Oxygen: Achieving a Rational Balance in Anesthetic Care

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Humans have evolved to thrive at or near 21% inspired oxygen (FiO₂ = 0.21). After achieving a patent airway during anesthesia, clinicians face 3 interrelated concerns regarding oxygen: delivery, utilization, and toxicity. Although delivery and utilization are met, toxicity is discounted. As with too little oxygen, too much is consequential. Toxicity in either case is dramatic, subtle, or delayed.¹⁻³

Contemporary medicine’s “culture of oxygen” assumes oxygen is always safe. This assumption is undeserved. Ingrained practice habits, pulse oximetry and the misinterpretation of blood gas data, and unfamiliarity with basic oxygen science contribute to the problem.⁵⁻⁹

On the positive side, new guidelines incorporate sound knowledge about oxygen toxicity into strategies to guarantee the use and delivery of oxygen while minimizing risk for harm from the gas.¹⁰⁻¹²

This article considers toxicity in relation to delivery and utilization as an omnipresent risk, especially in anesthesia care.¹³⁻¹⁵ The take-away message is simple: The best “antioxidant” is restricted use of oxygen. When a “lowest oxygen level acceptable” (LOLA) standard is matched to clinical need and adjusted using data, the toxicity of oxygen can be reduced, but never eliminated.

Oxygen Delivery

Guaranteeing oxygen delivery requires a patent airway. Open passages permit oxygen; carbon dioxide; nitrogen; water vapor; and other inhaled, exhaled, or metabolically generated gases to move along separate partial pressure gradients toward equilibrium.

Ventilation opens airways and alveoli so bidirectional gas flow is unimpeded. Alveolar–capillary gas exchange
reflects maintenance of an adequate partial pressure gradient.

Respiration requires oxygen to make adenosine triphosphate (ATP). Carbon dioxide and water are byproducts. Mitochondria make 90% of cellular ATP, which number in the billions, via oxidative phosphorylation. Supplying mitochondria with enough oxygen to respire requires reliable delivery.

Most anesthesia providers learn that oxygen delivery (DO₂) equals cardiac output (CO) multiplied by arterial oxygen content (CaO₂): DO₂ = CO x CaO₂. Factors ignored in this equation deserve review.

As a global measure, DO₂ is insensitive to local conditions. Organs behave individually. Vascular responsiveness is not uniform. Changes in oxygen tension affect delivery efficiency. Oxygen delivered directly to tissue bypasses circulatory delivery. Excessive direct oxygen exposure also promotes tissue injury. In addition to the lungs, gas-containing compartments, such as respiratory sinuses and gastrointestinal segments, experience direct-contact delivery and use. Theoretically, microbiome delivery produces metagenomic effects that might affect local delivery.

Parsing DO₂ is instructive. Cardiac output equals heart rate (HR) multiplied by stroke volume (SV): CO = HR x SV. It also equals mean arterial pressure (MAP) minus central venous pressure (CVP) divided by systemic vascular resistance (SVR): CO = MAP – CVP/SVR. Because both of these expressions equal CO, they equal each other: CO = HR x SV = MAP – CVP/SVR.

CaO₂ is more complex. Arterial hemoglobin concentration ([Hb] g/dL) multiplied by arterial oxygen saturation (SaO₂ %/100) multiplied by oxygen volume bound to normal Hb in a volume of blood (1.39 mL/g), added to the product of the oxygen solubility coefficient (0.003 mL O₂/100 mL plasma/mm Hg) times the arterial oxygen partial pressure (PaO₂ mm Hg) equals CaO₂.

For clinicians, this DO₂ formula offers 7 factors to manipulate: Hb, PaO₂, HR, SV, MAP, CVP, and SVR. This array may account for its popularity. Functional magnetic resonance imaging studies show that increasing FiO₂ to 1 increases tissue oxygen partial pressure (PtO₂) significantly in rat brain, kidney, liver, gut, muscle, and skin. It is no wonder that increasing FiO₂ when SaO₂ falls is a default maneuver to increase PaO₂ and PtO₂. The effect, however, produces a submolecular cost.

Use of Oxygen

The use and delivery of oxygen are metabolically linked by sensing mechanisms that are not completely understood. Normal perfusion is regulated by local oxygen use in all organs except the kidneys. This linkage means the influence of CO on oxygen delivery has limitations. Indeed, at low CO, the need to increase FiO₂ to enhance DO₂ is considered axiomatic. In the absence of significant hypoxemia, however, this intervention may not always be necessary or desirable. More research needs to be conducted to define relevant parameters.

