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A Review of Oxygen Physiology and Appropriate Management of Oxygen Levels in Premature Neonates

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ABSTRACT

Background: Although oxygen is the most widely used therapeutic agent in neonatal care, optimal oxygen management remains uncertain.

Purpose: We reviewed oxygen physiology and balance, key studies evaluating oxygen saturation targets, and strategies for oxygen use in the neonatal intensive care unit.

Results: Oxygen is a potent vasodilator involved in the transition at birth to breathing. Supplemental oxygen is administered to reverse/prevent hypoxia; however, excessive oxygen can be toxic owing to the formation of reactive oxygen species. Current neonatal resuscitation guidelines recommend using room air for term infants in need of support, with titration to achieve oxygen saturation levels similar to uncompromised term infants. In premature infants, targeting a higher oxygen saturation range (eg, 91%-95%) may be safer than targeting a lower range (eg, 85%-89%), but more evidence is needed. In combined analyses, lower oxygen saturation levels increased mortality, suggesting that the higher target may be safer, but higher targets are associated with an increased risk of developing disorders of oxidative stress.

Implications for Practice: Need for supplemental oxygen should be assessed according to the American Heart Association guidelines. If appropriate, oxygen should be administered using room air, with the goal of preventing hypoxia and avoiding hyperoxia. Use of oximeter alarms may help achieve this goal. Pulmonary vasodilators may improve oxygenation and reduce supplemental oxygen requirements.

Implications for Research: Implementation of wider target ranges for oxygen saturation may be more practical and lead to improved outcomes; however, controlled trials are necessary to determine the impact on mortality and disability.

Key Words: hyperoxia, hypoxia, neonatal resuscitation, neonate, oxygen, oxygen saturation, retinopathy of prematurity

Approximately 1 in 10 newborns requires assistance to begin breathing in an extrauterine environment at birth.[1] Thus, it is not surprising that supplemental oxygen is the most common therapeutic agent used in neonatal care worldwide.[2,3] Despite its common usage, insufficient knowledge of neonatal oxygenation[4] and uncertainty about optimal oxygen saturation[4,5] have been reported among neonatal healthcare practitioners. Balancing the oxygen needs of neonates is crucial to avoiding harm from too much or too little oxygen.[6] Along with neonatologists, neonatal nurses, nurse practitioners, and respiratory therapists are responsible for the management of oxygen supplementation and should fully understand how to promote optimal outcomes associated with neonatal oxygen use. The goals of this report are to provide an overview of oxygen physiology, highlight the importance of maintaining appropriate oxygen balance in neonates, and examine strategies for appropriate oxygen use in the neonatal intensive care unit setting.

PHYSIOLOGY OF TRANSITION OF PULMONARY CIRCULATION AT BIRTH AND PATHOPHYSIOLOGY OF NEONATAL HYPOXIA

In utero, the fetus receives oxygen through gas exchange occurring in the placenta.[7,8] Vascular resistance within the placenta is low during this period, whereas pulmonary vascular resistance is high and

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thus shunts blood flow toward the placenta. The fetal lungs and pulmonary vasculature grow and mature in this hypoxic environment in preparation for taking over gas exchange via the lungs at birth.[7,8] As air enters the lungs at birth, the normal transition to pulmonary gas exchange is facilitated by a decrease in pulmonary vasculature resistance and an increase in blood flow to the lungs in response to the vasodilatory effects of oxygen.[7-9] Left atrial pressure increases more than right atrial pressure, resulting in closure of the foramen ovale. As the low-resistance placental circulation is removed, systemic vascular resistance increases whereas pulmonary vascular resistance continues to decrease and blood flow is reversed.[7,8] The final step in establishing normal postnatal circulation is the closing of the ductus arteriosus, which typically occurs over the first few hours and days after birth. Endogenous nitric oxide (NO) assists in the pulmonary vascular transition at birth by relaxing vascular smooth muscle.[7,10,11]

