VIEWPOINT

Evolving Issues in Oxygen Therapy in Acute Care Medicine

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Supplemental content

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Oxygen therapy is one of the most ubiquitously applied therapies in modern medicine. Clinicians usually react rapidly to declining oxygen saturations. Although this response is appropriate in the setting of hypoxia, there are many circumstances in which excess oxygen is indiscriminately administered for extended periods.

Medicine has recently experienced a shift from "more is better" to "less is more" as more has been learned about the ability of the human body to adapt to extreme physiological conditions and about the inappropriate use of various therapies. Examples include hemoglobin thresholds and carbon dioxide levels. Attention in recent years has focused on the potential harms associated with excess oxygen therapy.

Oxygen toxicity was first recognized clinically in an outbreak of retinal hyperplasia in premature infants leading to childhood blindness in the 1940s. Reports of oxygen pneumonitis were first described in the 1970s when autopsy findings demonstrated lung injury across patients who were exposed to concentrations of oxygen greater than 0.60 for at least 3 days of mechanical ventilation. In critical care, an early focus on harms of hyperoxia was attenuated after recognition of ventilator–associated lung injury, which shifted the cause from hyperoxia to injurious ventilation.

Toxicity attributable to supplemental oxygen can be categorized into local effects and systemic effects. Local effects include absorptive atelectasis resulting from the displacement of alveolar nitrogen by high concentrations of oxygen. High-inspired oxygen (ie, hyperoxia) leads to excess reactive oxygen species (ROS), which in turn cause oxidative injury leading to poor mucociliary clearance, surfactant impairment, airway irritation, and alterations in the microbial flora of the airways.

Systemic effects of excess oxygen (ie, hyperoxemia), are typically not described until partial pressure of arterial oxygen (Pao_2) thresholds exceed 100 mm Hg, at which point oxyhemoglobin saturation is nearly complete and dissolved oxygen increases. ROS are a normal by-product of aerobic metabolism and have an essential role in host defense and signaling. Usually antioxidants prevent excess ROS accumulation; however, in the setting of either increased oxygen tension or an exogenous stimulus (toxins or physiologic stress), ROS production increases and outstrips antioxidant capacity. This leads to oxidative stress, inflammation, cell damage, and cell death. In addition, ROS superoxide anions can inactivate nitric oxide when Pao_2 exceeds 150 mm Hg and can induce vasoconstriction, which has been described in the coronary, retinal, and cerebral vascular beds.

Recent reports have suggested harms attributable to hyperoxia (defined as xxx) or hyperoxemia (defined as xxx) across a series of acute care conditions. The common themes include: the absence of cellular hypoxia, an acute physiologic disruption and liberal oxygen administration. In a multicenter cohort study[1] involving 1156 adults who had experienced cardiac arrest and hypoxic-ischemic encephalopathy, patients with hyperoxemia (Pao_2 >300 mm Hg) had increased risk of in-hospital mortality (63% for the hyperoxia group vs 45% for the normoxia group and 57% for the hypoxia group) compared with those with hypoxemia and those with normal oxygenation. The mechanism of death was attributed to worsening secondary brain injury due to increased oxidative stress or ROS formation. However, these results have not been inconsistent across subsequent studies.

In the AVOID trial,[2] 441 patients with ST-elevation myocardial infarction were randomly assigned to receive supplemental oxygen (8 L/min) compared with ambient air. The group that received liberal oxygen administration experienced larger myocardial infarct size (median, 20.3 g; interquartile range [IQR]. 9.6-29.6 g] vs median, 13.1 g; IQR, 5.2-23.6 g) at 6 months and higher frequency of recurrent myocardial infarction (5.5% vs 0.9%; $P = .006$). A physiologic study[3] invovling 46 third-trimester pregnant patients showed that maternal hyperoxia led to a decline in cardiac index that was more pronounced than it was among 20 nonpregnant study participants. Given the recognized harm associated with unrestricted oxygen in preterm infants leading to retinal hyperplasia, a strategy of permissive hypoxemia (saturation, 85%-89%) was compared with normoxia (saturation, 91%-95%) in 4965 extremely preterm infants (median gestational age of 26 weeks) across 5 randomized clinical trials.[4] There was no difference in the primary outcome, a composite of death or major disability at 24 months corrected age. Examining individual components of the composite, the normoxia group had a higher incidence of retinopathy of prematurity but had a lower risk of death and necrotizing enterocolitis.

Two clinical circumstances in which the effects of hyperoxia remain uncertain include intraoperative management and neurologic insults without hypoxic-ischemic encephalopathy (such as stroke and traumatic brain injury). In 2016, the World Health Organization (WHO) recommended use of a high fraction of inspired oxygen (FIo_2) of 0.80 during general anesthesia for adults undergoing surgery to reduce surgical site infections. However, an updated meta-analysis[5] that included 17 randomized clinical trials showed no benefit from a higher (0.80) vs lower (0.30-0.35) FIo_2 for the reduction of surgical site infections (absolute rates, 11.4% for the high FIo_2 group vs 13.1% for the low FIo_2 group;, risk ratio [RR], 0.89; 95% CI, 0.73-1.07). Short-term (ie,132 [SD,] 50 minutes) exposure to hyperoxia during cardiopulmonary bypass also has not been associated with adverse neurologic complications.[6] In 2018, the WHO modified its recommendation and called for higher-quality literature. The risks of hyperoxia in the setting of traumatic brain injury or stroke remain unclear. Theoretically, similar to the cardiac arrest population,

hyperoxemia could potentiate secondary brain injury; however, harms of hypoxemia in this population are well established and, therefore, some experts caution against rapid adoption of conservative oxygen protocols until more outcome data are available.

