# Oxygen: Too Much of a Good Thing?

An Interactive Case Study

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#### An Interactive Case Study

This review is based on the Mallinckrodt Pharmaceutical-sponsored presentation, "Oxygen: Too Much of a Good Thing?," by Denise Suttner, MD, at the National Association of Neonatal Nurses (NANN) 31st Annual Education Conference held in Dallas, Texas, on October 25, 2015. The presentation featured a case study of a post-term neonate with progressive hypoxic respiratory failure (HRF) associated with pulmonary hypertension (PULM HTN). A total of 198 neonatal nurses and neonatal nurse practitioners (NNPs) were polled during the presentation on various matters relating to the case using an audience response system. Results from this poll and a 2014 poll are discussed.

Neonates discharged from the NICU often face lifelong disabilities.<sup>1,2</sup> Because of the critical nature of the complex physiology, clinicians have a tendency to focus on the immediate impact rather than the long-term consequences of their treatment decisions. Knowing that critically ill newborns often struggle with lifelong disabilities following discharge from the NICU, consideration of long-term effects of therapies is critical for optimizing their outcome.

"Optimizing the quality of life for our critically ill newborns is at the forefront of efforts in neonatology. Recognizing that some therapies we administer may contribute to the neonate's life-long struggles, we are obligated to give critical thought to the appropriateness of their use." —Denise Suttner, MD

#### Support for the Therapeutic Use of Oxygen

Oxygen as a therapy has been administered to more newborns worldwide than any other treatment.<sup>3</sup> The therapeutic use of oxygen is primarily founded on 2 of its physiological effects: 1) oxygen is used by cells to produce the energy required to maintain physiological processes,<sup>4</sup> and 2) oxygen is a potent pulmonary vasodilator.<sup>5</sup>

The requirement of oxygen for aerobic cellular respiration is supported by rigorous scientific evidence. Oxygen is used in mitochondria, cellular organelles, to help generate adenosine triphosphate (ATP)–the universal currency of energy. As shown on the left in Figure 1A, oxygen reacts with 2 electrons and 2 hydrogen ions at the end of the electron transport chain to form water, a neutral byproduct. While limited amounts of ATP can also be produced in the absence of oxygen, aerobic respiration remains the principle energy-producing pathway.<sup>4</sup> The therapeutic use of oxygen as a vasodilator is mostly supported by data from animal studies. Experiments using fetal lambs have revealed that oxygen plays a role in the physiological drop in pulmonary vascular resistance at birth.<sup>6,7</sup> A study in dogs by Haas and Bergofsky provided insight into how pulmonary vasoconstriction modulates ventilation-perfusion (V/Q) matching during hypoxia.<sup>8</sup> Low oxygen environments (occurring during fetal development, for example) and periods of oxygen deficiency (hypoxia) were found to induce a vasoconstrictor response in the pulmonary vascular bed.<sup>6-8</sup> Oxygen can reverse this response by promoting vasodilation, as demonstrated by an in vitro study using pulmonary arterioles from term rat pups and in vivo studies performed in neonatal lambs.<sup>9-11</sup>

"Despite other therapeutic advances, oxygen therapy remains absolutely critical and it will always be an important treatment for our newborns. However, there is solid data proving that excessive oxygen can also be toxic and damage tissue in newborns." —Denise Suttner, MD

#### **Concerns Associated With Hyperoxia Exposure**

Hyperoxia is the presence of higher than normal concentrations of oxygen in a tissue.<sup>4</sup> Hyperoxia is not typically a naturally occurring phenomenon and can happen when high concentrations of supplemental oxygen are administered to the lungs. Several studies in ventilated newborn animals and infants have shown that hyperoxia exposure can cause acute lung injury. Observational studies in newborn pigs and baboons ventilated with room air or high concentrations of supplemental oxygen found significant lung damage in subjects exposed to 0.8-1.0 fraction of inspired oxygen (FiO2) compared with those exposed to room air.<sup>12,13</sup> Early postmortem observational