Neonatal hypoxic respiratory failure affects the normal transition of the pulmonary circulation due to vasoconstriction that prevents pulmonary vascular resistance from decreasing.[7] A sustained increase in pulmonary vascular resistance can lead to persistent pulmonary hypertension of the newborn (PPHN), which is of particular concern in preterm infants.[7] Preterm delivery exposes neonates to oxygen before the pulmonary circulation has matured enough to effectively manage oxygen exposure.[11,12]

CRITICAL BALANCE BETWEEN AVOIDING HYPOXIA AND HYPEROXIA

Oxygen and the Oxygen Delivery System

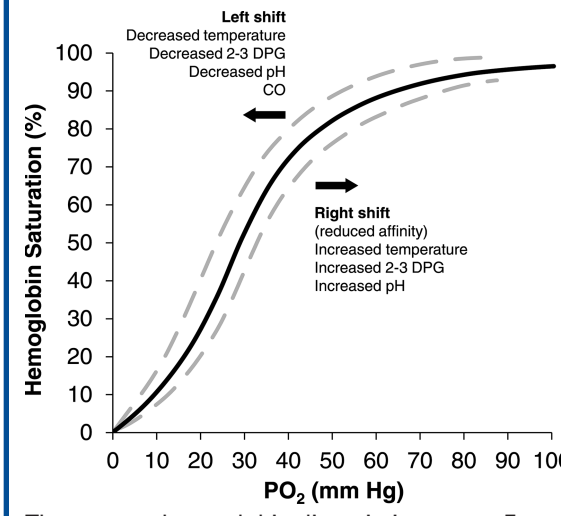
Hemoglobin is traditionally considered the oxygen carrier within the body[13]; however, it plays a more sophisticated role as an oxygen regulator.[14] The affinity of hemoglobin for oxygen varies according to the level of partial pressure of oxygen (Po2) in the blood and the level of hemoglobin saturation (Figure 1).[3,13,15] At low Po2, the affinity of hemoglobin for oxygen is low; hemoglobin releases oxygen into the tissues, and hemoglobin saturation remains low. As Po2 rises, the affinity of hemoglobin for oxygen increases, allowing more oxygen molecules to bind to hemoglobin until it is completely saturated with oxygen.[3] As shown in Figure 1, the dissociation of oxygen from hemoglobin is influenced by temperature, pH, and 2,3-diphosphoglycerate and carbon monoxide levels.[3,15]

Oxygen transport systems, including cardiac output and cellular respiration that fuels biologic processes, function to ensure appropriate oxygen balance in body tissue.[13,14] Maintenance of oxygen homeostasis is critical for preserving life, and any imbalance disrupts normal physiologic function.[13] Hypoxia, or oxygen deficiency, occurs when oxygen supply fails to meet oxygen consumption.[13] Hyperoxia is a condition of elevated oxygen levels that results in the generation of toxic reactive oxygen species (ROS).[2] Importantly, the changes in cellular metabolism associated with hypoxia can lead to accumulation of hypoxanthine, which also can generate toxic ROS, particularly during resuscitation of neonates.[2] Hypoxia or hyperoxia cannot be defined by a specific oxygen level (or Po2) because oxygen requirements vary by organ, tissue, and cellular physiology and function.[2,13]

Use of supplemental oxygen to reverse hypoxia in the neonate is intended to avoid death and serious disorders, such as stroke, myocardial infarction, or permanent brain damage, due to a lack of oxygen to the tissues.[13,16] However, administration of oxygen can be toxic; hyperoxia can cause oxygen toxicity, which is caused by the formation of ROS during reperfusion of hypoxic tissues, as well as during infection and inflammation.[16,17] Premature neonates are especially susceptible because they have limited antioxidant defense systems.[12,18] Oxidative stress occurs when ROS exceed the capacity of antioxidant mechanisms.[19]

Diseases commonly associated with oxygen supplementation and oxidative stress are outlined in Table 1[16,17,20-28] and summarized later. The development of retinopathy of prematurity (ROP) is stimulated by the relative hyperoxia associated with birth and use of supplemental oxygen.[16,20,29,30] However, data have also shown that as the metabolic demands of the developing eye increase, hypoxia occurs and stimulates production of vascular endothelial growth factor. High levels of vascular endothelial growth factor stimulate neovascularization of the retina, which can lead to retinal fibrosis and detachment.[16,30] Taken

FIGURE 1



The oxygen–hemoglobin dissociation curve. From AnaesthesiaUK.[15] 2,3 DPG indicates 2,3-diphosphoglycerate; CO, carbon monoxide.