Sensing mechanisms for the regulation of oxygen depend on local states of mitochondrial energy, substrate availability, levels of reactive oxygen species (ROS), antioxidant/prooxidant balances, calcium and other ion flux controls, maintenance of inner membrane/matrix electrochemical gradients, the functional states of mitochondrial transmembrane potential and

**Figure Key**

| ADP, adenosine diphosphate |
| ATP, adenosine triphosphate |
| CoQ, coenzyme Q10 |
| FAD, flavin adenine dinucleotide |
| IMM, inner mitochondrial membrane |
| NAD⁺, nicotinamide adenine dinucleotide, oxidized |
| NADH, nicotinamide adenine dinucleotide, reduced |
| OMM, outer mitochondrial membrane |
| PDH, pyruvate dehydrogenase |
| PDKI, phosphoinositide-dependent kinases |
| ROS, reactive oxygen species |
| TCA, tricarboxylic acid |

**Figure 1.** Oxygen use by the respiratory chain—oxygen accepts electrons at Complex IV to make ATP.
In damaging ways with lipids, proteins, DNA, and transcriptomes among ROS-susceptible structures promote cell death by triggering apoptosis and/or necrosis. Peroxidation of cardiolipin, abundant in the mitochondrial transition pore, and the injury status of mitochondrial DNA. Hypoxia-inducible factor plays a pivotal role in cellular responses to both hypoxia and hyperoxia. That eukaryotic cells adjust readily to shifting oxygen levels within a narrow range is key to life and health. More than 200 cellular reactions use oxygen. Although oxygen is the main biological oxidant to an array of reductants, it also builds molecules and regulates multiple non-respiratory chain functions.

Ultimately, all use of oxygen reflects PO₂, which in turn determines the partial pressure of mitochondrial oxygen (PmitO₂). The minimum PmitO₂ required to support metabolism is surprisingly low. The threshold above which the consumption of mitochondrial oxygen remains “supply independent” is 0.1 kPa or 0.75 mm Hg. Some lower estimates exist. As a result, PmitO₂ above such values may not enhance mitochondrial function.

Mitochondria consume 90% of all oxygen absorbed; non-mitochondrial use accounts for 10%. Of the 90% mitochondrial use, 80% is directly coupled to the synthesis of ATP, whereas 20% is uncoupled from production of the molecule. This process occurs through leakage of mitochondrial protons associated with free energy production, dissipation of heat, degradation of proteins, and the activity of sodium and calcium ion pumps.

The 80% of oxygen use coupled to production of ATP occurs at Complex IV (cytochrome C oxidase). At this site, oxygen accepts respiratory chain electrons needed to drive Complex IV-mediated (ATPase) ATP synthesis from inorganic phosphorous and adenosine 5′-diphosphate binding. Simultaneously, the 4-electron transfer to O₂ (dioxygen) pumps hydrogen ions from the mitochondrial intermembranous space back into the mitochondrial matrix. This action maintains the chemiosmotic gradient that supports the electrochemical balance in mitochondria that enables adequate respiratory chain function and mitochondrial integrity (Figure 1).

Notably, the respiratory chain efficiency is not 100%. Approximately 1% to 2% of the 80% mitochondrial oxygen use aimed at ATP production fails to make ATP. Electron escape produces single electron oxygen reductions inside mitochondria, especially at Complexes I and III, sites also affected by anesthetics. The superoxide ions formed are converted to diffusible hydrogen peroxide by the antioxidant superoxide dismutase, of which a specialized mitochondrial version exists. Superoxide and hydrogen peroxide become intermediaries in complex cell signaling events. Other ROS, such as highly reactive but short-lived hydroxyl radicals, and reactive nitrogen species (RNS) also form against defenses that are less understood. These react in damaging ways with lipids, proteins, DNA, and transition metals such as ferrous iron, sulfur, and copper. Together, abnormal levels of ROS and RNS amplify oxygen toxicity in all tissues but especially neurons, glia, and myelin in the nervous system.

**Oxygen Toxicity**

Comroe and colleagues first systematically studied human oxygen toxicity in 1945. Subjects exposed to 100% oxygen at sea level for 24 hours and at a simulated altitude of 18,000 feet showed signs and symptoms of oxygen toxicity that included cough, sore throat, nasal congestion, eye irritation, ear and dental discomfort, substernal distress, decreased vital capacity, decreased gastrointestinal lumen size, atelectasis, “pulmonary irritation,” fatigue, joint pain, paraesthesias, myalgias, dizziness, lightheadedness, and variable changes in blood pressure, respiratory rate, and hematologic parameters.

In their 1950 monograph, Comroe and Dripps catalogued more changes: nitrogen reduction, respiratory depression before respiratory stimulation, interference with elimination of carbon dioxide, circulatory depression, increased diastolic blood pressure, bradycardia, reduced CO, systemic arterial constriction, reduction in coronary blood flow, retinal artery constriction, depression of cerebral cortical function, changes in pulmonary blood flow, and suppression of bone marrow.

In 1951, Weschler and colleagues showed for the first time that cerebral oxygen consumption was reduced during thiopental anesthesia. In 1954, Gerschman showed that toxicity from oxygen and radiation shared a mechanism, anticipating future research into ROS. By 1956, Kinsey showed retrolental fibroplasia to be unequivocally linked to the duration of exposure to oxygen—the first pediatric condition to be so linked.