**Figure 1.** Model depicting the formation of reactive oxygen species (ROS) in cells exposed to normoxia (A) and hyperoxia (B). A) During periods of normoxia, most of the electrons traveling across the electron transport chain help promote ATP production before forming water. Oxygen can strip away electrons during this process to form a superoxide free radical. Superoxide is converted to a less reactive form of ROS, hydrogen peroxide, by superoxide dismutase (SOD). Cells are able to neutralize most of the superoxide and hydrogen peroxide produced during periods of normoxia using SOD, reduced glutathione (GSH), and catalase. Most cells are capable of managing a low basal level of oxidative stress. B) When cells are exposed to periods of hyperoxia, antioxidant defenses (such as SOD, GSH, and catalase) are overwhelmed. Hydrogen peroxide molecules react with metals in a Fenton reaction to form hydroxyl ions, a highly reactive form of ROS that can damage macromolecules. Oxidative stress becomes elevated during periods of hyperoxia.

studies in premature infants ventilated with >0.8 FiO2 for periods ranging from 3 hours to 135 days revealed an association with substantial damage to lung tissue and the pulmonary vasculature.<sup>14-15</sup>

Hyperoxemia is defined as high concentrations of oxygen in the systemic circulation. Since blood distributes oxygen from the lungs to the tissues, exposure to high levels of oxygen can lead to hyperoxemia.<sup>16</sup> Several studies suggest that hyperoxemia may contribute to organ damage and mortality.<sup>17-20</sup> In one retrospective cohort analysis of 139 infants (>37 weeks' gestation) with birth asphyxia, hyperoxemia and/or hypocapnia during the first 120 minutes of life were associated with death or severe neurodevelopmental disability.<sup>17</sup> In another retrospective cohort study of 120 infants (>36 weeks' gestational age) with perinatal acidosis, the incidence of hypoxic ischemic encephalopathy was found to increase with the degree of hyperoxemia measured upon admission.<sup>18</sup>

The oxygen content of blood is a combination of the oxygen carried by hemoglobin (Figure 2: green line), which is found in red blood cells, and the oxygen dissolved in the plasma (Figure 2: dotted blue line). Under normoxic conditions, most of the oxygen carried by blood is bound to hemoglobin, while a small concentration exists in the plasma. The oxygen-carrying capacity of hemoglobin is quickly saturated with increasing concentrations of oxygen. Once the hemoglobin is fully saturated, excess oxygen only serves to increase the amount of dissolved oxygen (Figure 2). Oxygen delivery to the tissues depends on the oxygen content, the cardiac output, and tissue perfusion. Dissolved oxygen contributes only a small fraction of the total blood oxygen content.<sup>21</sup> requirement for aerobic cellular respiration and from its promotion of normal pulmonary vascular tone. Excessive levels of dissolved oxygen offer minimal therapeutic benefit. Results from an oxygen titration study in term lambs demonstrated that pulmonary vasodilation occurs as arterial  $pO_2$  (PaO\_2) levels rise toward a PaO\_2 of 60 mm Hg. High PaO\_2 levels (>60 mm Hg) do not promote further vasodilation.<sup>10</sup> Besides providing marginal therapeutic benefit in reducing a patient's pulmonary vascular resistance (PVR), accumulating evidence suggests that high  $pO_2$ levels can cause harm by promoting cellular production of reactive oxygen species (ROS). High levels of ROS can damage macromolecules and promote cell death.<sup>4</sup>

ROS are reactive molecules and free radicals (chemical species with one unpaired electron) derived from molecular oxygen.<sup>22</sup> Free radicals, like superoxide  $(O_2^{-})$ , are produced in mitochondria when oxygen atoms strip away electrons normally utilized in ATP production.<sup>23</sup> Small quantities of ROS are produced under normoxic conditions but they are effectively neutralized by the combined action of enzymes and antioxidants.<sup>24,25</sup> An enzyme, such as superoxide dismutase (SOD), converts superoxide to less reactive molecules, for example: hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>).<sup>24</sup> Hydrogen peroxide is further neutralized by an antioxidant reduced glutathione (GSH) and/or the enzyme catalase to form water (Figure 1A).<sup>25,26</sup>

