Initiatives in Safe Patient Care

Enhancing patient safety through improved surveillance

Monitoring Oxygen Toxicity in the Preterm Infant: *Mechanisms, Critical Questions and Clinical Challenges*

CONTINUING EDUCATION FOR PHYSICIANS (CME) NURSES (CE)

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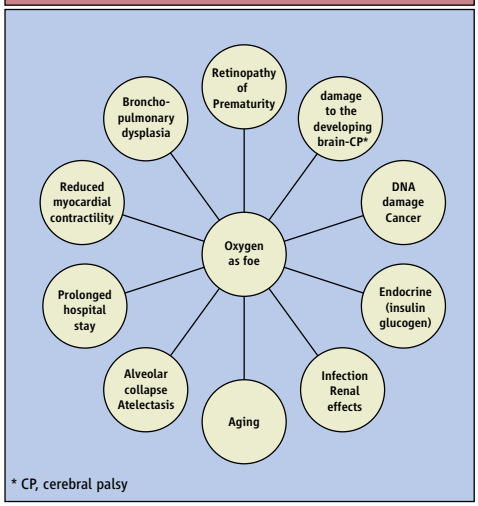
Throughout human evolution, physiologic gases vital for survival (oxygen, nitric oxide, carbon dioxide, and hydrogen sulfide) have been our allies, yet also our enemy when given or produced in excess because of their multiple toxic effects, especially in neonates with limited antioxidant defenses. Oxygen was discovered by the Polish alchemist, Michael Sedziwej as a "spiritus" emitted by the heating of "salpetre." The discovery was later reported by Scheele in 1773 but credited to Priestley in 1774 (as "dephlogistated air") and named "oxygen" by Lavoisier in 1777. Supplemental oxygen was administered to humans by Chaussier using a bellows ventilator in 1777, and remains the most commonly used drug in neonatal medicine.[1] Since the 1930s oxygen therapy has been a mainstay of neonatal care,[2] yet as commented by Tin in 2002, "Oxygen must have been given to more infants than any other medicinal product… despite that, we still know very little about how much infants actually need, or how much it is wise to give. Given that we have also known for nearly 50 years that it is easy to damage the eyes of preterm infants by giving too much oxygen, especially in the first weeks of life, the depth of our ignorance is really quite embarrassing."[3] Silverman further commented that oxygen therapy for neonatologists has been an "albatross."[4]

Although tissue hypoxia should be avoided, excessive oxygen administered to preterm infants, even for a short time provides limited benefit, and possibly great harm to the developing human. In this article, we review some of the existing controversies regarding the use and monitoring of both supplemental oxygen. As well, we review evidence suggesting how neonatal health care providers might more prudently use oxygen as a drug beyond the period of neonatal resuscitation. The contributors recognize that current foundations and recommendations regarding oxygen use during neonatal resuscitation and later during acute and convalescent care are undergoing disruptive innovation,

Figure 1. Conditions Associated with Unneccessary Use of Oxygen



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Oxygen Toxicity in the Preterm Infant

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Target Audience
This activity has been designed to meet the educational needs of health professionals involved in the care of preterm infants.

Statement of Need/Program Overview
This program will address optimal strategies to monitor oxygen delivery to specific tissues and the emerging strategies to monitor the generation of reactive oxygen species at the tissue level.

Educational Objectives
After completing this activity, the participant should be better able to:

1. Discuss appropriate strategies to minimize oxygen free radical injury to the developing eyes, brain, lung, and gastrointestinal tract.
2. Describe the effects of oxygen toxicity on the developing nervous system
3. Identify the ideal limits for establishing SpO_2 at specific gestational ages and postnatal ages
4. Describe the best initiatives to improve staff compliance to prescribed SpO_2 limits

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nonetheless, we have been given an opportunity to present a multidisciplinary perspective on how neonatologists, NICU nurses, and others a perspective oxygen at a "foe" in our care of preterm infants. (Figure 1).

Problems of Oxygen Monitoring in the NICU

Use of supplemental oxygen during infant resuscitation, oxygen administration and monitoring in the NICU and the precision and accuracy of oxygen saturation monitoring during neonatal intensive care (and its documentation) as well as shorter durations of exposure prescribed by pediatric anesthesiologists for surgery, continue to raise concerns about the cumulative "toxic" effects associated with oxygen therapy. Furthermore, technologies have evolved to enable closed-loop oxygen controllers synchronized with oxygen saturation monitoring devices, yet these are not being used except in experimental protocols, although this technology has been available for years. Newer technologies designed to measure tissue oxygen saturation using near infrared spectroscopy have been introduced at many centers; however, the interpretation of specific tissue/organ oxygenation continues remains controversial such that routine use in the NICU is rare.

Increased inspired oxygen has been evaluated as a treatment for retinopathy of prematurity, while other neonates with right-to-left intra-cardiac shunting at the level of the ductus arteriosus tolerate levels of SpO_2 substantially lower than those frequently prescribed by neonatologists. Currently, there is controversy regarding the optimal oxygen saturation targets for infants of varying gestational and postnatal ages, and how medical, nursing and respiratory therapy staffing patterns influence their ability as caregivers to maintain infants within prescribed oxygen saturation limits. Acknowledging these enormous gaps in our knowledge is important, yet care of nearly a half million preterm infants born annually in the U.S. must continue based on the best evidence available at this time. Hopefully, the insights provided by our panelists will serve to highlight critical questions facing neonatologists, NICU nurses, and respiratory therapists who strive daily to offer the best care possible.

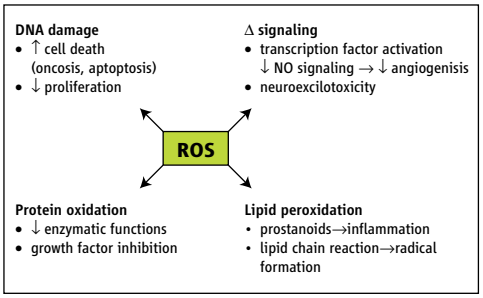
Physiology of Oxygen Transport and Transfer

Any discussion of oxygen toxicity at the tissue level requires a discussion of the role of red blood cells (RBC) and trans-mural oxygen gradients in microcirculation. RBCs enable the adequate transport of O_2 between lung capillaries and metabolizing tissues via intracellular hemoglobin (Hb). Appropriate allosteric interactions between Hb ligand-binding sites and an adjustable intracellular chemical environment favors the binding of O_2 to Hb in the lungs and release of O_2 in the tissues.[5] However, RBCs can also sense tissue requirements as they move through the microcirculation according to the degree of local tissue deoxygenation. When the tissues are hypoxic, the RBCs release vasodilatory compounds that enhance blood flow. O_2 delivery is matched to local O_2 demand via deoxygenation-dependent release of ATP from RBCs, which stimulates either the production of nitric oxide (NO) and other vasodilators in the endothelium or the release of vasoactive NO from S-nitroso-Hb upon deoxygenation.[6] In the final step, naturally occurring nitrite is reduced to vasoactive NO by deoxygenated Hb.[5,7]

Organs with high metabolic rate as well as high rates of blood flow in the neonatal period are the lungs and brain, which potentially lack protective mechanisms at the site of microvascular oxygen release.

It has been shown that in some tissues the oxygen supplied by capillaries is secondary to that provided by the arterioles. Tissues with high metabolic activity and corresponding higher rates of blood flow exhibit relatively shallow oxygen gradients in the arteriolar network, suggesting that the major oxygen exchange site is located in the capillaries.[8] The location of oxygen release may be an important factor in tissue toxicity generation. It has been suggested that the high metabolic rate of the arteriolar vessel wall may serve as a metabolic barrier to protect the parenchymal tissue from the high oxygen level of arteriolar blood and thus reduce the formation of oxygen free radicals in the perivascular tissue.[9,10] Organs with high metabolic rate as well as high rates of blood flow in the neonatal period are the lungs and brain, which potentially lack protective mechanisms at the site of microvascular oxygen release.

Figure 2.



Auten, RR, Davis, JM. Pediatr. Res. 2009;66(2):123 (With permission International Pediatric Res. Foundation)

Reactive Oxygen Species (ROS), macromolecular damage, altered signaling, ROS damage DNA strand breaks and base oxidation that, if unrepaired, induces apotosis or oncosis. Protein oxidation and nitration damages antioxidant enzymes, surfactant proteins, and anti-inflammatory pathways that can further propagate maladaptive inflammation. Lipid peroxidation products generate pro-inflammatory prostanoids, and can generate further radical formation through lipid chain reactions, possibly releasing damaging enzymes packaged in cellular organelles. Direct effects of ROS on signaling pathways include redox-sensitive transcription factors — e.g., HIF, NrF-2, and NK-kB, as well as indirect effects through inactivation of NO-based signaling.

