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REVIEW

Oxygen in critical care

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SUMMARY

Oxygen is widely used in critical care, yet there is surprisingly little evidence guiding its use. Most major guidelines recommending the use of oxygen therapy have yet to recommend titration to achieve normoxemia. As a consequence, a significant portion of critically ill patients are subjected to hyperoxia. Interest in ideal oxygen therapy is gathering pace and research is beginning to challenge previous presumptions that oxygen therapy is innocuous with increasing reports of potential harm. This review will summarize notable aspects of oxygen therapy, recent developments in the use of normobaric oxygen supplementation and issues regarding hyperoxia in critical care.

First experimented on by the Greeks in the second century BCE, oxygen was only accurately characterized by Joseph Priestly, a British clergyman in 1774. Carl Wilhelm Scheele, a Swedish pharmacist, is believed to be the first to produce the gas in 1772 but failed to have his findings published until 1777. Antoine Laurent Lavoisier, a French chemist, coined the name "*oxygène*" in 1777 from the Greek root words *oxys* (meaning the "sharp" taste of acid) and *genēs* (meaning "producer"), because he had mistaken that oxygen was a constituent of all acids.[1] Oxygen's first documented medical application was in 1783 when French physician Caillens described its twice-daily administration to a patient with tuberculosis. In the following two centuries, various methods of oxygen delivery, via intra-gastric, per rectal and subcutaneous routes were attempted for diverse ailments such as cholera and diabetes mellitus.

Broadly speaking, Critical Care Medicine (CCM) may be distilled into: (1) diagnosis and (2) targeted therapy for the underlying pathology, while (3) supporting organ function or maintaining homeostasis, and (4) preventing iatrogenic harm. Organ support or homeostatic maintenance in critical illness is inextricably linked with the provision of adequate substrates for function, of which oxygen is a key component.[2] In fact, many interventions in CCM are geared towards optimizing oxygen delivery (Table 1). This is reflected in the literature under many guises, such as the ideal hemoglobin concentration in the critically ill and development of more accurate measures of cardiac output amongst others. Oxygen is widely used in critical care, yet there is surprisingly little evidence guiding its use.

Oxygen should be regarded as a drug[4] with its distinct pharmacodynamics and side effects, though it is unique in that all patients have had prior lifelong exposure. While the beneficial effects of oxygen are often discussed, some of the adverse effects are less well known (Table 2). As with all other drugs, a therapeutic index likely exists for oxygen but is at present, unknown.

Physiological arterial partial pressure of oxygen (PaO_2) or normoxia is between 75 and 100 mmHg.[36] It is affected by many factors including posture, age, habitus[37] and physiological states such as pregnancy.[38] While there is no consensus on the definition of hyperoxia, hypoxemia is consistently defined as PaO_2 of less than 60 mmHg. The harmful effects of hypoxemia are well recognized in medicine and refractory arterial desaturation is often a trigger for emergent intervention and escalation of care to the intensive care unit (ICU).

Although oxygen therapy has been incorporated in several major guidelines, many of these have yet to recommend titration with the use of PaO_2 or pulse oximetry (SpO_2) to achieve normoxemia. As a consequence, a significant portion of patients are actually "over treated" and subjected to hyperoxia. Interest in ideal oxygen therapy is gathering pace and research is beginning to challenge previous presumptions that oxygen therapy is innocuous.[39] This review will summarize notable aspects of oxygen

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Table 1
Global delivery of oxygen, DO_2.

Global delivery of oxygen, DO_2 = cardiac output (CO) × arterial content of oxygen[3]
Arterial content of oxygen = [1.34 × hemoglobin concentration × arterial saturation of hemoglobin] + [0.003 × partial pressure of oxygen]
1.34 = Oxygen carrying capacity of 1 g/dL of hemoglobin
0.003 = solubility of oxygen in plasma
Increases in the partial pressure of oxygen only minimally increases the oxygen content of blood.

therapy and recent developments in the use of normobaric oxygen supplementation (NBO) and hyperoxia in critical care.

1. Neuro-critical care

Traumatic brain injury (TBI) and strokes are in the top 22 leading causes of mortality and morbidity in the United States[40] despite medical advances. Cerebral metabolism is high relative to other organ systems and the brain has a limited tolerance for anaerobic conditions. Although arterial oxygen tensions as low as 19.1 mmHg may be compatible with life in acclimatized individuals,[41] acute oxygen deprivation results in neurological dysfunction with prolonged hypoxia causing irreversible injury.

1.1. Ischemic stroke

Ischemic stroke occurs due to regional cerebral hypoperfusion following endothelial plaque rupture or vascular occlusion from embolism. The basis of thrombolytic therapy in early stroke is to achieve reperfusion to the ischemic region to minimize long-term neurological sequelae. Hence, theoretically, increasing the global oxygen supply should improve outcomes.