Liberal oxygen therapy has several established benefits. The most consistently described benefit is the bactericidal property associated with increased ROS formation through oxidative killing of bacteria. This may be particularly beneficial in the setting of wound infections for which tissue oxygen tensions may be reduced compared with normal tissue. The potential benefits of hyperoxia (infection clearance or shock reversal) were evaluated in the Hyperoxia and Hypertonic Saline in Patients With Septic Shock (HYPERS2S) trial[7] in which 442 patients with sepsis were exposed to 1.00 F_{IO_2} for 24 hours. The trial was stopped early due to a signal suggesting increased mortality in the hyperoxia group. In contrast, a recent study[8] that evaluated conservative oxygen therapy, defined as a target saturation of 91% to 95% vs usual-care oxygen (target saturation, 91%-100%) in 251 patients with sepsis demonstrated a suggestion of possible harm in the conservative group. Although this finding did not reach statistical significance, the 7% higher mortality in the conservative oxygen therapy group supports the hypothesis that a higher oxygen threshold may have some beneficial properties in the setting of sepsis. Discrepancies in the results of these 2 studies may be attributable to the differences in oxygen exposure in the liberal treatment group (100% F_{IO_2} vs a more conservative usual-care strategy).

The Oxygen-ICU trial,[9] which involved 480 critically ill patients with an anticipated intensive care unit (ICU) stay of at least 72 hours, demonstrated that a conservative oxygen approach (Pa_{O_2}, 70-100 mm Hg or target saturation, 94%-98%) was associated with a lower mortality than was a liberal approach (allowing Pa_{O_2} up to 150 mm Hg or target saturation, 97%-100%), mortality rates of 11.6% for the conservative approach vs 20.2% for the liberal approach (P = .01), respectively. However, the trial was stopped early because of difficulties with enrollment after an earthquake and may therefore have overestimated the treatment effect. The recently published ICU-ROX trial[10] has forced reevaluation of the potential harm attributable to oxygen. This trial compared a conservative oxygen strategy (target saturation, 91%-96%) to usual-care (target saturation, 91%-100%) in 1000 patients who were receiving mechanical ventilation. There was no significant difference in 28-day ventilator-free days or 90-day mortality. However, significant heterogeneity of treatment effect was observed, with the hypoxic-ischemic encephalopathy subgroup demonstrating more favorable outcomes with conservative oxygen. A key difference between this trial and the previous literature is that usual-care was neither hyperoxemia nor a more liberal oxygen strategy. Usual care in this study represented a saturation of between 91% and 100%, which is different from trials that target a Pa_{O_2} exceeding 200 or 300 or a fixed F_{IO_2} of 100%, which is usually considered hyperoxemia or hyperoxia. Only 55% of the hours of observation among patients in the control group had an oxygen saturation of 97% or more (in contrast to the Oxygen-ICU trial in which oxygen saturation in the control group ranged from 97%-100%). Therefore, in critical care settings in which the usual-care practice may be more liberal, the results of this trial may not be generalizable.

Clinicians should recognize that a "conservative oxygen strategy" does not mean permissive hypoxia, which has not been well studied in adults but is harmful in neonates. In a monitored setting, it appears generally safe to wean oxygen with a maximum saturation target of 96%. Outside of the setting of targeted oxygen therapy for wound infections, indiscriminate oxygen use resulting in hyperoxia or hyperoxemia is not necessary and may induce harm in certain acute care conditions.

Many important questions remain including (1) thresholds and duration of oxygen that may induce harm, (2) optimal ways to study excess oxygen (F_{IO_2}, saturation, or Pa_{O_2}), (3) interactions with acid-base disturbances, ventilator–induced lung injury or shock, and (4) long-term consequences. It is likely that there are different clinical conditions in which liberal oxygen may induce harm when combined with some degree of exogenous stimuli that causes a proliferation of ROS. The liberal oxygen threshold at which this occurs likely varies across different conditions and different intensities of the exogenous stimuli (eFigure in the Supplement). To date, more than 70 clinical trials of oxygen therapy have been registered and are ongoing or recently completed. The results of these studies will further inform the degree to which inappropriately titrated oxygen has contributed to iatrogenic adverse events and will help define the appropriate use and dose of oxygen in acute care medicine.

ARTICLE INFORMATION

Published Online: January 24, 2020. doi:10.1001/jama.2019.22029

Conflict of Interest Disclosures: Dr Ferguson reported that he has served as a consultant for Xenios and Baxter, receiving speaker fees from Getinge, outside the submitted work.

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