TABLE 1. Neonatal Diseases Related to Oxygen Supplementation and Oxidative Stress

Condition	Characteristics
Retinopathy of prematurity[16,20]	Primarily occurs in premature infants Abnormal vascularization of the retina Range of vision impairment, including blindness Goal of oxygen therapy: avoid high oxygen saturation levels and alternating hypoxia/hyperoxia
Chronic lung disease or bronchopulmonary dysplasia[16,17,21-23]	Involves all tissues of the developing lung Develops in stages Associated with prolonged use of supplemental oxygen at high concentrations (80%-100%), suggesting a pathogenic role for ROS Other factors also may be involved in pathogenesis
Intraventricular hemorrhage[24]	Serious and complex neurologic disorder High mortality and morbidity with cognitive disability and cerebral palsy Enhanced oxidative stress Gene studies implicate inflammatory, coagulation, and vascular pathways; also environment
Periventricular leukomalacia[17,25]	Associated with sustained hyperoxia and formation of ROS Major precursor for adverse neurologic outcomes
Cancer[26-28]	Increased incidence among neonates resuscitated with oxygen for ≥3 min Lymphatic leukemia is the most common cancer type (consistent with age group)

Abbreviation: ROS, reactive oxygen species.

together, these findings show that fluctuating levels of oxygen (ie, both hypoxia and hyperoxia) can lead to severe retinopathy.

Oxygen exposure inhibits lung growth and is an important factor in the pathogenesis of bronchopulmonary dysplasia in premature infants.[16,21-23] Other factors that contribute to bronchopulmonary dysplasia are gestational age, growth restriction, and mechanical ventilation.[31] The initial stages of lung injury are likely related to the formation of ROS in response to high oxygen levels in the underdeveloped lungs of premature neonates.[17]

Oxidative stress may also be responsible, at least in part, for 2 neurologic disorders of prematurity: intraventricular hemorrhage[24,32] and periventricular leukomalacia.[17,25] Although cerebral blood flow changes and gene–environment interactions may play a role in the etiology of intraventricular hemorrhage, the critical period of development is in the first 4 to 5 days of life, regardless of gestational age, which points to the transition to extrauterine life and the hypoxia associated with it.[17,32] With periventricular leukomalacia, exposure to sustained hyperoxia creates ROS that cause oxidative damage to oligodendrocytes in the white matter.[17,33]

Finally, an increased incidence of cancer, particularly lymphatic leukemia, has been reported in neonates with postpartum asphyxia and use of supplementary oxygen.[26-28] Two of these studies found that oxygen had to be received for 3 minutes or longer to affect the rate of cancer.[26,27]

GUIDELINES FOR OXYGEN USE IN THE DELIVERY ROOM

To reduce the potential risks of hypoxia or hyperoxia and associated oxidative stress on neonates at the time of birth, the American Heart Association developed, and recently updated, guidelines for optimal management of oxygen.[1,6,34] These guidelines for neonatal resuscitation are also applicable to neonates who have completed newborn transition but continue to require supplemental oxygen during the first weeks after birth.

For neonates requiring resuscitation, the first step is to clear the airway,[1,6] after which an assessment of oxygen need should be made.[6] Importantly, uncompromised neonates do not achieve extrauterine oxygen saturation values for approximately 10 minutes after birth and skin color may suggest cyanosis.[6] Pulse oximeters are recommended when resuscitation may be required, administration of positive pressure ventilation lasts for more than a few breaths, cyanosis persists, or administration of supplementary oxygen is needed.[1,6]

