Room Air Resuscitation and Targeted Oxygenation for Infants at Birth in the Delivery Room

Tracy Harach

ABSTRACT

The results of several clinical trials suggest that infants born depressed can be successfully resuscitated with room air. In 2010, the American Heart Association, American Academy of Pediatrics, Neonatal Resuscitation Program, and the International Liaison Committee published new guidelines to initiate the resuscitation of the term neonate with 21% oxygen. Although this recommendation cannot be extrapolated to the preterm neonate, the use of oxygen for resuscitation in this population can be used cautiously.

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When a term infant is born, rapid and complex physiological changes must occur for the infant to sustain life. Transitioning from intrauterine to extraterine life usually occurs spontaneously and does not require intervention from health care professionals. However, approximately 10% of newborns require some assistance to begin breathing at birth (International Liaison Committee on Resuscitation, 2006). The goal of resuscitation is to restore tissue oxygen delivery before irreversible damage occurs, which may lead to adverse long-term neurodevelopmental outcomes and even death. Traditionally, infants receiving resuscitation received 100% oxygen. However, in recent years, the guidelines for oxygen use during neonatal resuscitation have changed significantly based on evidence that high concentrations of oxygen immediately after birth are associated with short- and long-term harm to the organs. The organs primarily affected include the eyes, lungs, and brain. The brain may be affected so severely that the survival rate is decreased (Van Der Walt, 2006). Evidence also indicates a direct correlation between oxidative damage and a carcinogenic effect in these oxygen-exposed infants.

The new standard is to initiate the resuscitation of a term newborn with an oxygen concentration of 21%, the concentration in room air. The resuscitation of premature infants is not yet standardized, but the recommendation is to start at a low concentration of oxygen and titrate the oxygen based on the infant’s pulse oxygen saturation. The exposure to high concentrations of oxygen at birth may cause injury to tissues and organs due to resultant oxidative stress. The premature infant is extremely vulnerable to oxidative stress because the protective antioxidant defense system has not developed. Therefore, the choice of oxygen concentration for neonatal resuscitation requires an understanding of the risks and benefits of 100% oxygen and room air.

History of Oxygen

Oxygen was first identified in 1604 by the Polish alchemist and philosopher Michael Sendivogius. He warmed nitre and released the resultant gas that he named “aerial nitre.” Sendivogius (2004) described this substance as, “the elixir of life without which no mortal can live” (p. 432). This observation came approximately 170 years prior to the work of Carl Wilhelm Scheele and Joseph Priestly who were honored as the discoverers of oxygen. In 1774, Priestly heated mercuric oxide to release a gas. He demonstrated that mice lived longer in a jar of this “eminently breathable air” than those in the regular atmosphere (Van Der Walt, 2006).
The resuscitation of a term infant in the delivery room should begin with 21% oxygen.

This gas was named “oxygen” by Antoine Laurent Lavoisier in 1775, and it is now the most widely used therapeutic gas in medicine.

Oxygen, the second most common element on Earth, was quickly used in adult medicine and approximately 100 years ago was first used in newborn medicine. Today oxygen remains one of the most widely used drugs in neonatology (Saugstad, 2004). For many years, the safety of oxygen was not questioned. In 1950, as some clinicians started to question oxygen’s role in damaging the eyes of premature infants, the Apgar score was introduced. The Apgar score may have contributed to the excessive use of oxygen as clinicians were motivated to have the newborn become as pink as possible after birth. Saugstad reiterated that even as recently as a decade ago, the American Heart Association stated that brief exposure to 100% oxygen around the time of birth did not represent any risk. Although this fact was believed to be an obvious truth a decade ago, it is no longer valid. Recent research now shows that even a brief exposure to 100% oxygen immediately after birth may induce potentially long-term hazardous effects (Richmond & Goldsmith, 2006).