Oxidative damage occurs when these antioxidant mechanisms are overwhelmed. During periods of hyperoxia, mitochondria are flooded with oxygen and produce high levels of superoxide that cannot be effectively neutralized.<sup>23</sup> Active superoxide free radicals may chemically alter and damage macromolecules. In addition, excess  $H_2O_2$  can react with metals to form hydroxyl radicals that also cause molecular damage



The therapeutic effects of oxygen stem from its

**Figure 2.** Graph depicting the relationship between hemoglobin saturation (green line), dissolved O<sub>2</sub> (dotted blue line), and the oxygen content (dotted red line) of the blood. Please note that the cutoffs denoting hypoxemia, normoxia, and hyperoxemia are an approximation and not intended to be used as a clinical guide. Adapted from Goldsmith JP, Karotkin E. Assisted Ventilation of the Neonate. 5th ed. Saint Louis, MO: Elsevier Saunders; 2011.

(Figure 1B).<sup>4,27,28</sup> Cells that sustain high amounts of oxidative damage may undergo programmed cell death, or apoptosis, which can lead to tissue and organ injury.<sup>4</sup>

Newborns encounter high levels of oxidative stress at birth, and thus are particularly vulnerable to the effects of hyperoxia.<sup>29,30</sup> Fetuses develop in a hypoxic environment with an intrauterine  $pO_2$  of 20-35 mm Hg.<sup>21,29</sup> At birth, newborns are exposed to the much higher  $pO_2$ of 60-80 mm Hg.<sup>21,31</sup> In one study, newborns were found to exhibit elevated levels of oxidative damage following birth. An analysis of blood from a cohort of 77 full-term, healthy newborns revealed 5-fold higher levels of oxidative stress than those observed in healthy adults. These elevated levels of oxidative stress can persist for up to 6 months following birth.<sup>29</sup>

Supplemental oxygen administration further exacerbates oxidative stress in newborns, as suggested by several animal studies. Analysis of lung tissue from preterm lambs in a persistent pulmonary hypertension in a newborn (PPHN) model revealed elevated levels of oxidative stress in lambs ventilated with 1.0  $FiO_2$ .<sup>11</sup> Analysis of blood and lung tissue from ventilated term lambs showed increased SOD activity in lambs exposed to an  $FiO_2$  of 1.0 compared with lambs exposed to room air.<sup>32</sup> Analysis of brain tissue from 6 day-old newborn rats detected increased lipid peroxidation and cell death in subjects exposed to 100% oxygen compared with room air.<sup>33</sup> These data suggest that ROS may be a contributing factor to the tissue injury observed following hyperoxia exposure.

Hyperoxia exposure may be especially damaging to premature newborns. Animal studies suggest that fetuses develop antioxidant defenses during the last 10-15% of gestation in preparation for the hyperoxic challenge associated with birth.<sup>35-37</sup> The late development of these defenses can adversely affect neonates if they are born prematurely. Analyses of cord blood from 2 cohorts of newborns revealed that cord blood from preterm infants has less antioxidant enzyme activity than cord blood from term infants.<sup>37,38</sup> These data suggest that preterm newborns may have a reduced capacity to manage oxidative stress associated with birth. Moreover, exposure of premature newborns to high levels of supplemental oxygen may further exacerbate the hyperoxic challenge and cause harm.<sup>34,38,39</sup>

When carefully administered, oxygen is a drug that can help support life; however, over-administration of oxygen can have deleterious effects. Here, we present a hypothetical case study of progressive HRF associated with PULM HTN following administration of high concentration of oxygen in the absence of adjuvant therapies. Hyperoxia exposure could have been prevented with a better assessment of tissue oxygenation and early inter-

