RETINOPATHY OF PREMATURITY: THE EFFECTS
OF OXYGEN SATURATION TARGETS
IN AT-RISK NEONATES

by
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ABSTRACT

Retinopathy of prematurity (ROP) is a potentially blinding disorder, known to be associated with preterm birth, low birth weight, and the use of oxygen. An optimal oxygen saturation range of 85-93% is often targeted to minimize the risk of either hypoxia or hyperoxia. Yet maintaining premature infants within the targeted range can be difficult. Many infants spend significant amounts of time both above 93% and below 85%. The potential effect of this time out of the targeted range on the development of ROP and the risk of death is unknown. Using a longitudinal, retrospective, descriptive design, weekly 24-hour histograms of saturation levels were collected during a three year period for each infant at risk for ROP from the time of admission for each infant and coded for the percentage of time spent >93% or \( \leq \) 85%. Data were entered longitudinally until retinal maturity/ROP occurred (N=241ROP study) or until death/discharge (N=250 survival study). Infants were excluded from both studies if ROP was present prior to admission, or death/discharge occurred without an eye exam or data collection. Survival analysis using a discrete-time hazard model was used to explain the risk of developing ROP (Stage 1 or \( \geq \) Stage 2) or death, associated with the time above and below the targeted range, controlling for the effects of gestational age and birth weight using logistic regression. All models included a cubic time trend to reflect the average change in probability of developing ROP, or a quadratic time trend for the risk of death. For every 2.7% of the time the infant spent \( \leq \) 85%, the risk for ROP increased by 48
(p<0.038), and the risk of death increased by 11% (p<.001). The percentage of time an infant spent >93% decreased their risk of ROP and death. For every 10% of time spend >93%, the risk of ROP decreased 21%, and the risk of death decreased 11%. These data raise concerns about the appropriateness of current saturation targets. The upper limit of time for saturations >93% to be beneficial remains unknown and needs further research.
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CHAPTER 1

INTRODUCTION

Retinopathy of prematurity (ROP) is a disorder of retinal blood vessel development and is the second-leading cause of childhood blindness in the United States (Wheatley, Dickinson, Mackey, Craig, & Sale, 2002b). The National Center for Health Statistics report listed the incidence of infants born at risk for developing this eye disease (≤32 weeks gestation) as 2% of all live births. In 2008, 84,224 babies were born at or less than 32 weeks gestation in the United States (Peristats, 2012). The National Eye Institute has estimated that 14,000-16,000 of these infants are affected by some degree of ROP, and that 1,100-1,500 infants in the U.S develop ROP that is severe enough to require medical treatment on an annual basis. Of these, 400-600 become legally blind from ROP each year (National Eye Institute (NEI), 2010).

ROP was first associated with oxygen supplementation in premature infants in the 1940s. At that time, researchers noted the association between higher oxygenation and the development of abnormal vascular growth in the eye (Campbell, 1951). The disease process is biphasic, with an initial phase of vessel growth retardation from birth to approximately 30-32 weeks postmenstrual age, followed by a second phase of hypoxia-induced retinal vessel proliferation that begins around 32-34 weeks postmenstrual age (M. Chen et al., 2011).

The role of oxygen in the development of ROP has led to clinical management
setting lower and tighter oxygen saturation ranges commonly with a targeted range of 85-93% for at-risk premature infants, in order to decrease the risk for the development of ROP. While a number of studies have reported a decreased incidence of ROP by using lower saturation targets (Carlo et al., 2010; Chow, Wright, & Sola, 2003; J. P. Goldsmith & Greenspan, 2007; Greenspan & Goldsmith, 2006; Hagadorn et al., 2006; Hay & Bell, 2000; Johnston et al., 2011; Vanderveen, Mansfield, & Eichenwald, 2006), the evidence supporting this strategy is limited, and concern has been raised following the results of two large, multicenter, randomized control trials: SUPPORT and BOOST-II. These trials showed increased mortality in infants maintained with lower oxygen saturations of 85% to 89% versus higher ranges of 91% to 94% (Carlo et al., 2010; B. Stenson, Brocklehurst, & Tarnow-Mordi, 2011). Despite these results, the optimal target saturation to provide the best overall outcome for these infants remains unclear. The biphasic disease process, as well as concern for increased mortality, has led some clinical practices to adjust targeted oxygen saturations as the affected infants’ postmenstrual ages increase, and each individual’s eyes mature.

Oxygen targeting assumes that an individual infant can be maintained within the set target range. However, every newborn intensive care (NICU) nurse knows that this can be very challenging, with some infants’ saturations frequently above or below the targeted range. No one has reported the impact of the time the infant spends out of the targeted range on normal retinal development, as well as the development of ROP. Additionally, a number of infants are given respiratory support in the form of nasal cannula flow, continuous positive airway pressure (CPAP) or mechanical ventilation at 21% oxygen, the equivalent of room air (RA). Likewise, none have defined the optimal
hemoglobin oxygen saturation target for this population, leaving concern that high oxygen saturation while on 21% oxygen with increased flow could contribute to the development of ROP.