Fetal to Neonatal Transition

Fetal life occurs in a relatively hypoxic environment compared to extrauterine life. The placenta provides the fetus with an arterial partial pressure of oxygen (PaO₂) of approximately 25 to 30 mmHg. Fetal hemoglobin has a greater affinity for oxygen and favors placental oxygen uptake and increased oxygen saturation for a given PaO₂ (Escobar, Cernada, & Vento, 2011). At birth, with the initiation of spontaneous respirations, alveolar-capillary gas exchange begins and escalates the PaO₂ and oxygen saturation of the neonate. By one minute of age, a healthy term infant’s oxygen saturation is approximately 70%, and by 3 minutes it is approximately 80%. The PaO₂ will reach the 80 to 90 mmHg target between 5 and 10 minutes of life (Table 1). A term newborn not requiring resuscitation takes a median time of 7.9 minutes to reach oxygen saturation greater than 90% (Vento, Escobar, Cernada, Escrig, & Aguar, 2012).

This indicates that a term neonate experiencing a normal transition may not be pink until 5 to 10 minutes of life. The abrupt change in PaO₂ experienced by the newborn creates physiologic oxidative stress necessary to activate dormant trigger genes to allow successful postnatal adaptation and activation of metabolic pathways (Vento et al., 2012). However, infants that experience perinatal asphyxia after resuscitation generate a burst of reactive oxygen and nitrogen species. This process overwhelms the newborn antioxidant capacity and causes damage to cell structures, enzymes, ribonucleic acid (RNA), and deoxyribonucleic acid (DNA) (Escrig et al., 2008). When a high oxygen concentration is used during resuscitation, the oxidative stress is enhanced, which leads to increased damage of organs and an increase in mortality.

Oxidative Stress

The saying more is better does not apply to the oxygen used in neonatal resuscitation. The injury that hyperoxia can induce in the neonate can be detrimental, and to better understand this principle, it is important to understand the molecular form of oxygen. The single oxygen atom is unstable and therefore binds to a twin atom to form the molecular oxygen (O₂). This bond is quite unstable because the pair share only one pair of electrons. Two unpaired electrons remain in the outer shell and prevent it from forming new chemical bonds. Partial reduction of oxygen with just one electron at a time leads to the formation of reactive oxygen species (Vento et al., 2012). These species may include anion superoxide, hydroxyl radical, and hydrogen peroxide. Some of these chemicals are known as free radicals that increase during hyperoxia. Free radicals are highly reactive substances capable of giving rise to chain reactions (Solberg, Perrone, Saugstad, & Buonocore, 2012). Free radicals are atomic or molecular species that are able to oxidize cellular membranes, structural proteins, enzymes, and nucleic acids. Damage to DNA causes mutations

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<tr>
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Table 1: Average Oxygen Saturation for Term Infants that Require no Medical Intervention at Birth

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and cancer whereas destruction of proteins and lipids can lead to an excess of toxic by-products. Free radicals are implicated in inflammatory, toxic, and metabolic lesions; ischemia-reperfusion injury; carcinogenesis; and atherosclerosis (Van Der Walt, 2006).

Oxygen may be toxic and mutagenic with the potential to cause tissue damage through the production of reactive oxygen species. Reactive oxygen species are generated by oxygen metabolism produced in all biological systems. Reactive oxygen species, in moderate amounts, are essential for processes such as cell aerobic metabolism, biochemical processes, cellular differentiation, growth immunity, and defense against microorganisms (Solberg et al., 2012). The generation of these reactive oxygen species has the potential to cause damage if the antioxidant system is not adequately functioning. Oxidative stress, a process resulting in damage to cell structures and tissue, occurs when the reactive oxygen species exceeds the antioxidant capacity. Essentially, free radical formation production exceeds the body’s ability to neutralize them. Reactive oxygen species modulates the signal transduction pathways where excesses of these species may cause cell death by apoptotic and necrotic mechanisms. Oxidative stress is associated in several newborn diseases and may give rise to chronic lung disease, retinopathy of prematurity, and necrotizing enterocolitis. The premature infant is even more vulnerable than the term infant because the antioxidant defense system matures late in gestation (Escrig et al., 2008). Exposure to high oxygen levels, even for a brief period of time, can cause protractive oxidative stress.

