Of the two, hypoxia is more dangerous. The safest course is to use the least amount of oxygen necessary to provide adequate tissue oxygenation.

Tissue oxygenation is determined by tissue perfusion and blood oxygen content. The partial pressure of oxygen in plasma is a measure of dissolved oxygen while hemoglobin saturation tells us how much is bound. A normal person breathing room air will have a saturation of 97%. The total carrying capacity of 100 ml of blood when PaO\(_2\) = 100 torr and Hb = 15 gm/100 ml is 20.4 ml of O\(_2\). By comparison, when PaO\(_2\) is 60 torr, hemoglobin saturation is 90% and the total oxygen-carrying capacity of 100 ml of blood is 18.3 ml—a 40% drop in PaO\(_2\) results in only a 10% decrease in blood oxygen content. An oxygen content of 18.3 ml per 100 ml of blood is adequate for an awake resting patient with a PaO\(_2\) of 60 torr since, at rest, the body extracts 5.3 ml of O\(_2\) from each 100 ml of blood. It is reasonable to assume that a healthy, normothermic, anesthetized patient in normal sinus rhythm consumes a similar amount of oxygen. Of course, not all of our patients are “normal.”

In any given individual, adequate tissue oxygenation will depend on metabolic oxygen requirement and oxygen delivery. In the anesthetized patient, we can control oxygen delivery by varying ventilatory rate, tidal volume, FiO\(_2\), inspiratory to expiratory ratio, positive end-expiratory pressure (PEEP), and hemoglobin concentration. By contrast, our ability to decrease metabolic requirements...
is usually limited to increasing anesthetic depth, lowering ambient temperature and giving β blockers to treat tachycardia. An FIO₂ of 0.3 will maintain hemoglobin saturation at 100% in normal patients. But in patients with COPD, adult respiratory distress syndrome (ARDS), pneumonia or other conditions in which alveolar gas exchange is impaired, we may need to manipulate the factors under our control to maintain adequate tissue oxygenation. Indeed, some patients will become hypoxic even when oxygen delivery is normal, e.g., those in septic shock. Nonetheless, a saturation of 90% is often an acceptable minimum, especially in patients whose only pathology is impaired gas exchange, since increasing saturation to 100% may require very large increases in inspired oxygen tension and a concomitant increase in the risk of oxygen toxicity with little increase in oxygen-carrying capacity.

How we manage each of the variables controlling oxygen delivery to our patient’s best advantage will depend on the clinical situation. As always, we must balance all of the risks and determine the safest anesthetic plan. The possibility of oxygen toxicity is simply one more risk that must be assessed.

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