Evidence for Oxygen Use in the Hospitalized Patient: Is More Really the Enemy of Good?

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Oxygen in arguably one of the most frequently utilized drugs in modern healthcare, but is often administered to patients at caregivers' discretion with scant evidence as to its efficacy or safety. Although oxygen is administered for varied medical conditions in the hospital setting, published literature supports the use of oxygen to reverse hypoxemia, for trauma victims with traumatic brain injury and hemorrhagic shock, for resuscitation during cardiac arrest, and for carbon monoxide poisoning. Oxygen should be titrated to target an S_{pO_2} of 94–98%, except with carbon monoxide poisoning (100% oxygen), ARDS (88–95%), those at risk for hypercapnia (S_{pO_2} 88–92%), and premature infants (S_{pO_2} 88–94%). Evidence for use with other conditions for which oxygen is administered relies on anecdotal experiences, case reports, or small, underpowered studies. Definitive conclusions for oxygen use in these conditions where efficacy and/or safety are uncertain will require large randomized controlled clinical trials. *Key words: oxygen therapy; normoxia; hypoxemia; hyperoxemia; oxygen efficacy; oxygen safety.* [Respir Care 2013;58(10):1679–1693. © 2013 Daedalus Enterprises]

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Introduction

In 1772 Swedish pharmacist Carl Scheele discovered that when heating mercuric oxide and potassium nitrate, candles burned brighter. Scheele did not publish his findings until 1777. Meanwhile, chemist Joseph Priestley was conducting his own experiments with mercuric oxide. His experiments describing "dephlogisticated air" were published in 1775, which credited him with the discovery of oxygen.[1] At this time the chemical theory of phlogiston stated that by burning, the combustible components of a substance are released into the atmosphere. Priestley believed that by heating the mercury he was removing phlogiston (impurities) from the atmosphere, pulling it into the mercury, thus purifying the air. Priestley theorized that dephlogisticated air may have medical applications in serious cases of lung disease, but also warned that use in the healthy body may be harmful. His statement "As a candle burns out much faster in dephlogisticated than in common air, so we might, as may be said, live out too fast, and the animal powers be too soon exhausted in this pure kind of air" has applications today, as we seek to determine how much oxygen is too much. For the purpose of this paper, the discussion of oxygen therapy pertains only to adults, unless otherwise stated.

Early Oxygen Use

Following Priestley's published findings, Antoine Lavoisier repeated his and Scheele's experiments and proved that oxygen was a chemical element, disproving the phlogiston theory.[2] In 1778 he named the gas oxygen "acid former," due to his belief that it was a component of all acids. Five years later a French physician treated a patient suffering from tuberculosis with daily inhalations of oxygen, which is believed to be the first medical use of the gas.[1] Throughout most of the 19th century, pure oxygen therapy was not available to the public. Mostly diluted nitric oxide, "compound oxygen," was widely believed to be a panacea for many common ailments. George Holtzapple is credited with publishing the first case report describing the administration of intermittent oxygen therapy, to a 16-year-old male with lobar pneumonia, at York Hospital in 1885. The patient's cyanosis improved with oxygen therapy and he subsequently recovered.[3] It was not until 1890 that Albert Blodgett administered continuous flow oxygen to a patient with pneumonia to relieve shortness of breath.[4] He estimated that around 200 gallons of oxygen per day was needed for continuous administration: approximately 6 L/min.

Modern Oxygen Therapy

The understanding of therapy and physiology advanced quickly during the early 1900s, due to the gas poisonings during World War I, and advances in basic science.[1] Physiologists Adolph Fick and Paul Bert further advanced oxygen physiology by describing oxygen in units of partial pressure, which led to the understanding of the differences between arterial and venous blood oxygenation and the relationship to cardiac output and oxygen consumption. John Haldane published the first paper on the rational use of oxygen in 1917.[5] Much of what we consider to be the basic physiologic concepts of oxygenation can be attributed to Haldane. In his paper he describes the respiratory drive as regulated by carbon dioxide, the different types or causes of hypoxemia, and tissue hypoxemia in carbon monoxide (CO) poisoning. He further describes the mechanisms of ventilation-perfusion matching and mismatching and the role of supplemental oxygen as a treatment. Haldane was also the first to describe the effects of oxygen on the pulmonary system.

Oxygen use on the battlefield was first reported during World War I, primarily for the treatment of phosgene gas poisoning.[6] When mixed with water in the lungs, phosgene forms hydrochloric acid, damaging alveolar lining, and at high doses leads to pulmonary edema and eventually to what we know today as ARDS. Oxygen was also used in the treatment of trench nephritis, acute bronchitis, and severe hemorrhage. Oxygen treatment on the battlefield was accomplished by the use of equipment developed by Haldane, which consisted of a pressurized cylinder, pressure regulator, a reservoir, and mask, much like what is currently used today. Experiences learned from the war helped develop a basic understanding of rational oxygen use, ways to administer, and what did not work: mainly intermittent usage in a hypoxic patient. Evidence for oxygen use in trauma care was also gained from the war experience. Despite evidence of the benefit of continuous therapy on the battlefield and the publishing of Haldane's book, *Respiration*,[7] many physicians continued to prescribe intermittent oxygen therapy into the first half of the 20th century.

Indications for Oxygen Therapy

Supplemental oxygen is an important part of modern medical care. From prehospital to in-hospital care and anesthesia applications, to long-term usage in chronic lung disease, oxygen use has become so common that it is often taken for granted. Although it is considered a drug and should be prescribed as such, oxygen is often given to patients at the caregiver's whim, and frequently without a physician's order.[8,9] This occurrence in the hospital setting is common because oxygen is readily available, abundant, and cheap when employing the large liquid systems, as do most hospitals. Even after a century's experience and numerous publications concerning oxygen administration, the

question remains: what are the evidence-based indications for oxygen therapy in hospitalized patients?