Using various surrogates of cellular metabolism and injury (Table 1), preclinical experiments with animal models appears to support this hypothesis.[42–44] However, human studies are limited and long term outcomes much less conclusive. A study in 1999 found no statistical difference in one-year mortality or neurological disability between patients who received 3 L of oxygen per minute via nasal cannula for 24 h after admission and those who received no treatment.[45] A pilot study by Singhal et al., in 2005 showed that normobaric hyperoxia improved stroke scale scores by up to one week but that this improvement was not sustained at 3 months.[46] The follow-up to this study was terminated after recruitment of 85 patients due to an 'imbalance in deaths favoring the control arm', although the reason was not clearly attributed to oxygen therapy.[47] Padma et al.[48] recruited 40 patients with ischemic stroke for another pilot study in 2010 and again found no difference in outcomes at 3 months.

Roffe et al.[49] demonstrated a small but significant positive effect in the NIH Stroke Score at one week in patients given supplementary oxygen in the first 24 h post-stroke in a small study in 2011. However, baseline characteristics of the control and treatment groups differed and the follow-up duration was inadequate. The limitation of these studies is that the intervention relied on a fixed rate delivery of oxygen instead of specific PaO_2 targets. Although PaO_2 generally increases with oxygen supplementation, the baseline arterial saturations and extent of rise in PaO_2 with oxygen are unlikely to be equal in all patients. This likely impacts on the results of such studies.

In a recent cohort study by Rincon,[50] 2894 ventilated patients with acute ischemic stroke, subarachnoid hemorrhage, or intracerebral hemorrhage who had arterial blood gases sampled within 24 h of admission to the ICU were divided into three exposure groups: hyperoxia defined as PaO_2 more than or equal to 300 mmHg, hypoxia defined as any PaO_2 less than 60 mmHg, and normoxia. Mortality was higher in the hyperoxia group compared with normoxia (crude odds ratio (OR) 1.7 [95% CI 1.3–2.1]). Multivariate analysis adjusted for potential confounders found hyperoxia to be independently associated with increased in-hospital mortality (adjusted OR 1.2 [95% CI, 1.04–1.5]).

Given the available data, providing supplemental oxygen to achieve hyperoxia in a bid to improve ischemic stroke outcomes cannot be recommended. Accordingly, the American stroke association currently recommends oxygen supplementation only to maintain saturations above 94% [51].

1.2. Hemorrhagic stroke

In the secondary analysis of Rincon's study,[50] hyperoxic patients with intracranial hemorrhage had a higher mortality compared with the normoxia group (OR 1.3 [95% CI, 1.03–1.7]). No randomized controlled trial pertaining to this currently exists.

1.3. Traumatic brain injury

Severe TBI disrupts cerebrovascular anatomy and causes loss of cerebral auto-regulation. Focal ischemia results and is aggravated by a global reduction in cerebral perfusion due to elevated intracranial pressure. Most experimental animal models of TBI suggest hyperoxia improves surrogate markers of neuronal injury. However, some studies have demonstrated a paradoxical reduction of peri-lesional brain tissue perfusion with hyperoxia [52].

Human studies are only beginning to shed light on the effect of hyperoxia in TBI. Tolias et al.[53] showed improved cerebral

Table 2
Beneficial and adverse effects of oxygen.

Beneficial Effects of Oxygen	Adverse Effects of Oxygen
• Prevents hypoxic pulmonary vasoconstriction, thus reducing pulmonary pressure. • Reduced placental vascular resistance. • Reduced lipid peroxidation[5] • Induction of antioxidant enzymes and anti-inflammatory proteins[6] and anti-inflammatory cytokines such as interleukins 10, 11, and 13, and certain growth factors.[7] • Reduced neutrophil activation[8] • Anti-apoptotic effects in myocardium[9] and in brain.[10–12] • Normalization of cerebral extracellular homeostasis, reduced levels of excitotoxic metabolites such as glutamate, pyruvate and lactate.[13,14] • Blood–brain barrier stabilization.[15] • Reduced markers of cerebral tissue breakdown.[16,17] • Reduced postoperative infections.[18,19]	• Vasoconstriction in brain,[20] heart, skeletal muscle,[21] skin[22] due to reactive oxygen (ROS) and superoxide production[23] which inactivates nitric oxide, leading to decreases in tissue oxygen delivery and tissue oxygen utilization.[24] • Prolonged myocardial electrocardiographic changes during exercise,[25] reduced coronary perfusion, increased vascular resistance,[26–29] and decreased stroke volume[30] and cardiac output.[31,32] • Increased production of reactive oxygen (ROS) and nitrogen (RNS) results in transient immunosuppression. • Development of atelectasis,[33] inflammatory changes in the mucous membranes,[34] inhibition of mucociliary transport function, decreased bacterial clearance, as well as functional impairment of alveolar macrophages.[35]