Review - Systematic

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An exploration of the deleterious effects of hyperoxemia on the morbidity and mortality of hospitalized adult patients

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ABSTRACT

Background and purpose: To explore the deleterious effects of hyperoxia due to liberal oxygen use and clarify the significance of overuse and effects on morbidity and mortality in adult hospitalized patients. This literature review is also intended to bring awareness to nurse practitioners regarding the iatrogenic harm caused by excessive oxygenation and promote individualized patient care.

Methods: A review of existing literature was conducted using PubMed and CINAHL databases. The keywords "hyperoxia", "hyperoxemia", "oxygen toxicity," and "excessive oxygenation" were used to yield articles for consideration.

Results: Of the six studies compared for this review, five identified positive correlations between hyperoxia and adverse outcomes. The sixth study found no significant differences in morbidity or mortality with the use of liberal oxygenation versus a more conventional approach.

Conclusions: Overwhelming evidence suggests that states of hyperoxemia lead to increased mortality and morbidity. However, there is considerable variability on the threshold at which hyperoxia occurs. Further research is required to define levels of hyperoxia to better protect patients from iatrogenic harm.

Implications for practice: Nurse practitioners in all specialties can increase awareness of the dangers of excessive oxygenation and effect a change in practice through education.

Keywords: Excessive oxygenation; hyperoxemia; hyperoxia; oxygen toxicity.

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Introduction

In an effort to protect patients from hypoxia, supplemental oxygen is provided liberally in the acute care setting, but with little awareness of its potential to cause harm. Seemingly innocuous, the administration of oxygen is often given for longer durations and at higher doses than is required, even without a provider's order at times. Although adequate oxygenation is understood to be an essential component of recovery during certain acute illnesses (e.g., septic shock and myocardial infarction), empiric administration of oxygen without any evidence of hypoxia may do more harm than good. Recent studies have established strong connections between elevated levels of arterial oxygen and diffuse cellular injury, capable of causing hemodynamic and inflammatory changes that may potentially result in cataclysmic multisystem organ dysfunction (Llitjos, Mira, Duranteau, & Cariou, 2016).

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Despite this risk, the limits of safe oxygen administration in the acute care setting remain unclear, and liberal use continues. Patients are unwittingly exposed to the serious iatrogenic effects of receiving excessive amounts of oxygen. The purpose of this comprehensive review is to explore the deleterious effects of hyperoxemia due to liberal oxygen use and to clarify the significance between overuse and effects on morbidity and mortality in adult hospitalized patients.

Definition of terms

- Hyperoxia: an increase in the fraction of inspired oxygen (FiO_2) (Hafner, Beloncle, Koch, Radermacher, & Asfar, 2015)
- Hyperoxemia: an increase in the partial pressure of oxygen that can be measured in partial pressure of arterial blood (PaO_2) (Hafner et al. 2015).

Background and significance

The toxic effects of excessive oxygen have been consistently documented and reproduced in animal models

dating back to Antoine Lavoisier's experiments in 1783 (as reviewed in Kallet & Branson, 2016). Within the medical community, there was little interest in the effects of excessive oxygenation until the mid-20th century when military demands for high altitude aviation and scuba diving during World War II brought the notion of hyperoxia to the foreground (Kallet & Branson, 2016). However, it was not until the 1960s that reports of hyperoxic acute lung injury (HALI) in humans, both adults and neonates, began to appear in medical literature (Kallet & Branson, 2016; Kallet & Matthay, 2013). From that point forward, concern over the toxicity of oxygen grew as did revolutionary advances in respiratory medicine that offered more aggressive oxygen use, such as hyperbaric oxygen therapy and prolonged mechanical ventilation (Kallet & Branson, 2016; Kallet & Matthay, 2013).

Although there has been recent progress in the discourse surrounding hyperoxia and the potential for harm with oxygen overuse, further attention to this issue and corresponding solutions are still needed. Despite a long history of correlation between hyperoxia and increased morbidity, it is possible the significance of hyperoxia in relation to adverse patient outcomes may have been overstated in the past. Kallet and Branson (2016) offer that documented cases of acute respiratory failure may have developed as the result of poorly understood or unrecognized conditions at that time, such as acute respiratory distress syndrome and ventilator-induced lung injuries. In addition, the technical limitations of early mechanical ventilators may have played a role in unfortunate outcomes that were then falsely attributed to hyperoxemia (Kallet & Branson, 2016; Kallet & Matthay, 2013).