Use of 100% oxygen was previously recommended for resuscitation because of the known detrimental effects of hypoxia[35] and the positive effects of oxygen in promoting pulmonary vascularization.[7] However, over the past 20 to 30 years, research has determined that overexposure to oxygen immediately following hypoxia can lead to accumulation of oxygen free radicals and ischemia–reperfusion

injury.[35] In preclinical studies, toxicity associated with 100% oxygen resuscitation included increased pulmonary artery contractility and accumulation of ROS.[36-38] Given these findings, preclinical and clinical studies evaluated the efficacy and safety of room air (21% oxygen) for neonatal resuscitation.[39] Use of room air over higher fractions of inhaled oxygen has been shown to be safe and effective for neonatal resuscitation.[40,41] A meta-analysis of 10 studies identified a decreased risk of neonatal mortality with 21% oxygen compared with 100% oxygen (relative risk, 0.69; 95% confidence interval, 0.54-0.88).[39]

Randomized studies comparing high oxygen (≥65%) with low oxygen levels (21%-30%) for initiating neonatal resuscitation found no benefits associated with high oxygen level exposure.[1] In fact, the studies determined that neonates had 30% oxygen at the time of stabilization, regardless of whether they received high or low oxygen levels to initiate resuscitation. Thus, the current American Heart Association guidelines recommend the use of 21% oxygen for the initial resuscitation of infants 35 weeks' gestation or older and that resuscitation be initiated with room air (21%-30% oxygen at sea level) for infants born younger than 35 weeks' gestation.[1] These oxygen levels should then be titrated on the basis of preductal pulse oximetry to achieve oxygen saturation levels similar to uncompromised term infants.[1,6,34]

TARGET OXYGEN SATURATION RANGES

Normal oxygen saturation in healthy newborns is 93% or greater,[4] with a gradual increase to this level over the first 10 minutes after birth (Table 2).[1,6,34] However, optimal saturation levels for newborns on oxygen therapy are unclear.[4] Several large, key prospective studies have assessed different target oxygenation saturation levels and shown either no difference or mixed results in clinical outcomes,[42-45] whereas other studies have shown higher mortality in infants who were treated with lower target oxygen saturation levels than those treated with higher target levels (Table 3).[46,47]

TABLE 2. Targeted Preductal Oxygen Saturation After Birth[a]

Time After Birth	Target Oxygen Saturation
1 min	60%-65%
2 min	65%-70%
3 min	70%-75%
4 min	75%-80%
5 min	80%-85%
10 min	85%-95%

[a]Reproduced with permission from Pediatrics, vol. 126, pages e1400-e1413, Copyright © 2010 by the AAP.[6] Also from Wyckoff et al[1] and American Academy of Pediatrics.[34]

Results from published systematic reviews and meta-analyses also have been equivocal, with statistically mixed results of various outcome measures. In a 2009 Cochrane systematic review of 5 studies published before 2005, Askie et al[48] concluded that a policy of unrestricted or unmonitored oxygen therapy has potential harms, particularly ROP, without clear benefits compared with a restricted oxygen use protocol. In a 2014 meta-analysis of the Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT), 3 Benefits of Oxygen Saturation Targeting (BOOST) studies, and Canadian Oxygen Trial (COT), Saugstad and Aune[49] found that lower oxygen saturation target levels were associated with more deaths and more incidences of necrotizing enterocolitis, but less ROP, than higher target levels. Manja et al[50] also reviewed these 5 studies and found that the lower oxygen saturation target group had higher mortality before hospital discharge and a higher incidence of necrotizing enterocolitis than the higher oxygen saturation group, but no difference was observed for neurodevelopmental outcomes, ROP, or hearing loss. However, significant outcomes were associated with a low level of confidence; thus, the investigators concluded that the optimal target oxygen saturation in extremely preterm infants remains uncertain.[50]

The most recent pooled analysis included data from 2 BOOST II studies (correcting an oximeter calibration–algorithm artifact); investigators found that an oxygen saturation target range of 85% to 89% was associated with a significant increase in risk of the combined outcome of death or disability and the outcome of death alone compared with a higher target range of 91% to 95%.[51] Variations in study populations across the 5 major studies of the Neonatal Oxygen Prospective Meta-analysis Collaboration, of which the BOOST II studies were a part, may account for differences in mortality rates[51] and therefore limit the ability to determine statistical significance consistently for these differences. Moreover, achieved versus intended oxygen saturation was highly variable in these studies and may have influenced results.[52] However, taken together, these 5 studies suggest that lower oxygen saturation levels may increase the risk of death; thus, targeting oxygen saturation at 91% to 95% may be safer.[51,52] These higher target ranges must be monitored closely and should not exceed 95% at the risk of developing disorders associated with oxidative stress.[3,52] Importantly, the oxygen saturation target range may vary with advancing gestational age and postnatal age.[46]