### Is the Use of Oxygen in the NICU Changing?

"We're coming from a time when patients were managed with 100% oxygen for long periods. Now, we're rethinking the exposure to high levels of oxygen." –Denise Suttner, MD

A comparison of audience responses from 2014 and 2015 revealed that the use of oxygen by neonatal nurses and nurse practitioners may be changing. There was a reduction in the willingness of respondents to administer high concentrations of oxygen (>0.6 FiO<sub>2</sub>) to term and late preterm infants (>34 weeks' gestation) before considering other or additional interventions (Figure 3A). The percentage of respondents willing to administer >0.6 FiO<sub>2</sub> to these patients fell from 38% in 2014 to 14% in 2015 (Figure 3A). Also, the respondents reduced the amount of time that they were willing to administer FiO<sub>2</sub> of 0.6 to term and late preterm neonates (>34 weeks' gestation) before considering other interventions. The percentage of respondents who were willing to keep an infant on a FiO, of 0.6 for more than one hour decreased from 71% in 2014 to 55% in 2015 (Figure 3B). Furthermore, there was a modest increase in respondents who were unwilling to administer a FiO<sub>2</sub> of 1.0, from 14% of respondents in 2014 to 21% of respondents in 2015 (Figure 3C). There was no change in the practices of nurses and nurse practitioners who were willing to administer 1.0 FiO<sub>2</sub> (Figure 3C).

The data from the 2014 and 2015 symposia were combined and subanalyses were performed to determine whether oxygen use differed between types of units (Level 1-2, Level 3A/B, Level 3C [without ECMO], or Level 4 [with ECMO]) or between nurses and nurse practitioners. No differences were found in the pattern of oxygen use between units or between nurses and nurse practitioners (data not shown). ■

Facing page: Figures 3A-C.Graphs illustrating the audience response at the 2014 and 2015 NANN symposia.

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Figures 3A-C.

A. What is the highest Fi0<sub>2</sub> that you administer to term and late preterm infants (>34 weeks' gestation) before considering other or additional interventions?



**B.** How long do you typically permit term and late preterm neonates (>34 weeks')gestation) with HRF/PPHN to remain on a FiO<sub>2</sub> of 0.6 before considering additional interventions?



C. How long do you typically permit term and late preterm neonates (>34 weeks' gestation) with HRF/PPHN to remain on a FiO<sub>2</sub> of 1.0 before considering additional interventions?



#### **Case Study**

A post-term (40-6/7 week) 2.6 kg male infant was born to a healthy, 31-year-old first-time mother. Labor was induced due to poor growth and post-gestational date. A late deceleration occurred just prior to vaginal delivery. The infant required resuscitation at birth using room air. Respiratory distress continued after resuscitation and the right hand pulse oximetry SpO<sub>2</sub> measured 80%. The infant was transferred to the neonatal intensive care unit (NICU).

Noninvasive ventilation was initiated using nasal continuous positive airway pressure (N-CPAP) at a setting of 5 cm  $H_2O$  and the FiO<sub>2</sub> was increased from 0.21 to 0.30. An umbilical artery catheter was placed and an arterial blood gas (ABG) measurement was obtained. The initial ABG reading was: 7.28/50/45/-1. The infant's SpO<sub>2</sub> improved to 85%.

The patient had continued tachypnea and retractions after the first hour of life. In response, the CPAP settings were raised to 7 cm  $H_2O$  and the FiO<sub>2</sub> was increased to 0.50. As a result, the preductal SpO<sub>2</sub> increased to 92%. Another ABG measurement was obtained. The ABG reading was: 7.35/45/45/0. A postductal oximeter was placed on the infant's foot. The postductal SpO<sub>2</sub> measured 84%.