Supporting Research Studies

Spector, Klebanoff, Feusner, Georgieff, and Ross (2005) indicated an association between neonatal oxygen supplementation and childhood cancer. Their work on the Collaborative Perinatal Project (CPP) included 54,795 children born between 1959 and 1966 who were followed to age 8. Trained observers were present at birth and recorded the details of each birth and resuscitation. Children received multiple exams in the first year and again at age 7. The findings of the CPP included a significantly increased rate of childhood cancer diagnosed between the first week of life and age 8 among children who received oxygen for 3 minutes or longer. A total of 51 cancers were identified and confirmed by two pediatricians. This project represents one of the first studies that linked oxygen use at birth with its potential toxic effects later in life. Saugstad (2004) concluded that the association between oxygen exposure at birth and childhood lymphatic cancer may be a result of the oxidative stress leading to DNA damage.

Vento et al. (2012) measured the resultant oxidative stress markers in moderately asphyxiated term newborns after resuscitation with either 21% oxygen (room air) or 100% oxygen. They hypothesized that using room air instead of 100% oxygen for resuscitation would reduce oxidative stress with less production of oxygen free radicals. A total of 40 newborns were enrolled and placed into two separate experimental groups. A control group of 26 nonasphyxiated newborns served as the control. The room air–resuscitated group consisted of 19 moderately asphyxiated infants, and the 100% oxygen–resuscitated group consisted of 21 moderately asphyxiated infants. The researchers determined oxidative stress by measuring the reduced to oxidized glutathione ratio, a predetermined biochemical marker of oxidative stress. They found at 28 days of life that the 100% oxygen-resuscitated group still had oxidative stress markers whereas the 21% oxygen-resuscitated group had levels similar to the control group. In addition, the room air resuscitation group had a higher 5-minute Apgar score, required less time until the first cry and less time to develop a sustained respiratory pattern than the 100% resuscitated group. Vento et al. concluded that there was no clinical advantage for using 100% oxygen.

Davis, Tan, O’Donnell, and Schulze (2004) conducted a review and meta-analysis of five trials to establish whether resuscitation with room air decreased mortality or neurological disability in newborn infants compared with 100% oxygen. The trials consisted of 1,302 newborn infants with a median gestational age of 38 weeks. Findings indicated that infants resuscitated with room air breathed earlier and had higher Apgar scores than infants resuscitated with 100% oxygen. The authors reported no significant incidence of neurological disability in the group of newborns resuscitated with 21% oxygen. Finally, the authors concluded that one death would be prevented for every 20 neonates resuscitated with room air.
rather than 100% oxygen. Davis et al. recommended that for term and near term newborns, room air should be used initially with resuscitation and oxygen only used as a backup if the initial resuscitation is unsuccessful. The researchers did not find sufficient evidence to make recommendations for the premature infant.

Saugstad, Ramji, Soll, and Vento (2008) reviewed the findings of 10 studies that reported depressed infants who were resuscitated with 21% oxygen ($n=1,082$) or 100% oxygen ($n=1,051$). The outcomes of interest included neonatal mortality and hypoxic ischemic encephalopathy. The investigators found the risk of neonatal mortality was reduced in the group resuscitated with 21% oxygen as compared to the group resuscitated with 100% oxygen. The neonatal death rate was 4.6% higher in the 100% oxygen-resuscitation group versus the room air group. Based on these findings, the researchers predicted that for every 25 newborn infants resuscitated in room air one more infant would survive. A trend toward a decrease in the risk of hypoxic ischemic encephalopathy Stage two and three was also found in the group with room air resuscitation as compared to the group with 100% resuscitation.

Escrig et al. (2008) conducted a prospective, randomized clinical trial with infants fewer than or equal to 28 weeks of gestation who required resuscitation to examine the oxygen required to achieve an oxygen saturation of 85% at 10 minutes of life. Each infant was randomly assigned to either the low-oxygen group to receive 30% fraction of inspired oxygen or to the high-oxygen group that would receive 90% fraction of inspired oxygen. Nineteen infants were initially resuscitated with 30% oxygen and 23 neonates were resuscitated with 90% oxygen. Both groups had a preductal pulse oxygen saturation continuously monitored. During resuscitation, every 60 to 90 seconds the fraction of inspired oxygen was increased by 10% incremental steps if bradycardia, a heart rate fewer than 100 beats per minute, occurred. The fraction of inspired oxygen was decreased in the same incremental fashion if the pulse oxygen saturation became greater than 85%. In both groups, to reach a stable pulse oxygen saturation of 85% at 5 to 7 minutes of age, the oxygen had been titrated to 45% oxygen.