Mechanisms of Oxygen Toxicity and Tissue Injury

Excessive oxygenation of tissues causes the formation of reactive oxygen species (ROS), a collective term that broadly describes O_2-derived free radicals such as superoxide anion (superoxide [$O_2\cdot$] or oxygen-containing radicals such as hydroxyl (HO·), peroxyl ($RO_2\cdot$) and alkoxyl (RO·) as well as O_2-derived non-radical species such as hydrogen peroxide (H_2O_2) which results in lipid peroxidation, DNA base modification and strand scission, and acceleration protein sulfhydryl or carbonyl oxidation.[11,12] The mitochondrion is a major intracellular source of ROS. Of mitochondrial O_2 consumed, 1%-2% is diverted to the formation of ROS, mainly at the level of complex I and complex III of the respiratory chain, and this diversion is believed to be tissue dependent. Mitochondria-derived O_2- is dismutated to H_2O_2 by manganese superoxide dismutase, and in the presence of metal ions, highly reactive HO· is generated via Fenton and/or Haber-Weiss reactions, inflicting significant damage to cellular proteins, lipid, and DNA. Krebs cycle α-ketoglutarate dehydrogenase and pyruvate dehydrogenase have been implicated as significant mitochondrial $O_2\cdot$- and H_2O_2 sources. This elevated oxidant burden elicits further ROS production from mitochondria complexes and causes apoptosis. As major ROS generators mitochondria are often targets of high ROS exposure with adverse consequences including oxidative damage to mitochrondrial DNA and cell apoptosis and mtDNA damage. The precise mechanisms by which mtDNA damage causes apoptotic signaling is not completely understood. In the lung, superoxides can react with nitric oxide to form peroxynitrite (ONOO-) that disrupts lipids in surfactant and interferes with its biophysical function.[13] (Figure 2)

Droge proposed three different perspectives for looking at reactive oxygen species role in tissue damage.[11] The first perspective is the traditional understanding of oxidant stress as a precursor to tissue injury, which involves the complex interaction of free radical production, detoxification, and repair of radical damage. The second perspective is the view of ROS as critical messengers of signal transduction, which play an essential role in tumor cell proliferation or genomic instability that facilitates cell growth.[14,15] The third evolving perspective is the view of ROS as secondary "death markers" for cells that are switching to apoptotic or necrotic pathways following a toxic insult.[16] During tissue hypoxia, anaerobic metabolites such as lactate, hypoxanthine, xanthine, uric acid, malondialdehyde, and nitrotyrosine accumulate in tissues and can be reflected in plasma samples.[17]

After 3 days of oxygen exposure, increases in matrix metalloproteinases (MMPs) and monocyte chemoattractant protein-1(MCP-1) and decreases of T-cell cytokines (RANTES) have been observed, suggesting that these may used as markers of oxidative injury in preterm infants.[18] The immature lung exposed to hyperoxia leads to increased collagen deposition, endothelial cell damage, and apoptosis of type I and II alveolar cells.[19] Elevations of growth factors, such as transforming growth factor-beta (TGF-β), fibroblast growth factor (FBF), vascular endothelial growth factor (VEGF), and insulin-like growth factor (IGF), as well as MMPs have all been observed in the presence of ROS. Elevations of TGF-β have been related to the development of bronchopulmonary dysplasia (BPD) in animal models and in human infants, although the data is limited in the latter case. Microvascular proliferation and alveolar secondary crest formation is also blunted in the presence of reactive oxidant species.[20] In the developing lung, hyperoxia results in epithelial and endothelial cell loss as well as disordered proliferation and other changes that impede alveolar and microvascular development.[21,22] Severe hyperoxia decreases lung VEGF expression which may also disrupt microvascular development. VEGF may also be required for lung epithelial differentiation, however the mechanism by which VEGF is suppressed by hyperoxia remains an enigma.[23] Mansicalco et al. have shown that transcription factor p53 is increased in hyperoxic lung injury and may suppress VEGF mRNA expression.[24] Microvascular development is not altered, but type II cell proliferation and differentiation is decreased.

Blockade of VEGF receptors impairs microvascular development and alveolarization, both of which are required for normal lung growth. These researchers also documented oxidant DNA damage in fetal baboons treated with 100% oxygen (DNA guanine residues oxidized to 8-oxoG), similar to that found when neonatal rats were exposed to hyperoxia.[25] Noteworthy, mitochondrial DNA is more sensitive to oxidant injury than nuclear DNA,[26] possibly related to mitochondria as the primary source of reactive oxygen species. Moreover, using a transgenic mouse model, perinatal hyperoxia adversely affected alveolar development by disrupting the proper sequence and timing of type II cell proliferation and differentiation into type I cells critical for alveolar "repair."[27]

Oxygen exposure induced injury of the developing lung such as is found in animal models of BPD, is associated with TGF-β overexpression.[28,29] Excessive TGF-β signaling disrupts both alveologenesis and microvascular development in a pattern similar to that seen in the development of BPD. Fortunately, a strategy of neutralizing the effects of TGF-β by using neutralizing antibodies to reduce the toxic effects of oxygen on lung development[30,31] and alternatively fibroblast growth factor-10 (FGF-10) and keratinocyte growth factor (KGF) may mitigate the effects of TGF-β on the oxygen-induced injury.[32] The potential interaction of oxygen toxicity and bacterial products affecting Toll-like receptor activation which may inhibit FGF-10 expression, thus impeding the repair of the immature lung, has recently been reported, thus offering opportunities to influence the adverse effect of multiple interacting toxicities that result in the development of BPD.[33]

Table 1. **Recent Trials of SPO_2 Targets**

Experimental	
STOP-ROP	96-99%
BOOST	95-98%
SUPPORT*	85-89%
Control	
STOP-ROP	89-94%
BOOST	91-94%
SUPPORT*	91-95%

** A lower target range of SPO_2, as compared with a higher range did not significantly decrease the outcome of severe ROP or death, but it resulted in an increase in mortality and a substantial decrease in severe ROP among survivors.*

Interaction of Supplement Oxygen with Other Treatments

Interactions between inspired oxygen and other drugs used in the neonatal period is an important new area of investigation. Considerable evidence supports an injurious path from elevated inhaled oxygen concentrations to the production of reactive oxygen species by mitochondria during mechanical ventilation.[34] This damage includes airway epithelial cell and alveolar Type I cell death, as well as proliferation of Type II cells, hyaline membrane formation, edema, interstitial fibrosis, and pulmonary vascular remodeling.[35] Hyperoxia has been shown to include activation of all three major mitrogen-activated protein kinase pathways (MAPK) in experimental models.[36,37] We have documented that phospholipid mixtures of surfactant preparations which contain unsaturated acyl groups show partial loss of surface activity in the presence of reactive oxygen species.[38] Further, protein carbonyl concentrations after treatment with Fenton reagents were higher in endogenous as well as in synthetic peptide surfactant (lucinactant) when compared to beractant.[39] Surfactant surface tension characteristics were impaired more in animal-derived surfactants than synthetic surfactants, suggesting a higher sensitivity to lipid peroxidation among surfactants from animal-derived sources. Oxidation of polyunsaturated fatty acids can contribute to the generation of protein carbonyls by direct interaction of lipid oxidation products (unsaturated aldehydes) with lysine residues which potentially leads to disruption of surfactant function.[40] Fortunately, some surfactant preparations have been shown to be protective for airway epithelial cell exposed to hyperoxia as was shown with lucinactant contrasted to products derived from animal lungs.[41]

Noteworthy is the observation that both indomethacin and ibuprofen improved retinopathy in a mouse model when administered during a period of hyperoxia exposure. Animals that received indomethacin during hyperoxia exposure had a significantly lower median [25, 75th quartile] retinopathy score of 5 [4.6, 6] compared with animals that received higher levels of oxygen exposure [7.5,10].[42,43]

Midazolam is commonly used in NICUs for sedation, however, it has been shown to be neurotoxic for the developing brain and was associated with poorer neurologic outcomes among premature infants in a multicenter randomized clinical study.[44] Neonatal death, severe intraventricular hemorrhage (grades III or IV) and periventricular hemorrhage were more frequent with midazolam than with morphine.[45] A Cochrane meta-analysis advised not to use midazolam in premature infants until further clinical evaluations demonstrate its safety.[46] Sola suggested that a special precaution should be taken when midazolam and hyperoxemia are used in tandem (as may occur during anesthetic induction), and to date there have been no study that evaluates this potentially neurotoxic combination.[47]