STRATEGIES FOR ACHIEVING APPROPRIATE OXYGEN LEVELS

Despite uncertainty regarding oxygen saturation target ranges, studies have provided important

TABLE 3. Clinical Outcomes Associated With Target Oxygen Saturation in Preterm Infants

Study Population	Target Oxygen Saturation Levels Tested	Outcomes
BOOST[42] 358 neonates born <30 wk' GA requiring oxygen at 32 wk	Standard: 91%-94% High: 95%-98%	Growth and development at 12 mo: not significantly different between oxygen saturation groups
SUPPORT[43] 1316 neonates 24 to <28 wk' GA	Lower: 85%-89% Higher: 91%-95%	Composite endpoint of ROP and/or death: 28.3% in lower vs 32.1% in higher (RR = 0.90; 95% CI, 0.76-1.06; $P = .21$) Death before discharge: 19.9% for lower vs 16.2% for higher (RR = 1.27; 95% CI, 1.01-1.60; $P = .04$)
BOOST—New Zealand[44] 340 neonates <28 wk' GA	Lower: 85%-89% Higher: 91%-95%	Composite endpoint of death or major disability at 2 y: 38.9% for lower vs 45.2% for higher (RR = 1.15; 95% CI, 0.90-1.47; $P = .26$)
COT[45] 1147 neonates 23 to <28 wk' GA	Lower: 85%-89% Higher: 91%-95%	Composite endpoint of death or disability at 18 mo: 51.6% for lower vs 49.7% for higher (OR = 1.08; 95% CI, 0.85-1.37; $P = .52$)
BOOST II—UK, Australia, New Zealand (pooled data)[46] 1187 neonates <28 wk' GA	Lower: 85%-89% Higher: 91%-95%	Death: 23.1% in lower vs 15.9% in higher (RR = 1.45; 95% CI, 1.15-1.84; $P = .002$)
SUPPORT long-term follow-up[47] 1234 neonates 24 to <28 wk' GA	Lower: 85%-89% Higher: 91%-95%	Composite endpoint of death before assessment at 18-22 mo or neurodevelopmental impairment at 18-22 mo: 30.2% in lower vs 27.5% in higher (RR = 1.12; 95% CI, 0.94-1.32; $P = .21$) Death: 22.1% in lower vs 18.2% in higher (RR = 1.25; 95% CI, 1.00-1.55; $P = .046$)

Abbreviations: BOOST, Benefits of Oxygen Saturation Targeting; CI, confidence interval; COT, Canadian Oxygen Trial; GA, gestational age; OR, odds ratio; ROP, retinopathy of prematurity; RR, relative risk; SUPPORT, Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial.

strategies for administering supplemental oxygen in neonates. Room air (21% oxygen) should be used to initiate resuscitation in term and preterm neonates rather than 100% oxygen.[1] The target oxygen saturation level should be individualized for each patient, with the goal of preventing hypoxia and avoiding hyperoxia as much as possible.[52] Oximeter readings should be maintained at no higher than 94% to 95%.[3] Alarm limits are an important consideration to achieve these goals; the lower alarm should always be 85% or greater, and the high alarm should be set at 95%.[3,52] If oxygen saturation exceeds 95%, the fraction of inhaled oxygen should be reduced.[3] Maintaining a narrow oxygen saturation target is challenging and can lead to increased tolerance of oxygen saturation greater than 95%.[52]

In 2003, the Cedars-Sinai Medical Center and UCLA School of Medicine published a protocol for the management of supplemental oxygen use with oxygen saturation target levels of 85% to 93% and setting low and high alarms, respectively.[30] Implementation of this protocol has been associated with a significantly shorter length of hospital stay, decreased need for supplemental oxygen and steroids for chronic lung disease, and a lower rate of ROP in very low birth-weight infants.[30,53,54] In another study targeting oxygen saturation between 88% and 92% with alarm limits of 85% and 95%, respectively, the incidence of chronic lung disease was significantly reduced ($P = .001$) and fewer infants were discharged from the hospital with oxygen therapy than those with less restrictive oxygen protocols that were previously used.[55]