No difference in oxygen saturation was found at 4 minutes of life between the two groups. Both groups have attained the targeted pulse oxygen saturation independent of inspired oxygen concentration. However, in the first 5 minutes of life, the premature infants resuscitated with 90% oxygen received an average of 398.4 ml/kg more oxygen than the room air–resuscitated infants. No differences in mortality rates in the early neonatal period were documented between these two groups. The investigators concluded that the resuscitation of premature infants can safely be initiated with a low fraction of inspired oxygen (Escrig et al., 2008). The oxygen percentage could then be adjusted to the infant’s need based on the pulse oxygen saturation that ultimately reduces the oxygen load to the neonate.

**Practice Guidelines**

After a decade of debate, neonatal and pediatric organizations have issued updates and statements related to the use of oxygen in neonatal resuscitation. In 2010, the American Academy of Pediatrics (AAP) and the American Heart Association (AHA) published new guidelines in the 2010 summary of changes to the Neonatal Resuscitation Program (NRP). In summary, NRP recognizes the evidence that the healthy term infant’s blood oxygen level does not reach extraterine values until approximately 10 minutes. The infant’s cyanotic appearance immediately following birth may remain for several minutes as the PaO$_2$ begins to rise. Without intervention, the PaO$_2$ should reach postransition levels by 10 minutes. For this reason, color as an indicator of oxygenation has been removed from the NRP guidelines (NRP, 2010).

Optimal management of oxygen delivery is critical because hypoxia and hyperoxia can result in injury to multiple vital organs (NRP, 2010). The NRP guidelines indicate the meta-analyses of trials that concluded that resuscitation of term infants initiated with room air versus 100% oxygen showed an increased survival in the room air cohort. Therefore, the guidelines recommend beginning resuscitation of the term neonate at 21% oxygen and to increase the oxygen concentration based on the targeted preductal oxygen saturation levels at designated times following birth (Table 1) (NRP, p. 307). These levels can be achieved with the use of blended oxygen and a pulse-oximeter placed on the right hand or wrist. If blended air is unavailable, resuscitation should be initiated with room air (Solberg et al., 2012). The AAP also recommended that if the neonate is bradycardic after 90 seconds of resuscitation with the use of a lower oxygen concentration, the oxygen should be escalated to 100% until the recovery of a normal heart rate (NRP, p. 310). Oxygen blenders...
and pulse oxygen saturation monitors need to be present at every birth to achieve the delicate balance of administering the appropriate oxygen concentration based on the infant's needs.

Studies surrounding the term infant and use of room air oxygen in the delivery room have not been extrapolated to the preterm infant, who must be approached differently. The preterm neonate born at fewer than 34 weeks gestation is at higher risk of other factors, such as extended pulmonary vaso-constriction after birth that may require a higher than 21% oxygen concentration for resuscitation. Escrig et al. (2008) recommended initiating the resuscitation of a premature infant with 30% oxygen and titrating based on the infant's needs with the pulse oxygen saturation.

The preterm infant is also at a high risk for hypoxic reperfusion injury due to the intrauterine hypoxic environment and lack of antioxidant production. Therefore, NRP guidelines for the preterm infant are similar to the term infant and include placing a preductal pulse-oximeter at birth and providing the amount of oxygen necessary to maintain saturations in the interquartile range provided by NRP (Table 2). However, to achieve these parameters, NRP (2010) indicated that, “preterm newborns may achieve normal oxygen saturations more quickly if you start with a somewhat higher oxygen concentration” (p. 309).

Table 2: Neonatal Resuscitation Program Guidelines

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<thead>
<tr>
<th>Targeted Pre-ductal SpO₂ After Birth</th>
<th>1 minute</th>
<th>60%–65%</th>
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<tbody>
<tr>
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<td>2 minutes</td>
<td>65%–70%</td>
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Oxidative stress is enhanced in the preterm infant due to the lack of maturation of the defensive antioxidant system.

REFERENCE


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