The American Association for Respiratory Care provides guidance for in-hospital use of oxygen other than with mechanical ventilators and hyperbaric chambers.[10] The recommended indications are documented hypoxemia ($P_{aO_2} < 60$ mm Hg or $S_{aO_2} < 90\%$), suspected hypoxemia, severe trauma, acute myocardial infarction, and short-term therapy such as post-anesthesia recovery or surgical intervention. The British Thoracic Society's[11,12] and Western Australian Hospital's indications for supplemental oxygen are to maintain normal or near normal S_{pO_2} (94–98%) for all patients not at risk for hypercapnic respiratory failure, and S_{pO_2} of 88–92% for those at risk. This guidance specifically states that patients suffering from myocardial infarction and acute coronary syndrome have the same S_{pO_2} targets as above. Additionally, the guidance states that non-hypoxic breathless patients (other than CO poisoning) do not benefit from oxygen therapy and does not recommend supplementation. Both of the latter associations recommend the use of an oxygen alert card for those patients at risk for hypercapnic respiratory failure, so that in an emergency the appropriate low F_{IO_2} will be administered.

The remainder of this paper will detail the diseases/conditions for which oxygen is often prescribed as a treatment, and the available evidence to support or refute its use.

Oxygen Myths

John Downs presented the 2002 Donald F Egan Scientific Lecture entitled "Has Oxygen Administration Delayed Appropriate Respiratory Care? Fallacies Regarding Oxygen Therapy."[13] Downs outlined what he believed to be 3 commonly held beliefs and the related evidence regarding oxygen therapy.

Fallacy 1

$F_{IO_2} \leq 0.6$ is Safe. This is what we were all taught in respiratory school, or at least that $F_{IO_2} > 0.6$ produced more adverse effects and $F_{IO_2} < 0.6$ produced less. Downs collaborated on a study that treated 54 subjects with ARDS by using high levels of PEEP and decreasing F_{IO_2} as soon as possible.[14] The study reported an 80% survival rate. A decade later it was reported that subjects who had the lowest P_{aO_2}/F_{IO_2} (80 mm Hg) had the lowest mortality, as compared to those who had the highest P_{aO_2}/F_{IO_2} (~200 mm Hg).[15] The major emphasis was lowering the F_{IO_2} as soon as possible, by applying high levels of PEEP while tolerating a P_{aO_2} as low as 50 mm Hg. Most subjects were breathing F_{IO_2} of 0.3–0.4 within 6 hours of intubation.

Register et al conducted a study with subjects undergoing open heart surgery, all of whom were breathing room air preoperatively.[16] It was found that in subjects administered F_{IO_2} of 0.5 postoperatively had a greater degree of hypoxemia on room air on postoperative day 2 than those given sufficient oxygen to maintain $S_{pO_2} \geq 90\%$. After repeating the study using only room air intra- and post-operatively, and finding that most subjects did not have a decrease in blood oxygen levels, as compared to preoperative values, it was postulated that the hypoxemia experienced in the first study was due to the use of oxygen during and after surgery.[17]

Garner et al exposed rats with peritonitis to F_{IO_2} of 0.8, 0.4, or 0.21. Mortality was lowest in the F_{IO_2} 0.2 group, and highest in the F_{IO_2} 0.8 group.[18] Upon postmortem examination it was found that lung pathology did not differ between the groups but there was substantial liver damage with $F_{IO_2} > 0.21$. It was postulated that free radical formation caused the liver damage.

Fallacy 2

High F_{IO_2} is Protective. This stems from the belief that elevating the F_{IO_2} and subsequently the P_{aO_2} provides a margin of safety and time to react if a patient's clinical condition deteriorates. While this appears logical and is seen frequently in our ICU, the opposite may be the case. According to Downs, the only true indication for prophylactic hyperoxygenation is prior to tracheal intubation.[19] Downs further states that, hypothetically, a patient on F_{IO_2} of 1.0 and having a P_{aO_2} of 650 mm Hg, could drop to 90 mm Hg due to lung function deterioration over a period of 15–20 min, but the S_{pO_2} would not drop below 98%.[13] This drop would not be enough to indicate a problem. But over the next 5 minutes the S_{pO_2} would drop to 92%, alerting the caregiver to investigate. In this scenario the elapsed time until a problem is detected would be 20–25 min. If that same patient was on F_{IO_2} of 0.3 with a P_{aO_2} of 90 mm Hg and an S_{pO_2} of 99% and experienced the same problem, the S_{pO_2} would decrease to 94% within 10 min, alerting caregivers to a problem much earlier. Additionally, if a patient is already receiving F_{IO_2} of 1.0, there is no room to increase once a problem is detected.

Fallacy 3

Supplemental Oxygen is Useful. This stems from the "it may not help, but it won't hurt" mentality. In emergency departments, post-anesthesia care units, and during conscious sedation, oxygen is routinely administered despite the lack of evidence to support the practice. In fact, profound hypoventilation can occur without an S_{pO_2} decrease if oxygen is supplemented. Patients breathing room air who have a small decrease in ventilation will be alerted

much earlier by the S_{pO_2} reading, so the caregiver can intervene.[20] For this reason Downs suggests that post-operative patients not be administered oxygen unless S_{pO_2} is $< 90\%$ and simulation is ineffective.

Downs listed 6 primary conditions that can cause arterial hypoxemia and the specific treatments for each.[13] In only one condition, low F_{IO_2}, does he recommend that supplemental oxygen is the treatment of choice. His reasoning for the lack of recommendation for oxygen in the other conditions is the belief that, yes, P_{aO_2} will be increased, but will delay the diagnosis and treatment with the appropriate therapy.

Chronic Obstructive Pulmonary Disease

The World Health Organization estimates that there are 210 million people worldwide living with COPD, making it a major health issue in many countries.[21] It is estimated that in the United States alone the cost to manage patients with the disease exceeded $49 billion in 2010.[22] An additional $73 billion was associated with hospital admissions. Although oxygen is among the standard management treatments, it was shown over 50 years ago that high F_{IO_2} increases blood carbon dioxide concentration in some COPD patients.[23] The British Thoracic Society recommends that until an arterial blood gas is obtained, any patient with known or suspected COPD not be given an $F_{IO_2} > 0.28$.[24]

Denniston et al conducted a prospective audit of 97 subjects with the diagnosis of COPD admitted to the emergency department, representing 101 episodes of COPD exacerbation.[25] At some point in the pre-hospital or emergency department setting, 56% received an $F_{IO_2} > 0.28$. For those subjects who received an $F_{IO_2} > 0.28$, in-hospital mortality was 14% (8 of 57) versus 2% (1 of 44) for those who received an $F_{IO_2} \leq 0.28$. Demographics and smoking history were not different between the 2 groups. Interestingly, in the ambulance those subjects who either self-identified or were identified by the crew as having COPD received a mean F_{IO_2} of 0.47, versus 0.6 if they were not identified. Although the ambulance crew administered a lower F_{IO_2} to those subjects identified as having the diagnosis of COPD, it was still well above the recommended F_{IO_2}.