Although inhaled nitric oxide (NO) has not been approved for infants <34 weeks gestation, treatment of persistent pulmonary hypertension occurring in premature infants is often based on use of inhaled NO and elevated levels of oxygen. Cell-derived NO together with O_2 form cytotoxic nitrogen dioxide (NO_2) which when combined with O_2- forms highly reactive peroxynitrite (ONOO-), leading to tissue nitration and cytotoxicity.[48] Alternatively, both endogenous and exogenous NO have been shown to diminish the injurious effects of ROS.[49,50] Contrary to some clinical studies showing that inhaled NO did not reduce the occurrence of BPD,[51,52] the NO Chronic Lung Disease study group demonstrated benefits and improved survival among infants weighing <1250 grams given inhaled NO between days 7 and 21 by improving survival free from BPD at a corrected age of 36-40 weeks.[53] In vivo experiments clearly show that inhaled NO is an effective therapy in treatment of hyperoxic lung injury.[54,55]

Conclusion

Oxygen is widely used in infants from 22 weeks gestation to term and there is a need to develop better monitoring tools. The ILCOR guidelines and the forthcoming Neonatal Resuscitation Guideline revisions are expected to be more strict with regard to supplemental oxygen during neonatal resuscitation, with recommendations to increase FiO_2 immediately after birth and beyond. Promising new technologies based on near infrared spectroscopy and indices of perfusion require careful measurements. Data from well designed clinical trials are needed to determine their value in oxygen monitoring and safety thresholds. Further, the clinician needs better tools to measure total oxidant stress to afford better treatment of ongoing oxidant stress with antioxidant "cocktails."

Currently Unresolved Critical Clinical Questions regarding Oxygen Monitoring

1. Using currently available data, what SpO_2 limits should neonatologists strive to maintain in their treatment of critically ill infants?
2. How should gestational age at birth and postnatal age determine or modify these desired SpO_2 limits? How about recent packed red blood cell transfusions?
3. How should SpO_2 records (e.g., histograms) be documented among infants receiving ongoing supplemental oxygen therapy and how should time within pre-specified limits or outside these limits be documented and audited? Should these recordings be maintained as a part of the permanent medical record?
4. Among preterm infant who have achieved "stable" SpO_2 ranges within prescribed limits, but who occasionally require supplemental oxygen, how should SpO_2 alarms and limits be modified?
5. What incentives or motivators have been shown to influence adherence to SpO_2 limits, and how should compliance within these limits be audited? How soon will oxygen administration be controlled using closed-loop devices interfaced with air-oxygen blenders interfaced with ventilators or CPAP to adjust FiO_2 to achieve desired SO_2 limit and at what sampling frequency should they optimally function? Will these, in fact, be better than skilled NICU RNs and RCPs?
6. What are meaningful measures of ongoing oxidant exposure for the clinician, and how could these measures be used to quantify oxidant burden in preterm infants?
7. What novel approaches to antioxidant supplementation are on the horizon that hold promise to augment the defenses among extremely preterm infants?
8. What additional laboratory measures of oxidant burden should be available to the clinician to monitor oxygen toxicity or its reversal in clinical neonatology.
9. Does the product of oxygen desaturation and time (degree of desaturation x time) of have an advantage in determining clinically significant events, and what product should be deemed clinically useful?

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Steps Towards a More Rational Use of Supplemental Oxygen: *Lessons from the Experts*

Meeting the metabolic demands of the developing brain and nervous system by providing adequate substrates for cellular energy requirements has been an elusive goal of neonatologists. Sufficient oxygen delivery to the developing brain – a critical goal for neonatologists – is a function of hemoglobin type and content, SpO_2 level, paO_2, and cerebral blood flow, along with adequate glucose and alternative fuels. Dr. Kimura provides an enlightening discussion of how the developing brain is affected both by reactive oxygen species, and hyperoxia.

Neonatologists and pediatric cardiologists care for infants with congenital cyanotic heart disease who have hypoxemia, based on conventional SpO_2 limits even with prostaglandin treatment, and who await surgical correction. In the panel discussion, Dr. Dudell reviews lessons learned from the care of infants managed by necessity with "restrictive" oxygen saturation levels until surgical intervention.

The relative hyperoxia experienced by preterm infants exposed to higher levels of oxygen ex utero, as opposed to in utero, results in slowing, cessation, and even regression of retinal vasculature development. This regression then leads to retinal tissue hypoxia prompting a burst of angiogenic factors such as vascular endothelial growth factor, which results in an over and disorganized growth of the retinal vasculature seen in retinopathy of prematurity, discussed by Dr. Klein.

Even with today's uncertainty regarding optimal oxygen saturation limits nurses and respiratory therapists caring for infants do so within the context of following physician orders in the care that they provide.[1] To evaluate the success rate of maintaining prescribed SpO_2 limits, Ms. Sykes, an experienced NICU nurse reviews nursing techniques used at Tufts University Medical Center, to maximize opportunities for infants to remain within prescribed SpO_2 limits. Documentation has become a quality statement of how oxygen is being administered. Various NICUs have developed quality collaboratives for monitoring SpO_2 levels over time. The degree to which noncompliance becomes a quality issue is discussed among the panelists, as well as the impact on nursing and respiratory therapy staffing patterns in busy neonatal intensive care setting.

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Currently Unresolved Critical Clinical Questions regarding Oxygen Monitoring

Jonathan M. Klein, MD

Using currently available data, what SpO_2 limits should neonatologists strive to maintain in their treatment of critically ill premature infants to reduce retinopathy of prematurity (ROP)? Could there be a postmenstrual age and reason to target SpO_2 limits > 95% in premature infants in terms of treating ROP?

We strive to limit excess oxygen exposure to premature infants since there is no evidence that oxygen saturations > 95% are beneficial for premature infants. To the contrary, there is evidence that PO_2 > 80 mm Hg is harmful and increases the risk of ROP. We begin this process in the delivery rooms where we place all infants on pulse oximeters and have blenders set at 50% rather than 100% oxygen. This allows immediate titration of FiO_2 to avoid exposure to oxygen levels that would result in a saturation > 95% at birth. We know that by avoiding saturations > 95%, we limit the chance of these infants having a PO_2 > 80 mm Hg. This practice then continues in the NICU where we use oximeter limits based on gestational age and postmenstrual age (PMA) to try to limit unnecessary oxygen exposure.

Oxygen exposure plays a critical role in the development of ROP. We feel that one can reduce the incidence with a systematic process of oxygen saturation targeting. This process consists of setting saturation limits based on gestational and postmenstrual age and using a carefully prescribed system to maintain an infant within those saturation limits. I would like to briefly cover three points. The first is to review the relationship between oxygen and ROP. The second is to identify levels of oxygen saturation associated with reduction in ROP. The third, which is more controversial, examines the effects of increasing oxygen saturation on the progression of severe ROP once it has developed.

Relationship between Oxygen and ROP

ROP is a disease of abnormal retinal neovascularization of an incompletely vascularized retina, which can potentially lead to retinal detachment and blindness. Major risk factors for ROP include prematurity, birth weight, IUGR, and septicemia, which neonatologists cannot control. But the one risk factor we can control is hyperoxia or exposure to oxygen resulting in a PO_2 > 80 mm Hg. Patients at high-risk for ROP are premature infants with birth weights < 1500 g and gestational age ≤ 30 weeks. ROP may begin with a cycle of injury precipitated by a hyperoxic exposure in a premature infant, which leads to retinal vasoconstriction, which in turn leads to long-term retinal tissue hypoxia. This can result in the excess production of vascular growth factors which leads to abnormal blood vessel growth into the vitreous, traction on the retina, and possible retinal detachment leading to blindness. Looking at this cycle of injury, the most important point to stop the injury is at the beginning by minimizing hyperoxic exposure. Although controversial, a later point to intervene is at the prethreshold stage of ROP where increased oxygen may be used to suppress production of vascular growth factors.

Oxygen Saturation Levels Associated With Reduced ROP

Oxygen therapy is currently monitored through pulse oximetry. One of the first proponents of avoiding high oxygen saturation levels was Tin et al.[1] In a retrospective study of premature infants < 28 weeks, they analyzed the association between threshold ROP and oxygen saturation target range, which varied at different institutions according to physician discretion. They found that at institutions which targeted a range from 70% to 90%, the incidence of threshold ROP was 6%, whereas at a target range of 88% to 98%, the incidence was 28%.