Further assessments of the infant were made after 2 hours of life to facilitate a diagnosis. A chest X-ray showed normal inflation with dark lung fields. A cardiac ECHO was significant for normal structures with right-to-left shunting at the patent ductus arteriosus (PDA) and a flattened intraventricular septum. The UAC  $pO_2$  measured 45 mm Hg and the preductal saturation was 92%. The infant had clear clinical and diagnostic evidence of pulmonary hypertension.

At this juncture, in our 2015 audience, 77% of the nurses reported that they would routinely monitor pre- and post-ductal saturation in this type of patient. Roughly one-third of these respondents (27% of total respondents) would instead rely on an arterial  $pO_2$  measurement from the UAC and an oximetry reading from a pulse oximeter placed in a location determined by themselves or another clinician (data not shown). These data show that neonatal nurses are aware that pre- and post-ductal monitoring of the arterial saturation is an excellent method for continuously estimating the degree of pulmonary

hypertension. Pre-ductal saturation monitoring is also important as this is the oxygen saturation of the blood perfusing the brain and heart muscle.

When asked about how this patient would be treated in their unit, 45% of respondents said that this patient would be intubated and then, if the SpO<sub>2</sub> and arterial  $pO_{2}$  did not improve, adjuvant therapies would be started. Thirty-four percent of respondents would continue with the current strategy and the FiO<sub>2</sub> would be weaned based on the preductal saturation as long as the other markers of oxygen delivery (base deficit, lactate, NIRS, urine output) were reassuring. Only 19% of respondents would increase the FiO<sub>2</sub> (Figure 4A). These data show that there is an increasing movement among neonatal nurses to decrease hyperoxia exposure. Thirty-four percent of respondents are comfortable managing this patient "as is" providing the other markers of oxygen delivery remain reassuring.

In the case study, the FiO<sub>2</sub> was increased to 0.8 to improve oxygen saturation and to treat the pulmonary hypertension. In response to the increased oxygen, the infant's preductal SpO<sub>2</sub> increased from 92% to 96%. Another ABG measurement was obtained. The ABG reading was: 7.35/45/110/0. The postductal saturation increased from 84% to 96%. The general perception (88% of respondents) towards this approach was that the risk of high oxygen exposure was not warranted (data not shown). Interestingly, 82% of respondents who would increase the FiO<sub>2</sub> (Figure 4A) were among this majority. These data highlight that neonatal nurses are aware of the risks associated with oxygen toxicity and are genuinely leery of administering high concentrations of oxygen to neonates.

At this juncture, a poll of the audience revealed that over half of the respondents (54%) would continue to monitor preductal saturation closely, and the FiO<sub>2</sub> would be weaned for a preductal saturation >92%. And 22% of respondents would wean the FiO<sub>2</sub> for a preductal SpO<sub>2</sub> >96%. Only 18% of respondents would intubate the patient and add adjuvant therapies. Finally, 6% would transfer the patient to an ECMO center (Figure 4B). These data highlights that neonatal nurses are motivated to decrease the FiO<sub>2</sub> appropriately when there evidence of adequate oxygen saturation (preductal saturation >92%). A. The patient had clear lungs on chest X-ray, and was on an FiO<sub>2</sub> of .50 by N-CPAP. The preductal saturation was 92%, the postductal saturation was 84%, and the UAC pO, measured 45 mm Hg. What would be the next course of action in your unit? (n=116)



B. The FiQ<sub>2</sub> was increased from .50 to .80 causing the preductal saturation to increase from 92% to 96%, the postductal saturation to increase from 84% to 96%, and the pO<sub>2</sub> to increase from 45 mm Hg to 110 mm Hg. What would be the next course of action in your unit? (n=135)



Figure 4. Graphs illustrating the audience response at the 2015 NANN symposium.

#### Methods for Assessing Oxygen Delivery to Tissue in Neonates

Nurses are trained to view oxygen saturation readings below 92% as dangerous, and these views are often reinforced with oximeter alarms warning clinicians of a low saturation. Clinicians often respond to a perceived hypoxic challenge by administering more oxygen. The use of oxygen in some of these situations may not always be warranted.