Unlike hypoxia, there are currently no guidelines that identify thresholds at which hyperoxemia occurs (Llitjos et al., 2016). Even if guidelines were available, thresholds may vary based on illnesses that demand higher oxygen requirements such as after a cardiac arrest (Llitjos et al., 2016). To minimize the risk of the deleterious effects of hyperoxia, it is important that concerted efforts are placed on better defining this phenomenon. Without target limits, establishing guidelines for careful administration of oxygen will continue to be problematic, and harmful effects due to overuse will continue to occur.

It is widely understood that adequate oxygenation is essential for proper cellular function. In the setting of hypoxia, where concentrations of oxygen in the bloodstream are low, supplemental oxygen therapy is corrective and used to restore cellular function and maintain homeostasis. In contrast, providing supplemental oxygen without evidence of hypoxia can lead to hyperoxia. Time spent in a hyperoxic state can lead to an elevated concentration of oxygen in the blood, which in turn increases oxygen tension in the partial PaO_2 and tissues, known as hyperoxemia (Llitjos et al., 2016). The imbalance between normal oxygen requirements and hyperoxemia is thought to cause an overproduction of reactive oxygen intermediates (ROIs) such as superoxide anions, hydroxyl radicals, and hydrogen peroxide (Winslow, 2013). Reactive oxygen intermediates are potent inflammatory mediators and intracellular messengers and are highly reactive and unstable molecules. When overproduced, ROIs overwhelm the cell's natural antioxidant defenses and ultimately interact with it to cause toxicity, cell cycle modification, carcinogenesis, and cellular death (Llitjos et al., 2016).

Hyperoxemia is also thought to be responsible for triggering inflammatory pathways that can lead to secondary tissue damage in multiple organ systems throughout the body (Llitjos et al., 2016). The toxic effect on pulmonary tissue occurs by directly affecting the alveolar capillary border thus making the tissue more permeable to edema or hemorrhage and by indirectly interfering in gas exchange (Llitjos et al., 2016). The effects of hyperoxemia can also lower heart rate and increase vascular resistance, the combination of which reduces cardiac output (Llitjos et al., 2016). Systemic vasoconstriction from hyperoxemia negatively impacts the microcirculation at the capillary level (Llitjos et al., 2016). Hyperoxemia can also be toxic to the central nervous system, which can ultimately manifest in tonic-clonic seizures (Llitjos et al., 2016). However, seizure activity was mostly reported in areas with higher-than-normal atmospheric pressure such as in hyperbaric chambers or deep-sea diving (Llitjos et al., 2016).

Method

A review of existing literature was conducted using PubMed and CINAHL databases. The keywords "hyperoxia", "hyperoxemia", "oxygen toxicity" and "excessive oxygenation" were used to yield articles for consideration. Only recent articles published within the last 5 years were included. The search revealed six studies of various designs that were used to compare and contrast the effects of excessive oxygen on morbidity and mortality of hospitalized patients. More specifically, study designs included two randomized control trials (Girardis et al., 2016; Panwar et al., 2016), one prospective pilot study (Stolmeijer, Maaten, Zijlstra, & Lightenberg, 2014), and three retrospective analyses (Elmer et al, 2015; Helmerhorst et al., 2017; Rincon et al., 2014). The remaining four articles referenced were included for supportive information. The articles included in this review were confined to adult patients only. Due to differences in pathophysiology and potential differences in oxygen requirements, studies involving the pediatric populations were excluded.