In a prospective study, Chow et al looked at the effects of implementing strict guidelines for oximeter alarm limits and adjusting the FiO_2.[2] (The limits chosen were 85% to 93% in infants <32 weeks, and 85% to 95% in infants ≥32 weeks gestational age. They showed a reduction in the incidence of stage III to IV ROP from 12% in 1997 to < 3% by 2000-2001. During this same period, the Vermont-Oxford Network incidence of ROP stayed constant at 10% to 12%. The results of the first randomized multicenter trials examining the effects of oxygen saturation targets on survival without ROP will soon be available (SUPPORT and BOOST II). Infants < 28 weeks in these trials were randomized to a target saturation of 85% to 89% versus a target saturation of 91% to 95%. These studies will provide us with further knowledge regarding the risks and benefits of those saturation ranges, but both studies agreed in avoiding exposure to oxygen saturations > 95%.

Higher Oxygen Saturation Targets for Abatement of ROP

This is a very controversial issue regarding a specific point and diagnosis at which a there may be a reason to have saturations targeted at a range higher than 95%. This concept was studied in a multicenter randomized controlled trial which examined the hypothesis that vasoproliferative ROP worsens from deficient retinal oxygen delivery.[3] Premature infants with prethreshold ROP were treated with oxygen with target saturations of 96% to 99% (high group) versus an upper saturation limit of 94% (low group), which is the saturation level that is avoided to prevent the hyperoxic injury from initially occurring. The patients in this study had all reached prethreshold ROP, at which time they had a mean PMA of 35 weeks. In the BOOST trial,[4] premature infants were randomly assigned

at a PMA of 32 weeks to either 91% to 94% or 95% to 98% oxygen saturation. There was no significant benefit on growth and development when exposing all infants to these high saturation levels. However, when looking at the effects of higher saturation levels on just premature infants with prethreshold disease, the STOP-ROP Multicenter Study Group found a decreased incidence of progression to threshold ROP in the high saturation group of 41% versus 48% in the lower saturation group (p=.032) which did not reach significance at the pre-selected P-level of .025.

However, a subgroup analysis of infants without plus disease (dilated and tortuous vessels in at least 2 quadrants of the posterior pole) showed that the high saturation group had a significant reduction in progression to threshold with 32% reaching threshold versus 46% in the low saturation group (p=.004). There were some nonsignificant (p=.066) pulmonary consequences of being in the higher saturation group with 13.2% of the high saturation group having one or more episodes of pneumonia or exacerbation of chronic lung disease versus 8.5% in the conventional group. However, by 50 weeks PMA, more infants in the high saturation group remained hospitalized (12.7 vs. 6.8%, p=.012) and more were on oxygen (46.8% vs. 37%, p=.02), and diuretics (35.8% vs. 24.4%, p=.002). Thus the difficulty in the management of this disease is how to best achieve a balance between stopping progression to threshold disease while minimizing long-term pulmonary exacerbations.

Based on these data, we use higher saturation limits, but only to treat patients with prethreshold ROP, ideally before they reach plus disease when it is less effective. At the same time, to reduce risk, we limit the effective FiO_2 to 0.5 for these patients, understanding that the trade-off for reduced ROP progression is an increase in the overall need for oxygen, for duration of hospitalization, and need for diuretics (57% vs. 46%, p=.005), but we feel the benefit of reducing the risk of severe ROP to improve visual outcomes outweighs the above side effects, which are only temporary.

The choice of alarm limits should be based on PMA and the presence or absence of prethreshold ROP, with the understanding that there are risks associated with increasing oxygen exposure to obtain higher saturation limits. It is important that all NICUs track their incidence of ROP on a yearly basis and benchmark it with comparable data such as that collected by VON. It is important to do monthly audit spot checks for compliance with oximetry alarm limits prescribed by a preterm oximeter protocol that is openly posted on oximeters. It is important to choose a target saturation to minimize both hypoxic and hyperoxic exposure. The difficulty is determining where those exact saturation limits should be and when they should apply. High saturation levels > 95% in babies below 28 to 30 weeks gestation should be avoided unless prethreshold ROP has developed, which usually occurs around 35 weeks PMA (STOP-ROP 2000).

How should gestational age at birth and postnatal age determine or modify these desired SpO_2 limits, and among preterm infant who have achieved "stable" SpO_2 ranges within prescribed limits, but who occasionally require supplemental oxygen, how should SpO_2 alarms and limits be modified?

The purpose of oxygen saturation targets is to minimize hyperoxia by having an alarm set at an upper saturation limit primarily for premature babies ≤ 28 weeks. The upper alarm limit should not be set higher than 95% based on the oxyhemoglobin disassociation curve since saturations > 95% can correlate with a PO_2 > 80 mm Hg. However, this is a complex relationship which depends on both the ratio of fetal to adult hemoglobin and the algorithm used by the manufacturer of the oximeter to determine the ratio of the absorbance of red light to infrared light and how that ratio correlates to a specific saturation. Thus there are instances when even saturation levels < 95% could represent a PO_2 > 80.

Due to the known risks of hyperoxia discussed earlier, we reached the point where we felt that strict upper oximeter alarm limits should be utilized for premature patients. This decision was based on the work published by Tin in 2001 and by Chow in 2003 and we implemented the use of strict upper oximeter alarm limits in 2006. Where precisely to set the upper and lower oximeter alarm limits for premature infants is of great controversy due to the lack of guidance from randomized trials in this patient population. However, we thought it important to begin minimizing unnecessary exposure to high levels of oxygen by not tolerating saturations ≥95% in the ≤28 weeks population.

What incentives or motivators have been shown to influence adherence to SpO_2 limits, and how should compliance within these limits be audited? Does the product of oxygen desaturation and time have an advantage in determining clinically significant events?

To encourage adherence to saturation limits, we have placed cards on the oximeters with the alarm limits as well as the target saturations. The target saturation is a narrower range (5% to 6%) within the alarm parameters (13% to 15%) designed to encourage titration of oxygen prior to waiting for an alarm. The goal of publicly displaying these limits is that it makes the information transparent to parents, nurses, respiratory therapists, and physicians as to what the oximeter limits should be and thus promotes a team-based process of responsibility for managing oxygen exposure. Displaying these oximeter cards is a process that many other units throughout the country have utilized. The oximeter card serves two functions: (1) where the alarm limits should be set; and (2) what the target goal is for the patient so that when someone is controlling the FiO_2 they know where to aim rather than waiting for the alarm to go off before intervening. We use a standardized protocol with limits based on gestational and PMA to strictly control oxygen exposure with set upper alarm limits. We also use alarm limits to prevent excessively low saturations, but how low is safe has not yet been determined and is awaiting the results of the SUPPORT and BOOST II trials to add more knowledge to this issue.

For the ≤ 28 week population, the goal is to avoid saturation levels > 93% to 95% and at the same time, to avoid saturations < 80%. These alarm limits are based on studies discussed above,[1,2] but have not been subjected to randomized trials. The lower alarm limit is increased to 85% once the postmenstrual age is > 31 weeks. The card also states that in response to desaturation, oxygen should be increased in increments of no more than 5%. If the cause is central apnea, we encourage an increase in medical or mechanical support based on the etiology rather than increased oxygen exposure. This is similar to the protocols described by Chow et al.[2]

When implementing saturation limits, it is critical to have buy-in from all healthcare team members. This was encouraged by presenting this change as part of a quality improvement project to reduce ROP. To gain adherence to the SpO_2 limits, compliance with these limits is audited monthly by the nurses to see if the ordered limit is actually set on the oximeter. To minimize conflict, the cards also state that once the patient is on 21% oxygen and is saturating above the upper alarm limit, the upper alarm limit can be readjusted. To gain compliance, all healthcare team members including nurses, physicians, nurse practitioners, and respiratory therapists have received education on the effects of hyperoxia on the development of retinopathy of prematurity.

Three main things that support buy-in for oximeter alarm limits include: (1) a laminated bedside protocol (card) attached to every oximeter; (2) frequent in-service and educational events regarding the impact of hyperoxia on retinopathy of prematurity; and (3) follow outcomes and give positive feedback on a yearly basis. Since implementing our policy in 2006, we have seen a 40% to 50% reduction in the incidence of both all and severe ROP in VLBW infants while the baseline incidence for the Vermont-Oxford Network has remained unchanged. Other issues of oximetry management remain controversial, especially how to minimize false alarms due to motion artifact. One technique is to look at the product of oxygen desaturation over time. This appears to be a way to minimize unnecessary responses to motion desaturation, but this has not yet been well studied in randomized clinical trials.