In a prospective study including 972 subjects admitted to the emergency department with the diagnosis of COPD, Plant et al found that 20% had respiratory acidosis.[26] In 47% of the hypercapnic subjects, pH was inversely related to P_{aO_2}, with most being associated with a $P_{aO_2} > 75$ mm Hg. As in the aforementioned study by Denniston, the acidotic subjects had a higher in-hospital morality than the non-acidotic subjects (12.8% vs 6.9%).

A recent study comparing high flow with titrated oxygen administration in the pre-hospital setting in 405 subjects with COPD (214 confirmed) was conducted by Austin and colleagues.[27] Subjects were randomized into 2 groups: oxygen via nasal cannula titrated to S_{pO_2} of 88–92%, or 8–10 L/min of oxygen via non-rebreathing mask. Both groups received standard of care bronchodilator treatments enroute to the hospital. The study results showed that titrating oxygen to maintain an S_{pO_2} of 88–92% reduced the risk of death from hypercapnia and respiratory failure by 58% in all subjects, and by 78% in those with confirmed COPD. In the high flow oxygen group the number needed to harm was 14.

Evidence

The need for titrated oxygen is often ignored in the prehospital and emergency settings, presumably due to the belief that hypoxemia is worse for the patient than hyperoxemia. In the COPD patient population this may not be the case. The current literature provides overwhelming evidence that in patients with documented or suspected COPD, titrating oxygen to an S_{pO_2} of 88–92% reduces the risk of death due to respiratory failure, especially in those susceptible to hypercapnia. Since most oxygen therapy is initiated prehospital, protocols must be implemented to ensure appropriate oxygen therapy is administered throughout the prehospital and hospital course. An interesting concept of providing patients with cards stating that they have a COPD diagnosis and to titrate oxygen to keep the S_{pO_2} 88–92% has been suggested by the British Thoracic Society, in order to identify these patients quickly. A similar approach of a medical alert bracelet or necklace, much like is done for allergies, would also be effective.

Infants/Neonates

François Chaussier used oxygen in attempts to revive what he termed "near dead" infants, beginning in 1780,[28] but it was not until the 1930s that physicians began using oxygen routinely with neonates.[29] In 1938, Chapple reported delivering F_{IO_2} of approximately 0.46 to an incubator to treat preterm infants.[30] A decade later, Terry documented over 100 cases of a new type of blindness present in premature infants,[31] but it was not until 1951 that Campbell[32] linked supplemental oxygen to the cause of what was initially termed retrolental fibroplasia and is currently known as retinopathy of prematurity (ROP). The first randomized controlled trial (RCT) to study the association of supplemental oxygen with ROP was published in 1952 by Patz et al.[33] The infants were randomized to either an F_{IO_2} of 1.0 or titrated oxygen to treat hypoxemia. In the F_{IO_2} 1.0 group, 61% of the infants developed ROP, versus 16% in the titrated oxygen group.

In a retrospective study of risk factors for developing ROP in 2009, Hua et al[34] found that infants that breathed

F_{IO_2} of > 0.8 for any length of time, and those who received any supplemental oxygen for > 8 days had the highest incidence. Additionally, the lower the birth weight, the higher the incidence of ROP for those infants who received oxygen. This study concurred with a 1977 study by Kinsey et al, finding that birth weight < 1,200 g and length of exposure to oxygen increased ROP risk.[35]

Early studies that confirmed the association between oxygen and ROP helped to increase awareness of the problem, but, due to lack of ability to continuously measure arterial oxygenation, many premature infants were left profoundly hypoxic, for fear that administering oxygen would lead to ROP. The resulting hypoxia led to increased incidence of cerebral palsy. An early paper from 1961[36] reported that, in a study of 1,080 premature infants, supplemental oxygen administration for < 2 days showed a 17% increase in cerebral palsy, whereas oxygen exposure for > 10 days resulted in a 22% increase in ROP. This was the first study to show that there can be neither too little nor too much oxygen given to premature infants. In a multicenter RCT involving 358 preterm infants, Askie et al showed no difference in growth and development in those infants with S_{pO_2} of 91–94% than those with S_{pO_2} of 95% and above.[37]

The use of oxygen in the resuscitation of infants in the delivery room has received considerable attention in the last decade. In a paper reviewing the available literature on this subject, Richmond and Goldsmith[38] found that in both animal and human studies, although the results were mixed, there was a trend toward resuscitation with room air being as effective as using 100% oxygen. Animal studies showed that using air was nearly as effective as F_{IO_2} of 1.0 in reducing pulmonary vascular resistance and may prevent rebound pulmonary vascular resistance increases post-resuscitation. Most of the human studies only examined short-term outcomes, such as survival, Apgar score, and time to first breath, and most were not randomized.

The most recently published study, from the Benefits of Oxygen Saturation Targeting (BOOST) II Collaborative Group,[39] showed that in 3 RCTs including 2,448 extremely pre-term infants (< 28 weeks gestation), targeting oxygen saturation < 90% resulted in a statistically significant increased risk of death ($P = .002$), compared to the comparative group targeting saturation of 91–95%. Although the lower targeted saturation group had a significantly reduced incidence of ROP, the infants also had a significant increase in the rate of developing necrotizing enterocolitis.

Evidence

Judicious use of oxygen with neonates is warranted, although the safe F_{IO_2} and duration of use are still questionable. The literature clearly shows that administering oxygen despite an $S_{pO_2} \geq 90\%$ increases the risk of ROP and bronchopulmonary dysplasia. Conversely, maintaining an $S_{pO_2} < 85\%$ increases the risk of cerebral palsy. During resuscitation of infants in the delivery room, the use of room air or low levels of oxygen may reduce pulmonary vascular resistance and increase survival. Additional randomized human studies examining short- and long-term effects of various levels of oxygen use during resuscitation are needed.

The American Association for Respiratory Care clinical practice guideline recommends using caution when administering oxygen to preterm infants, infants with congenital heart lesions, those suffering from paraquat poisoning, or those receiving certain chemotherapy agents.[40] The guidance also cautions that oxygen flow may stimulate laryngeal nerves and alter respiratory patterns. Additionally, oxygen should be administered to treat hypoxemia and prevent hyperoxemia.