The purpose of this retrospective, longitudinal research study was to evaluate whether the development of ROP can be explained by the average percentage of time in a 24-hour period that the infant spends out of the targeted oxygen saturation range in the weeks prior to the development of ROP or retinal maturity. Additionally, the effects of higher oxygen saturation targets while an infant is receiving 21% oxygen was evaluated to determine whether this increases the risk of developing ROP. Finally, the study addressed whether death before discharge can be explained using the average percentage of time during 24 hours that the infant spends out of the targeted oxygen saturation range.

This study can lead to a better understanding of the effects of time spent in varying ranges of hemoglobin oxygen saturation upon neonatal mortality, as well as the important neonatal morbidity of ROP. This can lead to new approaches in clinical management of oxygen treatment for premature newborns.

**Specific Aims and Research Questions**

The study used an observational, retrospective, and longitudinal design, tracking standard practice in a level IV referral center NICU. Weekly 24-hour histogram reports, generated from the Phillips IntelliVue™ Monitor detailing individual patient oxygen saturation levels, were collected and evaluated for the percentage of time the infant spent above and/or below a targeted saturation of 85% and 93%. Multinomial logistic regression was used to evaluate nested patient data of at-risk infants cared for at Primary
Children’s Hospital, a free-standing children’s hospital, over a 3-year period. This research investigation/study addressed three specific study aims:

- **Specific Aim 1**: To evaluate the relationship that time out of targeted saturation range has on the development of ROP.
  
  - **RQ2.1**: Can the development of ROP be explained by the average 24-hour time out of targeted oxygen saturation range in the weeks prior to the development of ROP?
  
  - **RQ2.2**: Is there a relationship between the percentage of time the infants’ saturations are above the targeted oxygen saturation and the development of ROP?
  
  - **RQ2.3**: Is there a relationship between the percentage of time the infant saturations are below the targeted oxygen saturation and the development of ROP?

- **Specific Aim 2**: To evaluate the effect of allowing higher hemoglobin oxygen saturation targets on the development of ROP when the infant is breathing 21% oxygen.
  
  - **RQ1.1**: Do high oxygen saturations while breathing 21% oxygen increase the risk of ROP as compared to lower targeted saturation ranges for infants on greater than 21% oxygen?

- **Specific Aim 3**: To evaluate the relationship that time out of targeted saturation range has on the risk of death before discharge.¹

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¹ The original Aim 3 was to evaluate the relationship between the ability to achieve targeted saturation range and the time needed to reach mature retinal development. When the time out of saturation range was found to be a significant risk in the development of ROP, the third aim was changed from a prediction of retinal maturity to an explanation of death before discharge.
o RQ3.1: Can the risk of death be explained by the average percentage of time during 24 hours spent out of the targeted oxygen saturation range?

o RQ3.2: Is there a relationship between the percentage of time the infant saturations are above the targeted oxygen saturation and risk of death?

o RQ3.3: Is there a relationship between the percentage of time the infant saturations are below the targeted oxygen saturation and risk of death?

**Significance**

Even with a defined oxygen saturation range established, maintaining this range can be difficult, due to the frequent saturation fluctuations of a sick, premature infant. Despite multiple reports looking at the impact of oxygen saturation targets on the development of ROP, no report has examined the impact that failure to achieve oxygen targets may have on the development of this disease. Given the current practice of targeting specific ranges of oxygen saturations, it would be of significant interest to those caring for these infants to define the impact of the time an infant spends out of the targeted saturation range on the development of ROP, and whether time out of range can help explain increased risk for developing ROP. Understanding the impact of time out of targeted range due to hypoxia and/or hyperoxia on the development of ROP and infant survival will help in developing strategies for managing these infants. Additionally, defining the impact of higher oxygen saturation ranges for infants receiving 21% oxygen will be important in future management decisions for this patient population. Perhaps the targeted range for oxygen saturation is not as important as the ability to maintain saturation stability, resulting in a reduction in the amount of time an infant is out of this
range. The results of this study can help guide in the management of patients at risk for ROP by identifying or allaying concern for additional risk factors in the development.
References


CHAPTER 2

BACKGROUND AND LITERATURE REVIEW

Retinopathy of prematurity (ROP) is a potentially blinding disorder, caused as abnormal new blood vessels develop in the immature retina. It is the number one cause of blindness in infancy, and the second-leading cause of childhood blindness in the United States (Wheatley et al., 2002b). In 1942, an ophthalmologist from Boston, Theodore Terry, was the first to recognize a previously-undocumented form of blindness in children born prematurely and of low birth weight. He named the condition “retrolental fibroplasia,” based on an eye examination finding that showed a white fibrous mass behind the lens, obliterating the retinal vessels (Fisher, 1956; James & Lanman, 1976). The name was later changed in 1984 by consensus of an international group of pediatric ophthalmologists to retinopathy of prematurity (The Committee for the Classification of Retinopathy of Prematurity, 1984).