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Oxygen Toxicity in the Developing Brain

By Robert Kimura, MD

Half of surviving infants with gestational ages <25 weeks will develop significant developmental disabilities.[1,2] The explanation for these poor neurological outcomes appears to be multifactorial. In a recent review, Volpe describes the "recent insights into the full spectrum of the encephalopathy of prematurity and into the remarkable series of developmental events that occur in the brain during this period that indicate a complex amalgam of destructive and developmental mechanisms.[3] " Oxygen toxicity may be a factor in causing perinatal brain injury in extremely premature infants brain injury, as it is in retinopathy of prematurity (ROP). Infants in the immediate postnatal period have developmental deficiencies that may predispose them to oxygen toxicity. The fetus normally thrives in a low O_2 saturation environment. As a result, mechanisms for neutralizing oxygen radicals have not yet been activated. For example, the ability of the premature infant to synthesize glutathione, the major substrate that neutralizes oxygen radicals, is low.[4]

Could hyperoxia during the perinatal period actually result in injury to the immature neonate's brain? There are a few clinical studies that address this question. An observational study concluded that lowering the oxygen limits during neonatal intensive care had no detrimental effects on neurological outcomes of very low birth weight (VLBW) infants.[5] They actually noted a trend for better outcomes in their lower oxygen group. Deuolofeut and colleagues determined that for infants less than 1250 g, a decrease in oxygen limits from 92-100% to 85-93% improved neurological outcomes as measured by mental developmental index, although it did not affect psychomotor developmental index.[6] In a study of infants less than 2000 g, Collins and colleagues concluded that hyperoxia was a risk factor for patients who developed disabling cerebral palsy.[7] In contrast, Askie and coworkers reported no difference in developmental outcome in extremely low birth weight (ELBW) infants treated with a target oxygen saturation range of 95%-98% as compared to 91%-94%.[8]

The effect on outcome of high and low oxygen concentrations during postnatal resuscitation of hypoxic neonates has been extensively studied. During resuscitation, 100% oxygen is routinely used and O_2 saturations of 100% indicating PO_2 > 100 mm Hg are often observed. However, most meta-analyses have concluded that resuscitation at low oxygen concentrations is beneficial compared to 100% oxygen, without an increase in neural developmental disability. [9]

Some studies actually indicate improved neurological outcome in patients resuscitated with 21% oxygen. A recent meta-analysis of newborn resuscitation concluded that resuscitation with 21% oxygen significantly decreased neonatal mortality compared to 100% and that there was a trend towards decreasing the risk of severe hypoxic ischemic encephalopathy.[10] A multivariate analysis showed an association between adverse neurological outcomes and hyperoxia after intrapartum asphyxia.[11] Finer and colleagues noted that rigorous studies attempting to delineate both the positive and negative effects of high and low $F1O_2$ on neurological development in ELBW infants have not been done and have proposed a study to determine the appropriate initial FiO_2 during the resuscitation of ELBW infants.[12] A key focus of this study will be neurological outcomes.

What is the evidence of neonatal brain injury from oxygen toxicity using animal models? Some studies indicate that hyperoxia induces cerebral cellular injury. Resuscitation of hypoxemic piglets with 100% oxygen compared with 21% caused an increase in markers of cerebral injury (i.e., extracellular glycerol, matrix metalloproteinase expression). The cerebral injury was associated with a decrease in radical absorbance capacity, indicating an increase in oxygen radical production under hypoxia, followed by hyperoxic conditions.[13,14]

Other studies indicate that hyperoxia induces brain inflammation. Using NF-κB as a marker of brain inflammation, Dohlen and colleagues observed an increase in brain NF-κB activity in hypoxic mice reoxygenated with 100% oxygen compared to no increase in mice reoxygenated with 21%.[15] Another group showed that hyperoxia during ischemia-reperfusion in fetal sheep caused an increase in cerebral proinflammatory mediators.[16] Following 10 minutes of cord occlusion, fetal sheep were resuscitated with either 21% or 100% oxygen. Toll-like receptors TLR-2 and TLR-4 mRNA was increased in the cortex of fetuses resuscitated with 100% oxygen compared with 21%, indicating a hyperoxia-induced proinflammatory response.

What other possible mechanisms might explain hyperoxia-induced brain injury? Animal studies indicate an increase in oxygen radical production by the neonatal brain exposed to hyperoxemic conditions. Kutzsche and coworkers determined the effect of reoxygenation of hypoxic piglets with either 21% or 100% oxygen on neutrophil hydrogen peroxide (H_2O_2), a product of oxygen radical production, in arterial and cerebral venous blood.[17] There was no difference in neutrophil H_2O_2 concentration between arterial and cerebral venous blood in the piglets reoxygenated with 21% oxygen. In piglets reoxygenated with 100% O_2, neutrophil H_2O_2 concentration in cerebral venous blood was higher than in arterial blood, indicating H_2O_2 production within the cerebral circulation. This study suggests that reoxygenation with 100% oxygen increases oxygen radical production in the cerebral cortex. In studies of hypoxia-reoxygenation in newborn piglets, cerebral cortical H_2O_2 and oxidized glutathione concentrations were increased, indicating increased oxygen radical production.[18,19]

It has been hypothesized that oxygen radicals can damage the lipid bilayers of cells and mitochondria.[20] Using a neonatal pig model, Feet and colleagues measured the effects of hypoxemia (8% O_2) followed by reoxygenation on cerebral extracellular hypoxanthine concentrations.[21] Concentrations were significantly higher in animals reoxygenated with 100% oxygen as compared to 21%. Since hypoxanthine is a marker of hypoxia, these investigators speculated that reoxygenation with 100% oxygen actually increased cerebral hypoxic injury rather than correcting it. The mechanism may be that hyperoxia enhances mitochondrial injury which is associated with apoptosis.[20]

Changes in the control of neuronal cell apoptosis have been hypothesized as the cause of hyperoxia-induced neurodegeneration in animal models. In 3- and 6-day old mice, hyperoxia caused the cell death of pre-oligodendrocytes, but not mature oligodendrocytes.[22] The neuronal cell death was associated with changes in the caspase-dependent apoptotic pathway. Hyperoxia causes inactivation of factors that have anti-apoptotic properties. For example, the hyperoxia-induced activation of the caspase pathway in piglets is associated with the phosphorylation and resulting inactivation of Bcl-2,[23] Bcl-2 and Bcl-xl.[24] Other studies in mice indicate that hyperoxia caused an inactivation of the survival signaling proteins Ras.[25] SynRas-transgenic mice with overexpressing activated Ras were resistant to hyperoxia-induced neurotoxicity.

Summary

There is increasing evidence that hyperoxic conditions increase the production of oxygen radicals that may cause brain inflammation. The newborn and specifically the premature infant are particularly vulnerable to brain injury and altered development.[3] For resuscitation of hypoxic infants, the optimal inspired oxygen concentration is debated. Although at physiologic concentrations oxygen is a vital substrate for neuronal cell survival, concern for the toxic effects of hyperoxia still exists. Study trials have been proposed or are ongoing that attempt to determine the optimal oxygen saturation required for the best neurological developmental outcome.

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How Low is Too Low? Lessons Learned from Infants with Cyanotic Congenital Heart Disease

By Golde Dudell, MD

Although there is a large body of literature describing the role of hyperoxia on the development of retinopathy of prematurity (ROP), bronchopulmonary dysplasia and postasphyxial brain injury, recent studies comparing epithelial and vascular branching morphogenesis have focused on differences in organ development under conditions of normoxemia versus hypoxemia. It is important to realize that normal fetal development takes place in a relative hypoxemic uterine environment. Several studies have shown that the low fetal oxygen environment is beneficial for embryo development and for cardiovascular and kidney organogenesis.[1-4] Preliminary studies in rats have shown that a fetal oxygen tension maintains lung morphogenesis in vitro.[5] Midtrimester human fetal lung explants cultured at fetal oxygen tension had increased expression of vascular endothelial growth factor (VEGF) compared with explants cultured at ambient oxygen levels.[6] VEGF is a potent mitogen for endothelial cells, influencing angiogenesis and vasculogenesis.[7] VEGF expression is regulated by hypoxia-inducible factor (HIF)-1α, which encodes a transcription factor that is expressed in most, if not all, cells in response to hypoxia.[8,9] Moreover, HIF-1α is essential for embryonic vascularization and survival and hypoxia-induced pulmonary vascular remodeling, and tumor vascularization.[10] The influence of a relative hypoxic environment on epithelial and vascular branching morphogenesis was also investigated in two transgenic mouse models. At embryonic day 11.5, primitive lung buds were dissected and cultured at either 20% or 3% oxygen. The rate of branching of both tissue elements was increased in explants cultured at 3% oxygen compared with 20% oxygen. Low oxygen increased expression of VEGF, but not that of the VEGF receptor, Flk-1. Epithelial differentiation was maintained at low oxygen as shown by surfactant protein C in situ hybridization. When vascular development was inhibited with antisense oligonucleotides targeted against either hypoxia inducible factor-1 or VEGF, epithelial branching morphogenesis in vitro was dramatically abrogated suggesting that a low oxygen environment enhances branching of both distal lung epithelium and vascular tissue, and that pulmonary vascular development appears to be rate limiting for epithelial branching morphogenesis.[11] Fetal oxygen tension also has been shown to promote Tenascin-C dependent lung epithelial branching morphogenesis by limiting the proteolytic turnover of this extracellular matrix component within the adjacent mesenchyme.[12] Moreover, embryonic and neural stem cells have shown increased proliferation and differentiation in response to mild hypoxia.[13,14]