Table 1. Prehospital Trauma Life Support Recommendations for Administering Oxygen Based on Spontaneous Breathing Frequency

Breathing Frequency breaths/min	Airway Management
12–20	Observe
< 12	Assisted ventilation $F_{IO_2} \geq 0.85$
20–30	Administer oxygen $F_{IO_2} \geq 0.85$
> 30	Assisted ventilation $F_{IO_2} \geq 0.85$

(Data from reference 41.)

Trauma

Patients suffering from multiple traumatic injuries are nearly always placed on supplemental oxygen, even if not intubated. Oxygen use in emergency care has been mandated in Advanced Trauma Life Support,[41] Prehospital Trauma Life Support,[42] and Advanced Cardiac Life Support,[43] despite scant evidence regarding efficacy and/or safety in this patient population. Oxygen supplementation begins at the point of injury and continues until presentation to the emergency department, usually via a non-rebreathing mask at 15 L/min, often despite S_{pO_2} readings of 100%. It has been witnessed on numerous occasions in our facility's emergency department: a patient brought in by the life squad wearing a non-rebreathing mask while talking on a cell phone, with the mouthpiece tucked under the mask. Clearly, oxygen administration was not indicated in this situation. The Prehospital Trauma Life Support guidelines[42] for oxygen administration are based on the patient's spontaneous breathing frequency (Table 1). Other than with a normal breathing frequency,[12-20] the

recommendation is to administer an F_{IO_2} of at least 0.85, with no mention of arterial oxygenation parameters.

Much of what the civilian medical community has learned about treating trauma victims was born from the military experiences in treating the casualties of war. Few studies have been conducted to determine how much oxygen trauma patients require, and most are observational. Stockinger and McSwain[44] retrospectively reviewed data from 5,090 spontaneously breathing trauma patients who presented to a civilian trauma center, in an attempt to determine the oxygen needs of trauma patients, in order to advance knowledge for military needs. Forty-three percent of the patients received oxygen, and they died more often than those who did not receive oxygen (2.3% vs 1.1%). Even after correcting for Injury Severity Score, mechanism of injury, and age, those who did not receive oxygen had no worse outcome than those who received oxygen, suggesting that supplementing oxygen does not improve outcomes in trauma patients who are not in respiratory distress.

Barnes et al conducted a prospective study to determine oxygen requirements and usage during transcontinental flights transporting mechanically ventilated wounded war fighters from Iraq to Germany with the Air Force Critical Care Air Transport Teams.[45] During the 6–8 hour flight an integrated computer recorded the ventilator settings and pulse oximetry readings. Oxygen was titrated according to the standard of care guidelines, keeping $S_{pO_2} \geq 94\%$. Twenty-two patients' data were recorded, resulting in 117 hours of continuous data. After calculating oxygen usage (L/min), it was found that the mean usage was 3.24 L/min, with a mean F_{IO_2} of 0.49 for all patients. Sixty-eight percent of the patients required ≤ 3 L/min, suggesting that oxygen requirements for trauma patients may be much lower than what is currently being administered.

Hemorrhagic shock is the leading cause of death in trauma patients, and poses a different set of problems when trying to determine appropriate oxygen administration. Hemorrhagic shock is a result of blood loss that may lead to decreased oxygen supply and cellular hypoxia despite normal arterial oxygenation indicators. Knight et al performed a literature review to increase understanding of the effects of oxygen administration following hemorrhagic shock.[46] The review found that F_{IO_2} of 1.0 and resuscitation are the most common treatments following hemorrhagic shock, although there is concern that hyperoxia may increase free radical formation and further cell damage. The literature suggested serum lactate should be monitored to assess cellular hypoxia and possibly guide oxygen administration, although the appropriate level remains unclear.

Despite anecdotal and sparse research data, there is no consensus for determining in which trauma patients to administer oxygen, and how much. The United States Special Operations Command's Tactical Combat Casualty Care guidelines state that oxygen may be beneficial for the following patients[47]:

- Low oxygen saturation by pulse oximetry
- Injuries associated with impaired oxygenation
- Unconscious casualty
- Casualty in shock
- Casualty at altitude
- Casualty with traumatic brain injury (maintain $S_{pO_2} > 90\%$)

Traumatic brain injury represents challenges when caring for a trauma patient, and is a leading cause of death and disability.[48] Much of the available literature's focus is on prehospital management of traumatic brain injury. It is well known that secondary brain injury can develop as a result of several factors, including inappropriate ventilation, glycemic control, cerebral edema, hypotension, and cerebral hypoxia.[49-51] Hypoxia has been identified as an independent risk factor for poor outcome with traumatic brain injury.[50] Providing oxygen to the injured brain is crucial to mitigating secondary brain injury, but the appropriate level of P_{aO_2} remains unclear, since adequate arterial oxygenation may not always equate to adequate brain oxygenation. Chi et al performed a prospective cohort study in 150 trauma patients with suspected head injury undergoing helicopter transport.[52] The study goal was to determine the incidence of hypoxia and hypotension and to assess mortality and disability. Thirty-seven subjects had hypoxic episodes. The mortality for subjects without any secondary insults was 20%, versus 37% for those who had hypoxic episodes. Surviving subjects who experienced hypoxia also had a greater degree of disability at hospital discharge. In an attempt to determine the relationship between hypoxemia and hyperoxemia and outcome, Davis et al performed a retrospective review of 3,420 subjects treated for traumatic brain injury.[53] The study found that mild hyperoxemia (P_{aO_2} 110–487 mm Hg) was associated with increased survival, while hypoxemia ($P_{aO_2} < 110$ mm Hg) and extreme hyperoxemia ($P_{aO_2} > 487$ mm Hg) were associated with increased mortality.

Although monitoring and treating intracranial pressure remains the standard of care, devices to measure brain-tissue oxygenation are being utilized. Martini and associates[54] reviewed the available published literature on this practice and found that monitoring brain-tissue oxygenation has shown value in determining poor prognosis following traumatic brain injury, and that interventions to increase cerebral perfusion pressure and P_{aO_2} can result in increased brain-tissue oxygenation. The authors' review

also found that retrospective studies suggest that maintaining a target brain-tissue oxygenation (usually 20 mm Hg) may have potential benefits, but prospective studies showed no outcome benefits.