Results

Sufficient evidence is present in the literature that identifies the mechanisms behind the deleterious effects

of hyperoxemia. Unfortunately, exact limits at which these effects occur and how significantly they impact patient outcomes lack comparable delineation. Several recent studies involving critically ill hospitalized patients attempted to assess the clinical significance of hyperoxia on adverse patient outcomes, with somewhat mixed results (Elmer et al., 2015; Girardis et al., 2016; Helmerhorst et al., 2017; Panwar et al., 2016; Rincon et al., 2014; Stolmeijer, ter Maaten, Zijlstra, & Ligtenberg, 2014). Of the six studies reviewed, all compared the effects of hyperoxia on mortality and morbidity in the setting of an Intensive Care Unit (ICU) (Elmer et al., 2015; Girardis et al., 2016; Helmerhorst et al., 2017; Panwar et al., 2016; Rincon et al., 2014; Stolmeijer et al., 2014). One of the studies examined the relationship between the effects of hyperoxia on patient outcomes after cardiac arrest (Elmer et al., 2015), another following a stroke (Rincon et al., 2014), and another in the setting of sepsis (Stolmeijer et al., 2014). The remaining three studies were conducted in ICU patients, whereas their admitting diagnosis was not a factor (Girardis et al., 2016; Helmerhorst et al., 2017; Panwar et al., 2016).

Five out of six studies identified positive correlations between hyperoxia and adverse outcomes by use of metrics such as episodes of septic shock, bacteremia, organ injury, ventilator free days, and mortality (Elmer et al., 2015; Girardis et al., 2016; Helmerhorst et al., 2017; Panwar et al., 2016; Rincon et al., 2014; Stolmeijer et al., 2014). Rincon et al. (2014) conducted a retrospective cohort study of 2,894 stroke patients and identified that hyperoxemia, at PaO_2 levels of greater than 300 mmHg, was independently associated with increased in-hospital mortality after a stroke. Another retrospective cohort study, with a significantly smaller sample size but a similar target PaO_2 level for hyperoxemia, corroborated these results but surprisingly found that moderate permissive hyperoxemia (defined as PaO_2 of 101–299 mmHg) improved sequential organ failure assessment scores after cardiac arrest (Elmer et al., 2015). In contrast, Helmerhorst et al. (2017) found that severe hyperoxemia (defined as PaO_2 greater than 200 mmHg) was associated with higher mortality rates and fewer ventilator-free days; however, this study did not report any benefit of even mild permissive hyperoxemia. A potential explanation in the benefit of permissive hyperoxemia as noted by Elmer et al. (2015) versus the lack of such benefit as noted by Helmerhorst et al. (2017) could be attributed to the inherent oxygen demand of a disease process such as cardiac arrest versus an unknown diagnosis that was not disclosed. Two of the studies included randomized control trials in which oxygen was either given conservatively or conventionally also known as liberally (Table 1; Girardis et al., 2016; Panwar et al., 2016). In both studies, patients in the conservative group had lower mortality and fewer episodes of septic shock, liver failure, and bacteremia, whereas patients in the conventional or liberal group displayed higher morbidity and mortality (Girardis et al., 2016; Stolmeijer et al., 2014).

Lastly, the sixth study completed by Panwar et al. (2016) was a pilot randomized control trial that surprisingly found no significant differences in morbidity or mortality with the use of liberal oxygenation. The intent of this study was to explore the feasibility of a conservative strategy to oxygenation as opposed to a liberal, which had been the conventional approach (Panwar et al., 2016). Conservative oxygenation in this study was defined as keeping the SpO_2 between 88% and 92%; whereas liberal oxygenation was defined as maintaining a SpO_2 of 96% percent or above (Panwar et al., 2016). Panwar et al. (2016) revealed that there was no harm demonstrated with a lower target SpO_2, thus lending credibility to the notion that higher levels of oxygen administration are not beneficial and lower targets of oxygenation are safe for consideration. Of note, Panwar et al. (2016) was the only study of the six to use peripheral capillary oxygen saturation (SpO_2) as the sole measurement to assess oxygenation (the other five studies used PaO_2 gathered from an arterial blood gas). In addition, due to a small sample size (n = 103), results should be seen as exploratory. Of the six studies reviewed, Stolmeijer et al. (2014) was the only study of this relative size at 83 patients.