The oxygen partial pressure (pO_2) of the fetal arterial blood, which normally ranges from 25 to 30 mm Hg, is considerably lower than that of maternal arterial blood. Even though oxygen tension in fetal blood is only 20% to 25% of adult blood, fetal arterial blood oxygen content and oxyhemoglobin saturation are not much lower than those of an adult. Fetal hemoglobin (α2,δ2) is structurally different from adult hemoglobin (α2,β2). It has a greater affinity for oxygen than has adult hemoglobin. Consequently, fetal hemoglobin combines more rapidly with oxygen at low tension than does adult hemoglobin. With advancing gestation, progressive decrease in umbilical artery pO_2 is associated with an increase in fetal hemoglobin concentration, thus maintaining constant fetal oxygen content. Oxygen consumption in normal human fetuses between 28 and 40 weeks of gestation varied between 5.4–6.8 mL/kg/min, while adult oxygen consumption is estimated to be about 3.0–4.0 mL/kg/min in resting state.[15] Thus, oxygen consumption per kilogram in a normal fetus is almost double the consumption of the adult. Studies on moderately and severely anemic fetal lambs show that a high hemoglobin-oxygen affinity is critical for normal metabolism in fetuses subjected to a hypoxic stress.[16] In fetal lambs, mean oxygen extraction increased from 33.6% to 67.7% during a 75% reduction of umbilical blood flow. Similarly in fetal lambs, diminished oxygen delivery due to restriction of uterine artery blood flow increased mean oxygen extraction significantly from 33% to 43% and 54% at 1 and 24 hours, respectively. Overall fetal oxygen consumption remained unchanged from control values.[17] The fetus is therefore well equipped to use adaptive mechanisms to compensate for decreased oxygen delivery.

How does this relate to oxygen toxicity in the preterm? First, it suggests that even normoxia may be detrimental to organ growth that involves branching morphogenesis, i.e., lung, brain and kidney, and that avoiding hyperoxia as suggested by Sola et al may not be enough.[18] So the question becomes: can a preterm, like the fetus, thrive in a relatively hypoxic environment? Indeed, Tin et al. have reported decreased duration of mechanical ventilation and supplemental oxygen, reduction in the incidence of bronchopulmonary dysplasia, no difference in cerebral palsy rates and 4-fold decrease of threshold retinopathy among their cohort of 126 infants managed with a target SpO_2 of 70% to 90%.[19] We know that restrictive oxygen protocols in the preterm population in the past led to increased morbidity and neurodevelopmental impairment. However, since oxygenation was not monitored in this cohort, we have no idea of degree of hypoxemia to which they were exposed. Since we

now have the technology to monitor oxygenation, it is disappointing that we still are unable to define an optimal SpO_2 range for the preterm.

Neonatologists and pediatric cardiologists who deal with infants with cyanotic congenital heart disease also face the problem of maintaining adequate oxygen delivery and sustaining normal growth in the presence of hypoxemia. This can generally be accomplished in infants with cyanotic heart disease during the early neonatal period by balancing Qp/Qs ratio, avoiding pulmonary overcirculation and maintaining hemoglobin at fetal levels. Infants with balanced circulations such as tricuspid atresia with a ventricular septal defect (VSD), tetralogy of Fallot (TOF) or transposition of the great vessels (TGV) with a ventricular septal defect and pulmonary stenosis are often discharged home with a SpO_2 of 70% to 90% to await elective repair. Infants with hypoplastic left heart syndrome (HLHS) who develop pulmonary steal syndrome while awaiting cardiac surgery can benefit from treatment with subambient oxygen concentrations which result in pulmonary vasoconstriction and increased systemic blood flow. Infant measures of tissue oxygen delivery such as cerebral near infrared spectroscopy, often improve despite the drop in inspired oxygen concentration. Moreover, normalization of Qs at the expense of SaO_2 have been shown to be of benefit at all ages post-Fontan procedure where fenestration has been shown to improve postoperative outcome in standard-risk as well as high-risk patients.[20] The presence of a patent foramen ovale may also be beneficial in infants after repair of TOF when right ventricular dysfunction may lead to a low cardiac output state or total anomalous venous connection where pulmonary hypertension can compromise right ventricular output. Children and adults with primary or secondary pulmonary hypertension also benefit from atrial septostomy despite a drop in their SaO_2 due to the right to left atrial shunt.

In one study, 51 children over 10 years of age with TOF and 30 with TGV were assessed and compared with 33 children who had surgery for VSD. Children with TGA were operated on at a median age of 7.5 months, and those with TOF had surgery at a median age of 1.9 years. There was no evidence from IQ or neuropsychological testing that the duration of hypoxia before surgery had any adverse effect on the children's intellectual development.[21] Goldberg et al assessed 48 young children with functional single ventricle who underwent a Fontan procedure between 1992 and 1997.[22] The full scale IQ was significantly lower in children with HLHS (93.8 ± 7.3) and in those without (107.0 ± 7.0). Socioeconomic status, the use of deep hypothermic cardiac arrest and perioperative seizures were predictors of neurodevelopmental outcome. The extent or duration of preoperative hypoxemia was not an independent predictor of outcome. In general, preschool and early school age neurodevelopmental and behavioral outcome in patients post-Fontan, including those with HLHS, was good. Full scale IQ scores were generally in the normal range. Forbess et al. reported the outcome of 27 5-year old children post-Fontan procedure and compared them to an earlier Fontan group of 133 patients who underwent surgery in the 1970s and 1980s.[23] Compared with early Fontan group, the study sample was operated on at a younger age (2.7 vs. 7.3 years) and was more likely to have undergone a staged Norwood procedure and Fontan fenestration. Mean full scale IQ, verbal, and performance IQ scores were within 1 SD of the population mean (93 ± 16, 95 ± 15, and 91 ± 17, respectively) in the study sample while the mean full scale IQ and performance IQ were significantly lower than the population mean in the early Fontan group. Ikle et al assessed 26 children treated for HLHS by heart transplantation before 6 months of age.[24] Median MDI of 88 (< 50 to 102) and PDI of 86.5 (< 50 to 113) were both significantly lower than in the general population. Full scale IQ (FSIQ) were also significantly lower than expected (88.5 ± 13.0) with a mean verbal IQ of 90.5 ± 12.4, performance IQ of 88.9 ± 14.5. Measures of daily living were abnormal in 39%, socialization in 22%, communication in 48% and adaptive behavior in 52%. Children treated for HLHS with heart transplantation, despite early correction of hypoxemia, showed cognitive deficits and adaptive and behavioral abnormalities similar to those described in children undergoing staged Norwood repair. Forbes et al reported the neurodevelopmental outcome of 243 5-year-old children following repair or palliation of congenital heart disease between 1998 and 2001. Mean full scale, verbal, and performance IQ scores were in the normal range (96.8 ± 15.9, 97.8 ± 14.6, and 96.3 ± 17.1, respectively). In multiple regression analysis, lower socioeconomic status and the diagnosis of 22q11- syndrome predicted a lower FSIQ. A single ventricle diagnosis, longer postoperative ICU stay, and cumulative duration of hypothermic circulatory arrest were not predictors of lower FSIQ. These findings suggest that mild to moderate hypoxemia during infancy and early childhood generally does not result in major neurodevelopmental impairment.

Therefore, are SpO_2 goals of 70% to 90% safe in the preterm infant? One would predict that the answer would be yes. However, preliminary results of the recently completed SUPPORT trial of SpO_2 targets of 85% to 89% versus 90-95% shows a significant decrease in retinopathy of prematurity (9% vs. 19%, p<.001) but a significant increase in mortality (20% versus 16%, p=.045) in the lower SpO_2 range after adjustment for center, gestational age and multiple births with no difference in the primary outcome of death or severe retinopathy. A possible explanation for this inability of the preterm to tolerate mild hypoxemia may relate to the simultaneous adoption of other restrictive strategies. A number of publications suggest that restricted red blood cell transfusion protocols and permissive hypotension are safe. However, as permissive strategies are combined, their effect on oxygen delivery are compounded and tissue hypoxia may ensue. Like infants with cyanotic congenital heart disease, hemoglobin must be kept near fetal levels and cardiac output must be optimized in if one is going to adopt restrictive oxygen protocols in the preterm.