In neonates with PPHN, acute respiratory failure is characterized by systemic hypoxia, and standard therapy includes mechanical ventilation with oxygen.[11] To reduce supplemental oxygen needs and avoid hyperoxia, pulmonary vasodilators have been studied. Treatment with inhaled NO (iNO) has been shown to improve oxygenation in neonates with PPHN.[56-58] Moreover, iNO reduces the need for extracorporeal membrane oxygenation, a labor-intensive and costly procedure.[57,58] Other vasodilators, such as sildenafil,

Summary of Recommendations for Practice and Research	
What we know:	• Use of room air (21% oxygen) is effective and safe for neonatal resuscitation. • Use of 100% oxygen leads to accumulation of ROS. • ROS are, in part, associated with neonatal disorders, including ROP, chronic lung disease, and necrotizing enterocolitis. • Lower oxygen saturation target ranges (85%-89%) increase mortality. • Higher oxygen saturation target ranges increase ROP.
What needs to be studied:	• Effect of wider oxygen saturation target ranges (eg, 87%-94% or 85%-93%) on death and disability. • Ability to adhere to oxygen saturation target ranges.
What we can do today:	• Follow recent American Heart Association guidelines regarding need for supplemental oxygen. • Use alarm settings on oximeters to prevent hypoxia (<85%) and avoid hyperoxia (>95%). • Offer pulmonary vasodilators, such as iNO, as a strategy to reduce oxygen needs in neonates with pulmonary hypertension and hypoxia.

prostacyclin, bosentan, and milrinone, have been evaluated in neonates who do not respond adequately to iNO or where iNO and extracorporeal membrane oxygenation may not be available. However, none of these agents are approved for use in neonates with PPHN, and the efficacy and safety profiles of these agents have not been established in this setting. Data from a few small exploratory studies of sildenafil, a type 5 phosphodiesterase inhibitor, suggest that sildenafil treatment results in pulmonary vasodilation and may improve oxygenation in term and near-term infants with PPHN or hypoxemic respiratory failure.[59,60] However, treatment-related adverse events, such as hypotension and total anomalous pulmonary venous return, have been reported in some of the neonates who received sildenafil in these exploratory studies.[59,60] Several case studies and small case series have reported improved oxygenation with the administration of inhaled prostacyclin in neonates with PPHN who did not receive or respond to iNO.[61-64] Bosentan is an oral dual endothelin receptor antagonist that reduces pulmonary vascular resistance and pulmonary arterial pressure to reverse pulmonary hypertension.[65,66] In a prospective, randomized, double-blind, placebo-controlled study, the effect of bosentan was evaluated in neonates of 34 weeks' gestational age or older who were receiving mechanical ventilation and had pulmonary hypertension.[67] In this study, bosentan significantly improved oxygenation ($P < .05$), decreased the duration of mechanical ventilation compared with placebo ($P < .001$), and was well tolerated.[67] Results from an initial study of milrinone, a phosphodiesterase 3 inhibitor, suggest that it has activity in neonates with PPHN and was well tolerated in the 11 infants who were studied[68]; further study is warranted.

CONCLUSION

Therapeutic oxygen is an important treatment option for hypoxic respiratory failure in premature infants; however, excessive exposure to oxygen can lead to oxidative stress, which has the potential to damage multiple organ systems in the neonate, including the eyes, lungs, and intestines. Large, prospective clinical studies have failed to provide a conclusive recommendation for oxygen saturation target ranges, but targeting oxygen saturation in the range of 91% to 95% may be safer than targeting lower ranges (eg, 85%-89%). Use of wider target ranges (85%-93%) by several institutions has improved outcomes in very low birth-weight infants, but these ranges have not been rigorously evaluated in large clinical studies; more evidence is needed. Early intervention with a pulmonary vasodilator may help avoid exposure to high oxygen levels.

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