Evidence

Many trauma patients need little or no oxygen. Oxygen administration should be titrated to achieve normoxemia for all trauma patients except for traumatic brain injury and hemorrhagic shock with increased lactate. There is some evidence that mild to moderate hyperoxemia may increase survival with traumatic brain injury. Hypoxemia and extreme hyperoxemia with traumatic brain injury are associated with a worse outcome. The evidence is still unclear on whether to monitor and target brain-tissue oxygenation and to manipulate physiologic parameters to maintain that target, especially with mounting evidence that hyperoxemia may have deleterious effects. Adequately powered randomized clinical trials are necessary to evaluate the outcome benefits of this practice.

ARDS

ARDS was first described by Ashbaugh et al in 1967. Historically, the mortality rate for ARDS was reportedly 40–60%[55-58] by most accounts, until the turn of the 21st century, when new therapeutic studies emerged that improved outcome. The ARDS Network clinical trial, published in 2001, was the first evidence that ARDS mortality can be improved by changes in mechanical ventilation practice.[59] This landmark study showed that reducing tidal volumes to as low as 4–6 mL/kg of ideal body weight reduced mortality by 22%. Additionally the study supported oxygenation by the use of a PEEP/F_{IO_2} table to maximize lung recruitment and minimize oxygen exposure, due to earlier evidence in animal models that high F_{IO_2} may be toxic. The targeted range for oxygenation was P_{aO_2} 55–88 mm Hg and S_{pO_2} 88–95%. Although the best strategy for using PEEP and F_{IO_2} has not been identified, mounting evidence suggests the use of the lowest F_{IO_2} possible and the use of adequate PEEP to increase oxygenation without producing cardiovascular side effects.[60]

Kallet and Branson[61] performed a literature review in an effort to determine if the ARDS Network study's PEEP/F_{IO_2} table is the best method for maintaining oxygenation and minimizing oxygen exposure. The authors found that, since the PEEP required for most patients with ARDS is relatively low, the use of the ARDS Network PEEP/F_{IO_2} table is supported by high level evidence, although there is a small subset of patients who may require an individualized approach to setting PEEP and F_{IO_2}.

Evidence

ARDS is a condition that is difficult to manage and that requires a balance between ventilating with low tidal volumes and providing the right level of PEEP to support oxygenation and minimizing the harmful effects of high oxygen exposure. Although the results of the ARDS Network trial provide the best evidence for use of the PEEP/F_{IO_2} table to adjust these variables, and the evidence in the literature suggests the table may be adequate, there is no consensus as to how to best adjust PEEP and F_{IO_2} for all patients with ARDS. The most important factor to consider is to balance the risk of pressure injury to the lung, by using excessive PEEP and tidal volume, and the risk of oxygen toxicity.

Myocardial Infarction

According to Centers for Disease Control statistics, heart disease is the leading cause of death in the United States, accounting for more than 600,000 fatalities annually.[62] Myocardial infarction accounts for more than half of these deaths. For more than 100 years oxygen has been used to treat myocardial infarction and angina,[63] with little evidence as to the efficacy or potential harm of this practice. Oxygen administration can cause vasoconstriction, regardless of arterial saturation, and raise blood pressure and lower cardiac oxygen consumption, heart rate, and cardiac index.[64-66] Foster et al found that as P_{aO_2} increased, so did arterial pressure and systemic vascular resistance.[67] Kenmure et al[68] and Thomas et al[69] found an increase in blood pressure and decrease in cardiac output when patients suffering from a myocardial infarction breathed F_{IO_2} of 0.4. McNulty et al, using a Doppler flow wire, showed in 18 subjects that coronary vascular resistance increased by 41% and coronary blood flow decreased by 29% when the subjects breathed F_{IO_2} of 1.0 for 15 min.[70] These works showed the physiologic effects of oxygen administration on the coronary system, but the effect on outcome was not evaluated.

Wijesinghe et al performed a review of the published literature that included RCTs of oxygen therapy in myocardial infarction.[71] Of 51 potential studies, only 2 met the inclusion criteria. One of the studies of 200 subjects randomized to either room air or 6 L/min oxygen for 24 hours after having a myocardial infarction found that deaths and the incidence of ventricular tachycardia were higher in the oxygen group, but the difference was not statistically significant. Opiate use was not different between the groups. The other study randomized 50 subjects to either room air or 4 L/min oxygen for 24 hours. Although more subjects experienced an episode of oxygen desaturation, 80% in the room air group ($P < .01$), there was statistically no dif-

ference in the incidence of ventricular tachycardia and opiate use between groups. Mortality was not evaluated.

Kones's review of oxygen use for acute myocardial infarction found there are no large randomized studies available for evaluation.[72] He found that the evidence supporting oxygen use in patients having acute myocardial infarction but who had normal oxygen saturation was old and of poor quality. Kones noted that recent physiological evidence that oxygen use in this patient population that are not hypoxemic suggests that there is no evidence of benefit and may be harmful. His conclusion was that, in these patients, oxygen should be administered only if saturation drops below 94%, although there is no evidence to support this recommended saturation level.

A recent Cochrane Collaborative meta-analysis cited 3 RCTs comparing groups given oxygen or air when experiencing a myocardial infarction.[73] The 3 studies included 387 subjects, with 14 of those dying. Of those 14, nearly 3 times as many subjects in the oxygen group died, compared to those given air. Although this suggests that oxygen administration may be harmful, definitive conclusions cannot be drawn because the studies had small numbers of subjects, so the results may have happened by chance. The authors' conclusion was that a large RCT is required to refute or confirm these findings.

Evidence

There is no conclusive evidence for or against using supplemental oxygen for patients experiencing a myocardial infarction. Standard practice is still as pervasive as it was 100 years ago: apply oxygen to all myocardial infarction patients. What little evidence there is in the current literature suggests giving oxygen to hypoxemic patients experiencing a myocardial infarction to maintain arterial saturation of 94–98%. Large RCTs are required to definitively determine the correct practice.