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Nurse Opinion on Oxygen Toxicity in the Infant with Very Low Birth Weight

by Sally Syke, RN, BSN

Every NICU nurse currently practicing has undoubtedly received multiple educational in-services addressing oxygen toxicity and its complications. Much of the frontline effort in decreasing these complications lies in the hands of the bedside nurse. Despite such attention, a study published in 2008 indicated that of the nurses surveyed in neonatal intensive care units (NICU) with policies, only 64% were aware of such policy.[1] Of those nurses, only 37% could correctly identify the upper and lower SpO_2 limits cited in their policy. With such an important task as reducing oxygen toxicity and associated morbidities, why such concerning results?

In a pledge to decrease our incidence of ROP and avoid hyperoxia in the spring of 2009 we launched a massive campaign to reverse our trend. We began analyzing all FiO2 concentrations, placed all resuscitation bags on blenders and installed blenders in every labor/delivery/recovery (LDR) room and C/S room to ensure resuscitation of the VLBW is initiated utilizing 0.4% FiO2. Utilizing a true multidisciplinary team approach, we reviewed literature and revised our clinical practice guidelines. We developed multiple patient profiles for our new CRMs which included preset saturation alarm limits and ranges. Based on post-menstrual age and the need for supplemental oxygen, we established overall lower parameters for O2 saturation ranges for our VLBWs to 86-92%. The "Seemore the OWL" (Oxygen With Love) program was instituted to remind everyone of the importance in maintaining lower saturation ranges. We injected a tremendous amount of time and energy into staff education, as nursing is the one true constant in monitoring for and preventing hyperoxia. Breakdown of VON data for 2009 revealed that after our educational efforts and practice changes were instituted, we saw a dramatic decrease in our laser treatment rate to 2%, well below the VON average. Nurses verify the correct patient profile and alarm limits are set for each patient and volunteers from our nursing staff perform random audits on alarm limits to verify correct settings. Visualization of alarm limits during daily patient care rounds has also begun. Temptation to reset the high alarm limit to 100% does exist as this contributes to a quieter patient environment and decreases the frequency of answering alarms. Prior experiences of a NICU nurse does influence personal opinion regarding saturations. Personal bias has proved to be one of the most frustrating and difficult obstacles faced when trying to change nursing practice.

Minute by minute manipulation of FiO_2 and saturation management is the responsibility of the bedside nurse. Tighter saturation parameters translate into more frequent alarms often requiring almost continuous FiO_2 adjustment. During routine care of the VLBW infant, desaturation is a fact of life, yet our management of it varies. When it occurs, we must quickly decide if an increase in oxygen is necessary or if we can anxiously watch and wait for self correction. Is it more detrimental to expose the baby to constant fluctuations in FiO_2 to maintain range, possibly contributing to even more frequent spells, or allowing the baby to ride out the episode without any adjustment? Should we increase oxygen at the start of the patient encounter or only after the low alarm is triggered? The severity of patient illness also impacts the likelihood of ROP development, despite our best practice in maintaining identified sat ranges. Generally, increasing the FiO_2 in small, slow increments of 1%-5% is accepted as safe practice in preventing hyperoxia; however it is difficult to monitor individual, independent nursing practice. While some identify hyperoxia as the root of all evil, others believe wide fluctuations in saturations, PaO_2s and FiO_2s are key. While many units have guidelines to address response to desaturation, a nurse's prior experience with similar cases will influence practice.

With the advancement in cardiorespiratory monitoring, histogram capability is becoming the standard of care. This capability allows us to accurately identify the percentage of time a baby is or is not within their determined saturation range. This information is then incorporated into daily patient care rounds to assist in determining if care and treatment decisions are successful in achieving goals. Technology isn't cheap, so how do we manage patients when this technology isn't available? In some units, the nurse is required to document each baby's oxygen saturation level every hour. Does this practice accurately reflect a baby's true saturation level? Does this capture the amount of time and energy a nurse spends trying to keep a baby within his or her set parameter? Without additional information, this number is but a moment in time. What were the baby's saturations the other 3,599 seconds of the hour? Histograms provide a more accurate assessment of saturation levels over 24 hours. Yet, some nurses have questioned the way this information will be interpreted. Is it for medical use or is it a way to determine if a nurse is doing her job? Is this a way to "blame" a nurse for not keeping her baby in a tighter range? If histograms become part of the medical record, will this be a way to look at the nurse as contributing to the development of a baby's ROP?

Many institutions in today's healthcare market are struggling with nurse staff allocations. With less opportunity to provide individualized care, nurses are asked to care for more, smaller and sicker babies. Frustration increases and attention to the small details declines. Less than rapid response to a high saturation alarm is inevitable. If a high saturation alarm is triggered while you are at the beginning of a cue-based infant feeding session with another patient, you simply are incapable of responding to the alarm. When you are responding to a baby's episode of apnea and desaturation and another baby's alarm is triggered, who else can respond? If the other nurse assigned to your room is in the delivery room or at lunch, you are alone with your patients and hers too. You look at the monitor and realize it is "just a high sat." It's not life threatening so you have time to make sure the apneic baby recovers before responding. Was this final incident responsible for starting the cascade of events leading to ROP? Does anyone really know? The need for assistance in maintaining patients within such tight parameters occurs each time we step away from the bedside. When we participate in patient rounds, answer phone calls or take lunch breaks someone must always be available to respond to alarms. We know that we should at times be sitting almost constant vigil at the bedside of these labile babies, but often assignments include 1 or 2 additional patients. We often look to our respiratory therapy (RT) colleagues for assistance in maintaining appropriate SpO_2 ranges. However, nurses far outnumber RTs in any unit. In large units, little opportunity exists for them to assist everyone in the minute-by-minute management of labile babies. Thus, the task of preventing hyperoxia is truly ours to bear. Nurses know oxygen toxicity is real but often are left feeling inadequate in attempts to avoid it. Nurses understand a baby's lifetime with or without eyesight or respiratory compromise is at stake. These potential consequences will not only have a lifelong affect on the individual and family but on society and healthcare overall.

With the advancement in cardiorespiratory monitoring, histogram capability is becoming the standard

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For Physicians

Oxygen Toxicity and the Premature Infant
Project ID: 7137 ES 15

Method of Participation

There are no fees for participating and receiving CME credit for this activity. Participants must

1 Read the learning objectives;
2 Study the educational activity;
3 Complete the posttest by recording answer in the answer key on the evaluation form;
4 Complete the evaluation form;
5 Fax the evaluation form with answer key to Postgraduate Institute for Medicine.

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1. **Hemodynamic monitoring can improve patient outcome if:**
   a. It accurately measures the variable it claims to measure
   b. It is associated with a treatment that improves outcome
   c. It allows for the rapid diagnosis of circulatory insufficiency
   d. None of the above

2. **Goal-directed therapy includes what essential elements?**
   a. Patient selection, appropriate monitoring, resuscitation to target oxygen delivery
   b. Patient selection, appropriate monitoring, resuscitation to target mean arterial pressure
   c. Appropriate monitoring, resuscitation to target mean arterial pressure and oxygen delivery
   d. Appropriate monitoring, resuscitation to target mean arterial pressure and avoidance of hypoxemia

3. **Essential characteristics of minimally invasive hemodynamic monitoring devices which allow them guide goal-directed therapy include all but which quality:**
   a. Accurate measure of cardiac output and its changes over very short periods of time
   b. Measures of stroke volume variation during positive pressure breathing
   c. Minimal drift of absolute measures due to error
   d. Ease in setting up, calibrating and displaying relevant hemodynamic data

4. **Functional hemodynamic monitoring principles used to assess volume responsiveness include which parameters:**
   a. Mean arterial pressure, mixed venous O_2 saturation, central venous pressure
   b. Intrathoracic fluid content, stroke volume variation, mean arterial pressure
   c. Pulse pressure variation, change in cardiac output in response to passive leg raising
   d. Cardiac output, mixed venous O_2 saturation, mean arterial pressure

5. **The central venous pressure:**
   a. Predicts fluid responsiveness
   b. Correlates well with intravascular volume measured by the isotope method
   c. Is an indicator of left ventricular preload
   d. Is a measure of right atrial pressure

6. **An example of a dynamic preload parameter would be:**
   a. Central venous pressure (CVP)
   b. Pulmonary capillary occlusion pressure (PCOP)
   c. Pulse pressure variance (PPV)
   d. Hourly urine output

7. **What is one of the main limitations of current goal directed therapy protocols?**
   a. Early initiation of resuscitation measures
   b. Use of static rather than dynamic resuscitation endpoints to guide fluid therapy
   c. The potential for complications associated with resuscitation efforts
   d. Overuse of technology in monitoring patients

8. **When prescribing intravenous fluids it is essential to consider which one of the following information?**
   a. Serum lactate
   b. Stroke volume
   c. Clinical history including the stage of the disease process
   d. Central venous pressure

9. **Which of the following are important when using new technology to assess dynamic parameters?**
   a. Understanding how the device measures and calculates parameters
   b. Understanding the limitations of the measured parameters in a given patient condition.
   c. Staff familiarity with set up and operation
   d. All of the above

10. **CVP is a reliable measurement of volume status because:**
    a. Pressure variables are compared to volume variables
    b. The CVP is a calibrated number
    c. CVP between 8-12 mm/hg always identifies a filled patient
    d. None of the above

Answer Key	1	2	3	4	5	6	7	8	9	10
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Name _____ Degree _____

Organization _____ Specialty _____

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For Physicians Only

I certify my actual time to complete this educational activity to be as follows:

☐ I participated in the entire activity and claim 1.0 credits.