It took years of work by many scientists to discover oxidative stress, ROS, and the details of oxygen toxicity beneath clinically observed signs and symptoms. Oxygen toxicity occurs when intra-mitochondrial prooxidant/antioxidant factors are unbalanced (Figure 2). Excessive ROS overwhelm intra-mitochondrial antioxidants; which decline with age; chain reactions among ROS-susceptible structures promote cell death by triggering apoptosis and/or necrosis. Peroxidation of cardiolipin, abundant in the mitochondrial matrix...

**Figure 2.** Oxygen partial pressure (PO₂) and reactive oxygen species (ROS) generation; harm from too little and too much oxygen share ROS as a mechanism.
inner membrane, is critical to apoptosis. Release of cytochrome C into the intermembranous space triggers a caspase cascade, which produces intrinsic apoptosis. Extrinsnic apoptosis, triggered by mitochondrial outer membrane events, may be relevant to anesthesia in ways that are unexplored.

Hyperoxia, which elevates PtO2 and PmitO2 above biologically necessary levels, feeds ROS-mediated chain reactions by mass action. Whereas anoxia-hyperoxia after ischemia-reperfusion pathologically swings PtO2 and PmitO2 to raise ROS concentrations inside injured mitochondria and cells, similar shifts exist when normally perfused uninjured cells are whipped between normoxic and hyperoxic conditions. Unfortunately, iatrogenically induced shifts in PO2 are common during routine anesthetic care. When the airway is patent and cellular oxygen use is reduced below unanesthetized levels, there is little rationale for routine oxygen supplementation above awake or baseline concentrations.

**Clinical Implications**

Toxicity equals physiologic effects and submolecular events. Some are clinically apparent, like absorption atelectasis or arterial vasoconstriction; some are not, like lipid peroxidation and mitochondrial and nuclear DNA damage.

Three clinical examples beyond the neonatology literature may suffice to illustrate that more oxygen is not always better or necessary. As proof grows that oxygen moderation is possible and desirable, skeptics remain. It is hard to break the oxygen habit and go against the prevailing culture.

Oxygen cannot be stored in the lungs but breathing 100% oxygen (FiO2 = 1) can increase the time to “significant” desaturation, itself a slippery metric as PaO2 is more important, after breathing ceases. Preoxygenation and denitrogenation have been studied using blood gases and imaging studies since the 1940s into the 2000s, but not in relation to cellular events that might ensue even from brief hyperoxic/hyperoxic exposures. Oxidative stress biomarker studies relevant to clinical anesthesia practice remain to be done. Despite no biomarker evidence, Lindahl and others have advanced rational arguments for “dialing back oxygen” before, during, and after intubation and extubation, and during recovery. Clinicians need not heed their data or advice.

Another example where clinical hyperoxia has proven problematic is traumatic brain injury. Small but provocative studies looking at blood flow using positron emission tomography scans and patient outcomes have led to recommendations not to use 100% oxygen in such settings. Safe levels are not defined but maintaining normoxia is advisable. Furthermore, the combination of hyperoxemia and hyperventilation causing hypocarbia together reduces cerebral blood flow so that both mechanisms contribute to extension of ischemic region and penumbral damage.

A third example where oxygen caution is advisable is in caring for patients with diseases linked to oxidative stress. These include autism spectrum disorder, Alzheimer’s disease, Parkinson’s disease, type 1 diabetes, cancer, and cardiovascular disease. Patients with these conditions frequently require surgery. Because they are already burdened with oxidative stress, hyperoxemia and hyperoxia impose an additional burden that may accelerate a disease process. That said, healthy individuals are also at risk for increased oxidative stress during surgery. Using the least amount of oxygen required to support homeostasis remains a rational caution.

**Conclusion**

In the introduction, a LOLA standard was offered as a clinical “antioxidant” strategy. Like Martin and Grocott’s “precise control of arterial oxygenation” (PCOA) and “permissive hypoxaemia” (PH) concepts,40 a LOLA standard addresses a shared concern: hyperoxemia. Like PCOA and PH, LOLA calls for data-driven, scientifically sound use of oxygen.

A significant challenge to LOLA exists, however: human nature. Pulse oximetry facilitates monitoring of SaO2; it also biases toward oversupplementation. At 100%, SaO2/PaO2 Hb-oxygen dissociation relationships can vary 6-fold (100-600 mm Hg). The tone drop with a decrease in SaO2 from 100% to 97% is disproportionate to its physiologic significance. The response might be to increase FiO2. With pulse oximeter chirps restored to 100%, the patient again risks being overdosed. Invisibly, ROS accumulate beyond need and intrinsic antioxidant capacity; invisibly, damage is undetected or misinterpreted at the postoperative check.

Clinicians use supplemental oxygen to “guarantee” the delivery of the gas. But oxygen’s therapeutic window is not infinite. The value of a LOLA or PCOA standard is the awareness that overdosage of oxygen demands a solution. If safety is freedom from harm, one safety goal should be minimizing submolecular damage. This goal can be achieved even as science addresses any remaining questions.41

**References**