The oxygen content of the blood does not always reflect the oxygen delivery to tissues. The measurement of oxygen content can be done by pulse oximetry; however, this does not differentiate between degrees of hyperoxia. Blood gas measurements can provide insight into ventilation/perfusion (V/Q) matching and the adequacy of alveolar ventilation. However, neither of these methods elucidate how well oxygen is delivered to the systemic vascular bed and peripheral tissues.<sup>40</sup> There are other methods that nurses can use to better assess oxygen delivery so that oxygen is only administered when it is necessary (Figure 5).

One indicator of poor oxygen delivery is the presence of high levels of lactate in the blood. In the absence of oxygen, ATP is generated anaerobically through the metabolism of glucose to pyruvate. Pyruvate is metabolized to lactic acid, and lactic acid is buffered by serum proteins, hemoglobin, and bicarbonate in the arterial blood. The buffering of lactic acid in the blood is accompanied by increases in the base deficit and the accumulation of lactate (the neutralized form of lactic acid).<sup>39</sup> Base deficit and lactate measurements are routinely obtained as part of an ABG panel. An analysis of 278 serial simultaneous ABG measurements from 75 mechanically ventilated neonates with indwelling arterial catheters (median gestational age 29 [23-40] weeks, median birthweight 1340 [550-4080] g) suggested that blood lactate concentrations provide an early warning signal for deterioration or a complication in ill, ventilated neonates. Infants with the highest lactate measurements (>5 mmol/l) had the highest mortality (57%). Moreover, clinically significant elevations of lactate often preceded worsening conditions.<sup>40</sup> Obtaining serial lactate measurements with routine ABG sampling can provide insight into oxygen delivery and may also serve as an early warning sign of physiological decline.

Oxygen delivery can also be assessed by measuring urine output and performing a thorough physical examination of the infant. Normal urine output is between 1-2 mL/kg/



Figure 5. Methods for assessing oxygen delivery in a neonate.

hr. Reduced urine output is indicative of poor cardiovascular health and reduced kidney function. A decrease in spontaneous activity and signs of poor perfusion (cyanosis, capillary refill, fontanelle fullness, peripheral pulses) can also suggest poor oxygen delivery.<sup>41-43</sup>

Near infrared spectroscopy (NIRS) is a novel noninvasive method of directly measuring the oxygenation of tissues. Similar to pulse oximetry, NIRS measures light-absorbance differences between oxygenated and deoxygenated hemoglobin in tissue.<sup>39</sup> It can be used to measure cerebral blood flow, cerebral blood volume, and peripheral oxygen consumption.<sup>44</sup> NIRS slowly becoming integrated into routine clinical practice. If available, it can provide the clinician with an accurate, real-time measurement of tissue oxygenation.<sup>39</sup>

Assessing a patient's oxygenation is a multifactorial process. The more information a clinician has to draw upon, the more confidence he/she will have in the assessment. Utilization of multiple resources is essential to determining the proper level of oxygen supplementation for a patient over the course of treatment.

ventions to improve oxygenation without increasing the  $\mathrm{FiO}_{\mathrm{2}}.$ 

"Unintended hyperoxia can be prevented with careful assessment of oxygen delivery to patient tissues. You have to think about those adjunctive therapies and whether these should maybe be administered earlier than you would have done 10 or 15 years ago."-Denise Suttner, MD