Cardiac Arrest

Cardiac arrest often results from a myocardial infarction. Even if return of spontaneous circulation is achieved, nearly 60% of these patients will not survive.[74] The high mortality has been associated with anoxic brain injury, cardiac stunning, and reperfusion injury.[75] High concentration oxygen administration during the post-cardiac-arrest period has been questioned as a potential contributor to the high mortality after return of spontaneous circulation. Kilgannon and associates conducted 2 multicenter cohort studies[76,77] using the Project IMPACT critical care database to examine the effect of hyperoxia after cardiac arrest and the effect on mortality. The first study[76] included 6,326 subjects, and the end point was in-hospital mortality. The subjects were divided into 3 groups: hyperoxia (defined as $P_{aO_2} \geq 300$ mm Hg), hypoxia (defined as $P_{aO_2} < 60$ mm Hg or $P_{aO_2}/F_{IO_2} < 300$ mm Hg), and normoxia (defined as P_{aO_2} 60–300 mm Hg).

Of the 6,326 subjects, 18% had hyperoxia, 63% had hypoxia, and 19% had normoxia. The hyperoxia group had significantly higher in-hospital mortality (63%) than did the normoxia group (45%) or the hypoxia group (57%). In the second study[77] using the Project IMPACT database, Kilgannon's group evaluated 4,459 subjects post-cardiac-arrest to determine the relationship between P_{aO_2} and in-hospital mortality. Of the 4,459 subjects, 54% died. The observed P_{aO_2} values were divided into 5 groups: 60–99, 100–199, 200–299, 300–399, and $\geq$ 400 mm Hg. The results of the study showed that there was an association between increased P_{aO_2} and increased mortality, even in those subjects who did not have supranormal P_{aO_2}. For every 100 mm Hg increase in P_{aO_2} there was a 24% increase in the relative risk of death. Interestingly, a 25% increase in P_{aO_2} resulted in a 6% relative risk of death. The results of this study suggest that since a relatively small increase in P_{aO_2} increases mortality, limiting supplemental oxygen as much as possible after cardiac arrest may be beneficial. It is hypothesized that increased free radical formation caused by high concentration delivery, along with reperfusion injury, may be responsible for the increased mortality.

Evidence

Retrospective studies show that hyperoxia, and possibly normoxia, when supplementing oxygen to post-cardiac-arrest patients may increase mortality. Subjects with hyperoxemia had significantly higher mortality that those with hypoxemia or normoxemia, suggesting that maintaining normoxemia (S_{pO_2} 94–98%) should be the standard practice until large clinical trials are conducted to provide definitive guidelines.

Congestive Heart Failure

Patients with congestive heart failure often suffer from dyspnea and hypoxia. High concentration oxygen is often given to these patients, despite previous studies showing that administering F_{IO_2} of 1.0 to healthy subjects decreases cardiac output and increases systemic vascular resistance.[78,79] Little is known about the hemodynamic effects of oxygen administration in these patients. Haque et al conducted a small study in which 22 subjects with class 3 and 4 heart failure were divided into 3 separate experiments.[80] Experiment 1 involved 10 subjects having hemodynamic variables measured while breathing room air and then after breathing an F_{IO_2} of 1.0 for 20 min. Experiment 2 involved 7 subjects having the same hemodynamic measurements collected after breathing room air

and then after 5 min on F_{IO_2} of 0.24, 0.40, and 1.0. F_{IO_2} of 1.0 significantly reduced cardiac output and stroke volume, and increased pulmonary capillary wedge pressure and systemic vascular resistance, as compared to breathing room air ($P < .01$). Graded oxygen showed a progressive decrease in cardiac output ($P < .001$) and stroke volume ($P < .02$), and an increase in systemic vascular resistance ($P < .005$). Additionally, S_{aO_2} progressively increased, from 93.6 ± 1.5% on room air to 100.0 ± 0% on F_{IO_2} of 1.0. Based on the results of this small study, the authors recommend that, in the absence of hypoxemia, oxygen should be used cautiously with patients suffering from severe congestive heart failure.

Table 2. Indications for Supplemental Oxygen Therapy

Dyspnea
Respiratory arrest
Documented COPD
$P_{aO_2} < 65$ mm Hg
$S_{aO_2} < 92\%$
Heart rate > 100 beats/min
Breathing frequency > 24 breaths/min
Central cyanosis
Cardiac arrest
Systolic blood pressure < 90 mm Hg

(Data from reference 80.)

Evidence

Evidence for use of oxygen with congestive heart failure is scarce. The few available studies are small and too underpowered to make a determination about oxygen administration in these patients. The available literature suggests that inducing hyperoxemia in patients with congestive heart failure may be harmful. Oxygen use should be limited to those patients who exhibit hypoxemia and should be titrated to achieve normoxia. Large RCTs are needed to confirm these findings.

Stroke

Oxygen is frequently administered to patients suffering from a stroke in the prehospital setting, and is often continued in the hospital, despite current guidelines that recommend not administering oxygen to non-hypoxic patients.[81] The pervasive idea that oxygen therapy is beneficial stems from the fact that ischemic stroke causes a decrease in oxygen to the brain, resulting in tissue hypoxia and cell death. The prevailing logic is that neuroprotection can be achieved by raising oxygen levels in ischemic tissues.[82] Extending the logic further, it was thought that hyperbaric oxygen therapy, which can produce extreme hyperoxemia, would be beneficial for stroke patients, but clinical trials failed to show any benefit.[83-85] It is well established that hyperoxemia increases free radical formation and could induce cerebral vasoconstriction and reduced blood flow.[79,86] Animal studies have shown increased mortality when exposed to high oxygen levels following cerebral ischemia.[87,88]

Pancioli and associates performed a retrospective chart review of 167 non-intubated, ischemic stroke patients totaling 600 in-patient days at a university hospital to determine whether these patients had indications for supplemental oxygen.[89] The criteria used for supplemental oxygen therapy are listed in Table 2. Sixty-one percent of the subjects received supplemental oxygen at some point during their hospital stay, which accounted for 322 days of receiving oxygen. Of those 322 days, 46% met at least one of the pre-established criteria for oxygen use. Of the 348 days in which criteria for supplemental oxygen were not met, the subjects still received oxygen 46% of the time. The authors estimated that not giving oxygen when it is not indicated could produce up to 45% savings in resources. Ronning and Guldvog[90] conducted an RCT including 500 subjects to determine whether F_{IO_2} of 1.0 for the first 24 hours after stroke would reduce mortality, neurological impairment, or disability, as compared to receiving no oxygen. The subjects in the room air group had a higher 1 year survival, but the difference was not statistically significant ($P = .30$). For subjects with severe stroke there was a statistically nonsignificant tendency toward a higher 1 year survival in the oxygen group ($P = .60$). Neurological impairment and disability did not differ between the 2 groups. The authors concluded that oxygen should not routinely be given to patients suffering from acute stroke.