Conclusions and implications for practice

The purpose of this literature review was to explore the harmful effects of hyperoxia due to excessive oxygenation and to examine the significance of those effects on morbidity and mortality. The findings from the six studies of this review affirm the already widely demonstrated deleterious effects of hyperoxia and show that strategies for lower target levels of oxygenation can be safely considered. The only exception appears to be related to specific disease processes such as cardiac arrest, whereas moderate permissive hyperoxemia for a period of time may improve organ function and survival (Elmer et al., 2015). Elmer et al. (2015) describe these findings as clinically important and thus requiring further investigation.

Despite the resounding evidence that the administration of excessive oxygen places patients at the hands of iatrogenic harm, considerable variability remains regarding therapeutic levels of oxygen (Llitjos et al., 2016; Vincent, Taccone, & He, 2017). Although terms such as normoxia and hyperoxia exist, operational definitions are not consistent. As a result, the threshold at which cellular damage occurs remains undefined and is, therefore, difficult to protect against (Vincent et al., 2017). Within the six studies reviewed, normoxia is identified as a value between 60 and 300 mmHg, whereas hyperoxemia is identified as a value between 100 and upwards of 300 mmHg (Elmer et al., 2015; Girardis et al., 2016; Helmerhorst et al., 2017; Panwar et al., 2016; Rincon et al., 2014; Stolmeijer

Table 1. Measurements of oxygenation as defined by authors (PaO_2 mm Hg and SpO_2%)

Author(s)	Study Purpose	Hypoxia	Normoxia	Hyperoxia
Elmer et al., 2015	Review of the association between early hyperoxemia and poor outcomes with consideration of disease-specific markers of illness severity and care processes.	<60 mmHg	60–100 mmHg	101–299 mmHg (moderate) ≥300 mmHg (severe)
Girardis et al., 2016	Assessment of whether conservative oxygen protocols improve outcomes in ICU patients.	—	70–100 mmHg (conservative use)	>150 mmHg (conventional/ liberal use)
Helmerhorst et al., 2017	Evaluation of past and present metrics of arterial hyperoxemia and assessment of these metrics in association with clinical outcomes in various subgroups of ICU patients.	—	—	120–200 mmHg (mild) >200 mmHg (severe)
Panwar et al., 2016	Conservative oxygenation strategy as feasible alternative to liberal use among ICU patients requiring IMV.	—	SpO_2 88%–92% (conservative use)	SpO_2 ≥ 96% (liberal use)
Rincon et al., 2014	To define the relationship between hyperoxemia and outcome in stroke patients requiring IMV.	—	60–300 mmHg	>300 mmHg
Stolmeijer et al., 2014	Investigation of the incidence of hyperoxia and hypoxia with reduced FiO_2 in patients hospitalized with sepsis.		71–100 mmHg	>100 mmHg

Note: Stolmeijer et al., 2014 units converted to millimeters of mercury (mmHg) from kilopascals (kPa) for ease of comparison.
FiO_2 = fraction of inspired oxygen; ICU = intensive care unit; IMV = invasive mechanical ventilation; PaO_2 = partial pressure of arterial oxygenation.

et al., 2014). As shown in Table 1, values that are considered to be severely hyperoxic in certain studies are considered normoxic in others. To find the delicate balance between the risk of hypoxia and hyperoxia, further research needs to be conducted to determine this value.

Meanwhile, the evidence of the harm caused by excessive oxygenation is apparent but the phenomenon continues in health care institutions (Girardis et al., 2016; Llitjos et al., 2017). Supplemental oxygen is routinely and liberally administered by hospital staff in reaction to a perceived risk of hypoxia, often without a provider's order or an awareness of the potential harm (Llitjos et al., 2017). Industry-wide education on the effects of hyperoxia may reduce the incidence of related injury to patients and help to alleviate distress among caregivers who fear they are not providing adequate care. Nurse practitioners are uniquely suited to champion education regarding best practices for oxygen therapy so that a change in practice can occur. In the future, when the parameters of oxygen therapy are better established, a collaborative approach between providers, nurses, and respiratory therapists will be necessary to deliver a tailored and conservative approach to patients' oxygen requirements.

Competing interests: *The author reports no conflicts of interest.*

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