**Recommendations for Reducing Supplemental Oxygen** 

At one juncture of the case study, the patient was treated with N-CPAP at a setting of 7 cm H<sub>2</sub>O and a FiO<sub>2</sub> of 0.5, yet his preductal saturation remained at 92%, his postductal saturation was 84%, and his UAC pO<sub>2</sub> measured 45 mm Hg. In a poll of the audience, 45% of the respondents would intubate this patient and if the SpO<sub>2</sub> and arterial pO<sub>2</sub> did not improve, would have started adjuvant therapies (Figure 4A). In the actual case, a decision was made to inappropriately increase the FiO, to 0.8 in an effort to increase the patient's oxygen saturation and treat the pulmonary hypertension. As a result of this action, the patient's preductal SpO<sub>2</sub> increased from 92% to 96%, the postductal saturation increased from 84% to 96%, and UAC pO<sub>2</sub> increased to 110 mm Hg. When the audience was again polled on their next action for the patient (Figure 4B), only 31% of the respondents who initially supported intubation and use of adjuvant therapies chose the same answer at this stage of case study (data not shown). At this point 76% of respondents chose to wean the patient from the high concentration of oxygen (Figure 4B). Importantly, the

principle concern of most of the audience focused on the toxic concentration of oxygen that was now being administered.

Neonatal nurses face these types of decisions every day. Early efforts to reduce hyperoxia exposure may prevent neonates from enduring periods of oxidative stress.

Increased exposure to supplemental oxygen can be prevented in several ways (Figure 6). Adjusting the ventilator settings to optimize the mean airway pressure (P<sub>aw</sub>) can improve oxygenation without increasing the FiO<sub>2</sub>. Other methods for improving oxygenation in neonates involve the use of exogenous surfactant therapy or inhaled pulmonary vasodilators.<sup>45, 46</sup> Surfactant therapy has been shown to promote rapid improvement in oxygenation and decrease the requirement of ventilatory support.<sup>45</sup> Inhaled pulmonary vasodilators also improve oxygenation in neonates with pulmonary hypertension, albeit through a different mechanism.<sup>46</sup>

#### Discussion

A long-term follow-up (mean age 7.1 years) study of 109 patients treated for PPHN as neonates revealed an association of respiratory and neurological morbidities when evaluated later in life.<sup>47</sup> Twenty-four percent of this population exhibited respiratory problems (primarily reactive airways disease). Sixty percent of patients had abnormal chest radiographs with hyperexpansion and/or changes consistent with chronic lung disease. Twenty-six percent of patients required at least one rehospitalization since discharge. Twenty-eight percent of patients used chronic medications, mostly for reactive airways disease



Figure 6. Model outlining the risks and benefits of increasing or decreasing oxygen exposure.

or allergies. Of the 108 patients who underwent cognitive and behavioral testing, 9.2% of patients exhibited severe neurocognitive disability and 7.4% of patients suffered a moderate intellectual disability.<sup>47</sup> While these patients are clinical success stories after having survived a serious illness very early in life, their lifelong disabilities highlight the importance of using treatment strategies that leave the smallest long-term footprint. Accumulating evidence suggests that reducing hyperoxia exposure may be one opportunity to help these patients.

Several strategies can be employed to reassure clinicians that a patient is adequately oxygenated, even at the low end of an oxygen saturation target range (Figure 5). In addition, there are several ways to improve oxygenation without administering more oxygen (Figure 6). Polling data from the NANN symposia in 2014 and 2015 suggest that nurses are using oxygen more conservatively than before. However, 1.0 FiO<sub>2</sub> is still being used in the NICU (Figures 2A and 2C). While more human studies are required to definitively prove that hyperoxia is detrimental to newborns, the breadth of evidence in animals support this hypothesis. Oxygen is a drug that has therapeutic value when used in moderation. Potential harm arises when tissues are exposed to hyperoxia. Hyperoxia induces oxidative stress and damages tissue. Newborns have high basal levels of oxidative stress associated with birth. Hyperoxia exposure from oxygen supplementation only adds to these inherent levels of stress. Efforts to prevent newborns from encountering periods of hyperoxia may help reduce the long-term footprint of treatment without impacting the short-term clinical goal of survival.

#### **Additional Resources**

For more information on oxygen toxicity, please visit: http://www.oxygenisadrug.com.

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