Evidence

The American Heart Association Stroke Council recommends against oxygen usage for stroke patients. Animal models suggest that giving high levels of oxygen in those with cerebral ischemia may be harmful. The limited evidence in the literature suggests that giving oxygen to patients suffering from acute stroke does not produce any benefit in outcomes, although there may be a small mortality benefit, which needs to be studied further, for those patients having suffered from a severe stroke. A further benefit for not routinely giving oxygen to stroke patients may be in decreased use of resources.

Wound Infection

Surgical wound infection is a serious complication that can increase hospital stays and costs,[91-93] and increase morbidity and mortality.[94,95] Bacterial tissue contamination

establishes wound infections within a few hours post-surgery,[96] so interventions during this time have the greatest potential to prevent a severe infection. Prophylactic antibiotic therapy is the most common perioperative intervention to prevent wound infection. Due to laboratory evidence that oxidative bactericidal activity is highly dependent on increasing the oxygen tension in a wound,[97] it has been suggested that providing high levels of perioperative oxygen may attenuate bacterial wound infections.

Greif and associates[98] conducted an RCT including patients undergoing colorectal surgery to receive F_{IO_2} of either 0.3 or 0.8 intraoperatively, and for 2 hours postoperatively. All subjects received prophylactic antibiotic therapy. Wounds that were culture positive were considered infected. Subjects in the F_{IO_2} 0.8 group had significantly less wound infections, versus those in the F_{IO_2} 0.3 group (5% vs 11%, $P = .01$). Hospital lengths of stay were similar.

In a smaller study, conducted in Israel, 38 subjects undergoing elective colorectal surgery were also randomized to receive the same oxygen concentrations and length of therapy as in the Greif study.[99] The wound infection rate in the F_{IO_2} 0.8 group was higher than in the F_{IO_2} 0.3 group, but the difference was not statistically significant ($P = .53$), although this could have been due to the small sample size. Even though the infection rates were not lower in the high oxygen group, the authors could not make a definitive recommendation for the use or non-use of high oxygen concentration.

Evidence

The current evidence for use of high concentration oxygen to reduce surgical wound infections is mixed. Larger RCTs are required to clarify the issue. Until such trials are conducted, maintaining normoxemia in these patients should be the standard of care, especially with mounting evidence that prolonged hyperoxemia may have other untoward effects.

Postoperative Nausea and Vomiting

Postoperative nausea and vomiting (PONV) is common, with an occurrence of 20–70% despite current pharmaceutical interventions.[100-102] The unpleasantness for the patient notwithstanding, PONV can increase the risk of aspiration pneumonia and can lead to delayed discharge and unexpected hospital admissions following surgery.[103] Recent research suggests that supplemental oxygen may have a positive effect on PONV following selected surgical procedures.

Greif et al conducted an RCT in 231 subjects undergoing colon resection, to receive F_{IO_2} of either 0.8 or 0.3 during surgery and 2 hours afterward.[104] The incidence of PONV during the first 24 hours postoperatively was recorded. PONV was observed in 17% of the subjects who received F_{IO_2} 0.8, versus 30% in the F_{IO_2} 0.3 group ($P = .03$).

Ghods et al[105] randomized 106 subjects undergoing cesarean birth to receive 8 L/min oxygen for 6 hours postoperatively or 5 L/min in the recovery room and no oxygen thereafter, and evaluated the incidence of PONV during the first 6 postoperative hours. PONV occurred in 28% of subjects in the 8 L/min group, and nearly 25% in the control group. The difference between groups was not statistically significant ($P = .66$).

Joris et al[106] conducted an RCT randomizing 150 subjects to receive either F_{IO_2} of 0.3, F_{IO_2} of 0.8, or F_{IO_2} of 0.3 oxygen with droperidol, during thyroidectomy, and evaluated the incidence of PONV for 24 hours post-surgery. There was no difference in the incidence of PONV in the F_{IO_2} 0.3 and 0.8 groups (48% vs 46%), but the group receiving F_{IO_2} of 0.3 plus droperidol was 22%, which was statistically different from the other 2 groups ($P = .004$). Time to first meal was significantly shorter in the droperidol group.

Treschan et al[107] randomly assigned 210 subjects having strabismus surgery to the same study arms as the Joris study, with the difference being the use of ondansetron instead of droperidol. PONV was evaluated postoperatively at 6 and 24 hours. As opposed to the Joris study, there was no statistical difference in the incidence of PONV between any of the 3 groups ($P = .28$), although the incidence was lower for the ondansetron group (28%) versus the F_{IO_2} 0.8 group (38%) and the F_{IO_2} 0.3 group (41%). The low number of subjects in each group may account for the lack of statistical significance.

Evidence

Evidence for the use of supplemental oxygen to treat/prevent PONV is mixed. Despite Akca and Sessler's[108] claim, after reviewing 3 studies, that oxygen use may best prevent PONV following abdominal surgery, this is not always the case, because one study they reviewed showed no difference. Much larger clinical trials must be done to provide more compelling evidence.

Cluster Headache

The first description of cluster headaches (CH) was given by London neurologist Wilfred Harris in 1926.[109] His treatment for these subjects was alcohol injections around the supraorbital and infraorbital nerve. Horton first described the use of oxygen for the treatment of CH in 1952,[110] and was brought to the forefront by Kudrow in 1981.[111] This first systematic study compared oxygen by mask at 7 L/min for 15 min versus sublingual ergotamine. The study showed that both treatments were effective in aborting CH

attacks, but oxygen aborted over 70% of the attacks in 82% of the subjects, whereas ergotamine worked as well in only 70% of the subjects. The average response time with oxygen to abort the CH was 6 min, versus 10–12 min with ergotamine.

In 1985, Fogan conducted a small double-blind crossover study comparing oxygen versus air, both at 6 L/min, for the treatment of CH.[112] Subjects scored their degree of relief with each therapy, with the relief score being significantly higher when inhaling oxygen versus air ($P = .01$). The average relief score was 1.93 for oxygen inhalation and 0.77 for air inhalation, out of a possible 3.