☐ I participated in only part of the activity and claim _____ credits.

Evaluation

Please rate your level of agreement by circling the appropriate rating:

1 = Strongly Disagree 2 = Disagree 3 = Neutral
4 = Agree 5 = Strongly Agree

Learning Objectives
After participating in this activity, I am now better able to:

1. Define the appropriate resuscitation targets and priorities at reaching these targets in surgical patients
   1 2 3 4 5
2. Explain the methods by which the predefined goals can be most effectively achieved with minimal patient risk.
   1 2 3 4 5
3. Describe the appropriate monitoring devices to achieve resuscitation targets in surgical patients.
   1 2 3 4 5

Based upon your participation in this activity, choose the statement(s) that apply:

☐ I gained new strategies/skills/information that I can apply to my area of practice.

☐ I plan to implement new strategies/skills/information into my practice.

What strategies/changes do you plan to implement into your practice?

What barriers do you see to making a change in your practice?_____

Which of the following best describes the impact of this activity on your performance?

☐ I will implement the information in my area of practice.

☐ I need more information before I can change my practice behavior.

☐ This activity will not change my practice, as my current practice is consistent with the information presented.

☐ This activity will not change my practice, as I do not agree with the information presented.

Please rate your level of agreement by circling the appropriate rating:

1 = Strongly Disagree 2 = Disagree 3 = Neutral
4 = Agree 5 = Strongly Agree

The content presented:

Enhanced my current knowledge base
1 2 3 4 5

Addressed my most pressing questions
1 2 3 4 5

Promoted improvements or quality in health care
1 2 3 4 5

Was scientifically rigorous and evidence-based
1 2 3 4 5

Avoided commercial bias or influence
1 2 3 4 5

Would you be willing to participate in a post-activity follow-up survey? ☐ Yes ☐ No

Please list any topics you would like to see addressed in future educational activities:

_____

_____

This test may be taken online at www.saxetesting.com

For Nurses and Respiratory Therapists

1. **Evaluation of oxidant burden in the preterm infant is best assessed by:**
   A. Measurement of malondialdehydate in the serum
   B. Matrix metalloproteinases and monocyte chemoattractant protein 1 in the serum
   C. Elevation of transforming growth factor beta
   D. All of the above

2. **Surfactant preparations exposed to high concentrations of ROS has been shown to:**
   A. Have inhibition of surface activity
   B. Demonstrate increased conversion of large aggregates to small aggregates
   C. Have equal inhibition regardless of source
   D. A and B

3. **Inhaled nitric oxide may react with supplemental oxygen to form which of the following cytotoxic oxidants:**
   A. Peroxynitrite
   B. Nitrogen dioxide
   C. Nitrous Oxide
   D. A and B

4. **In a retrospective evaluating the lower limits of desired SpO_2, a lower limit of 70% was found to be associated with a twofold greater incidence of cerebral palsy but a fourfold lowering of retinopathy of prematurity.**
   A True
   B False

5. **Meta-analysis of the combined use of supplemental oxygen and midazolam have concluded that that there is an increased occurrence of severe intraventicular hemorrhage when contrasted with the use of midazolam and morphine.**
   A True
   B False

6. **According to the results of the SUPPORT Study Group, a lower target range of oxygenation (85%-89%) as compared with a higher range (91%-95%) did not significantly decrease the composite outcomes of severe retinopathy or death and it resulted in an increase in mortality and a substantial decrease in severe retinopathy of prematurity among survivors.**
   A. True
   B. False

7. **The STOP-ROP multicenter Study Group found a decreased incidence of progression to threshold retinopathy of prematurity which did not reach significance at the pre-selected P level.**
   A. True
   B. False

8. **In the study by Askie and co-workers evaluating oxygen saturation targets and outcomes in extremely premature infants, there was a significant decrease in normal developmental outcomes with saturation goals of 91%-94% were compared to goals of 95%-98%**
   A. True
   B. False

9. **A likely explanation for the inability of ill preterm infants to tolerate mild hypoxemia is:**
   A. Adverse effects on cerebral oxygenation associated with early PDA closure with indomethacin
   B. Simultaneous adoption of lower tolerated hematocrits in the range of 30% and permission hypotension
   C. The widespread adoption of early caffeine therapy to reduce bronchopulmonary dysplasia
   D. A and B

10. **A useful nursing strategy in assiting NICU nurses to maintain infants within prescribed SaO_2 limits include:**
    A. Reassessing R.N. staffing patterns to permit minute to minute manipulation of FiO_2 and SaO_2 management with prescribed ranges
    B. Having SaO_2 limited prescribed attached to the incubator or warmer to remind all caregivers and the parents of prescribed SaO_2 limits
    C. Careful monitoring of ROP of prematurity trends over specified time periods to determine the impact of strategies to maintain prescribed SaO_2 limits on ROP on specific NICU outcomes and to compare these outcomes with other NICUs
    D. All of the above

Participant's Evaluation

This program has been approved for 1.5 contact hours of continuing education (CRCE) by the American Association for Respiratory Care (AARC). AARC is accredited as an approver of continuing education in respiratory care.

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5. Upon completion, you may print out your certificate immediately. If you are an AARC member, your results are automatically forwarded to the AARC.
6. Accreditation expires Jan. 12, 2017. (RTs) and Jan. 16, 2017 (Nurses)
7. This test can only be taken online. Please go to www.saxetesting.com/init and register. Once the test has been sucessfully completed, you may print out your certificate immediately.

The goal of this program is to educate healthcare professionals on oxygen toxicity in preterm infants.

What is the highest degree you have earned?
Circle one. 1. Diploma 2. Associate 3. Bachelor 4. Masters 5. Doctorate

Strongly Agree 1 2 3 4 5 6 Strongly Disagree

Indicate to what degree the program met the objectives:

1 Discuss appropriate strategies to minimize oxygen free radial injury to the developing eyes, brain, lung, and gastrointestinal tract.
Strongly Agree 1 2 3 4 5 6 Strongly Disagree

2. Describe the effects of oxygen toxicity on the developing nervous system
Strongly Agree 1 2 3 4 5 6 Strongly Disagree

3 Identify the ideal limits for establishing $Sp0_2$ at specific gestational ages and postnatal ages
Strongly Agree 1 2 3 4 5 6 Strongly Disagree

4 Describe the best initiatives to improve staff compliance to prescribed $Sp0_2$ limits
Strongly Agree 1 2 3 4 5 6 Strongly Disagree

5. Please indicate your agreement with the following statement. "The content of this course was presented without bias of any product or drug."
Strongly Agree 1 2 3 4 5 6 Strongly Disagree

Answers

1	A ☐	B ☐	C ☐	D ☐	9	A ☐	B ☐	C ☐	D ☐
2	A ☐	B ☐	C ☐	D ☐	10	A ☐	B ☐	C ☐	D ☐
3	A ☐	B ☐	C ☐	D ☐	11	A ☐	B ☐	C ☐	D ☐
4	A ☐	B ☐	C ☐	D ☐	12	A ☐	B ☐	C ☐	D ☐
5	A ☐	B ☐	C ☐	D ☐	13	A ☐	B ☐	C ☐	D ☐
6	A ☐	B ☐	C ☐	D ☐	14	A ☐	B ☐	C ☐	D ☐
7	A ☐	B ☐	C ☐	D ☐	15	A ☐	B ☐	C ☐	D ☐
8	A ☐	B ☐	C ☐	D ☐	16	A ☐	B ☐	C ☐	D ☐

All tests must be taken online at
http://www.saxetesting.com/init

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