More recently, Garza conducted a double-blind RCT of 109 subjects with CH to alternately receive 12 L/min oxygen or air via mask for 15 min at the onset of an attack.[113] The primary end point was complete or adequate pain relief at 15 min. The results showed that the primary end point was reached 78% of the time with oxygen inhalation, versus 20% with air ($P = .001$). Oxygen was also superior to air concerning the secondary end points of pain free at 30 min, pain reduction at 60 min, and need for additional medication 15 min after treatment.

Although the efficacy of oxygen administration for treatment of CH is well documented, there have been observations of rebound CH post-treatment. The rebound effect is defined as a CH that returns more rapidly than usual following complete relief after oxygen inhalation, or an increased number of attacks in a 24 hour period. Geerlings et al performed a retrospective study and found 8 subjects who experienced rebound CH.[114] In these subjects the mean duration until the next CH was 39 min after using oxygen to treat the previous CH versus 933 min if oxygen was not used. The mean frequency of CH per day was 4.1 when using oxygen, versus 2.5 without using oxygen. It is hypothesized that use of lower flow (7 L/min or less) may lead to rebound CH in susceptible patients. Cohen et al evaluated the effectiveness of using 12–15 L/min oxygen for treatment of CH.[115] While headache relief was comparable to studies using lower flows, no rebound CH were reported.

Evidence

The literature overwhelmingly shows that oxygen is an effective treatment for CH, without any documented side effects. However, in susceptible patients, rebound CH may occur following a previous oxygen treatment, but the mechanism is unclear. It has been suggested that higher oxygen flow may attenuate the rebound effect, but the evidence is mostly anecdotal. Studies are required to determine if higher oxygen flow minimizes rebound CH and to determine the appropriate flow to use.

Carbon Monoxide Poisoning

Carbon monoxide (CO) poisoning is the leading cause of poisoning death in the United States. CO poisoning is sometimes overlooked because the clinical signs and symptoms are not the same for all patients. It is well established that hemoglobin's affinity for CO is over 200 times higher than for oxygen and that blood CO levels in excess of 20% can affect the brain and heart, due to their high metabolic rate.[116] Tissue hypoxia is the hallmark of CO poisoning, so oxygen is the standard treatment, although pulse oximetry readings are unreliable due to the device being unable to distinguish between oxygen and CO bound to the hemoglobin. In the late 1800s, Haldane showed that high oxygen tension can counteract the hemoglobin to CO affinity.[117] The half-life of CO while breathing room air is approximately 5 hours. Breathing normobaric F_{IO_2} of 1.0 reduces the half-life to 1 hour, and hyperbaric oxygen therapy reduces the half-life to 20 min.[118-120]

Evidence

All CO poisoned patients should receive an F_{IO_2} of 1.0 at atmospheric pressure for at least 6 hours or longer, depending on blood CO level. If available, hyperbaric oxygen should be used for patients with severe CO poisoning (ie, CO level $> 20\%$, unconscious, those with neurologic deficit, or pregnant women with or without symptoms).[116]

Breathlessness

One of the most controversial and misunderstood uses of supplemental oxygen is for patients experiencing breathlessness. Breathlessness is a common symptom of advanced lung, cardiac, and neuromuscular disease, and the intensity increases as death approaches.[121,122] Even with increased understanding of breathlessness and the pharmacologic and non-pharmacological interventions available, it remains difficult to manage. Breathlessness makes caregivers and healthcare providers feel helpless, further complicating management. Upon conducting a survey, Abernethy and associates found that 70% of clinicians would prescribe oxygen for breathlessness despite normal oxygen saturation, and 35% would prescribe oxygen if the patient asked for it.[123] Hypoxemia does not appear to be the driving force in chronic breathlessness.

Abernethy et al conducted a double-blind RCT in 239 subjects with refractory breathlessness, and evaluated the effectiveness of administering 2 L/min oxygen, as compared to 2 L/min air.[124] The study results showed that morning breathlessness improved more in the oxygen group, but improved more in the evening with the air group. Improvement in quality of life was no different between groups, nor was there a difference in breathless-

ness over a 24 hour period. Breathlessness scores of subjects with moderate to severe breathlessness improved most, irrespective of the treatment arm. The authors concluded that the study results suggest it is the flow of gas through the nasal passages that improves the feeling of breathlessness, regardless of whether oxygen or air is used.

Johnson et al conducted a meta-analysis of the available literature focusing on oxygen to treat chronic refractory breathlessness.[125] Of the 13 studies reviewed, 2 showed a benefit when supplementing oxygen to breathless subjects. These 2 studies involved COPD patients, and the benefit of oxygen administration was small and limited to breathlessness as a result of exertional desaturation in one study. The remaining studies show no benefit of administering oxygen as opposed to air.

Evidence

Most studies show that oxygen is no better than air for chronic breathlessness in the absence of hypoxemia. There was a modest improvement in breathlessness in COPD patients with exertional desaturation in one small study. Larger, adequately powered RCTs are needed to confirm the results of the smaller studies.

What the Literature Says

Oxygen is administered for many diseases and conditions in hospitalized patients. The evidence in the literature suggests that supplemental oxygen is clearly indicated in the following instances: reversal of hypoxemia, traumatic brain injury, hemorrhagic shock, resuscitation during cardiac arrest, and CO poisoning.

Oxygen should be administered to target an S_{pO_2} of 94–98%, except with CO poisoning, due to the inaccuracy of pulse oximetry. Patients with COPD, neuromuscular disease, and obesity who are at risk for hypercapnia should have a target S_{pO_2} of 88–92%. Patients with ARDS should have a target S_{pO_2} of 88–95%, due to evidence from the ARDS Network trial. Infants should have a target S_{pO_2} of 88–94%, depending on gestational age, to prevent ROP, bronchopulmonary dysplasia, and cerebral palsy.

Summary

Oxygen is a popular drug and is often administered indiscriminately. The belief that oxygen is harmless and the attitude of "if a little is good, more is better" is common in today's healthcare environment. Severinghaus and Astrup proclaimed that "If introduced today, this gas might have difficulty getting approved by the Food and Drug Administration."[126] Priestley's words may be even truer today: "The air which nature has provided for us is as good as we deserve."[1]

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