Despite efforts to thwart the development of ROP since its initial recognition by Terry, ROP continues to pose a challenging problem in the care of premature infants. The National Eye Institute estimates that 14,000 - 16,000 infants born in the United states will develop some degree of ROP annually (National Eye Institute (NEI), 2010).

ROP, as the name suggests, is a disease of prematurity, due to an interruption in the development of the immature retina. Once vascularization of the retina is complete, the vessels are no longer susceptible to injury at birth (S. Lee, 1999). Fortunately, the vast
majority of infants that develop ROP self-resolve without treatment, but an estimated 6-9% progress and need treatment (Early Treatment For Retinopathy Of Prematurity Cooperative Group, 2003). Unfortunately, this means 400-600 infants will become legally blind from ROP each year (National Eye Institute (NEI), 2010), despite treatment intended to avoid this outcome (Cryotherapy for Retinopathy of Prematurity Cooperative Group, 1996).

**Normal Retinal Development**

The vascular supply for the retina consists of two main parts: 1) the choroidal vessels that underlie the retina and 2) the retinal vessels that serve the inner retina. Vascular development for the choroid is complete by 22 weeks gestation (McLeod, Hasegawa, Prow, Merges, & Lutty, 2006). The choroid provides nutrition through diffusion to the early retina. The choroidal vessels are permeable, with a high venous PaO2. They lack the ability to autoregulate in response to hyperoxia. Therefore, during times of hyperoxia, PaO2 levels rise across the thickness of the retina, and the retinal vessels respond by constricting (Madan & Good, 2005). As the retina matures, there is little change in the choroid blood supply, despite the high rate of growth and development in the retina during mid to late gestation. As a result, the retina requires its own vascular supply for adequate nutrition (Quinn, 2004). Normal retinal vascular development begins at the optic disc at about 16 weeks gestation, through a process of vasculogenesis. Vasculogenesis is the *de novo* development of vasculature, involving the proliferation, differentiation and organization of blood vessels from endothelial progenitors known as angioblasts (McLeod et al., 2006). To accomplish vasculogenesis, circulating angioblasts develop early retinal vessels in the region surrounding the optic
nerve. Angiogenesis then proceeds to extend the retinal vasculature to the periphery by 36-40 weeks gestation, through formation of new blood vessels from existing vessels (Harrell & Brandon, 2007; Mintz-Hittner, 2011).

The developing retinal vessels reach only 70% of the distance from the optic disc to the periphery by 27 weeks gestation (Madan & Good, 2005). Retinal vascular development is ideally accomplished while the fetus is in the womb in a relatively hypoxic environment where the average PaO2 is 25-35, the infant’s red blood cells have fetal hemoglobin with an increased oxygen affinity (Blackburn, 2012) and the fetus has lower metabolic demands (Quinn, 2004).

The retinal vasculature is comprised of two laminar but interconnected layers: the primary superficial layer and the ganglion cell layer, which lies deeper in the retina. The layers are joined by fine capillaries (Hughes, Yang, & Chan-Ling, 2000). Vasculogenesis in the retina is believed to be responsible for early vessel formation in the inner plexus but is not responsible for vessel formation in the temporal and peripheral regions of the human retina (Hughes et al., 2000). The formation of the primary vascular layer in the retina is intimately associated with the development of cells in the nerve fiber/ganglion region, known as astrocytes (Garino, 2010; Stone et al., 1995). Astrocytes are glial cells that give biochemical support to endothelial cells, sense physiologic hypoxia and express vascular endothelial growth factor (VEGF) to promote vascular growth (Hartnett, 2010b). VEGF is one of the most important factors in vascular development and is associated with pathologic retinal angiogenesis (Hartnett, 2010b; Mintz-Hittner, 2011; Smith, 2003). Astrocytes emerge from the optic nerve and migrate just ahead of the developing vascular network (Dorrell, Aguilar, & Friedlander, 2002). This places them in a position to
respond to different levels of oxygen, from hypoxia to hyperoxia, in the still avascular areas of the retina (Chan-Ling, Gock, & Stone, 1995; Quinn, 2004; Stone et al., 1995). Astrocytes are present only in retinas in which retinal vasculature forms and is restricted to the inner layer of retina, allowing them to respond to hypoxia of the inner layers by expressing VEGF, which is essential to induce the formation of the superficial layer of blood vessels (Raghuveer & Bloom, 2011; Stone et al., 1995). The normal formation of retinal vessels depends on a period of physiologic hypoxia in order to stimulate the release of VEGF by the astrocytes (Chan-Ling et al., 1995; Forsythe et al., 1996; Levy, Levy, Wegner, & Goldberg, 1995; Quinn, 2004). Hyperoxia will inhibit new blood vessel formation by down-regulating VEGF expression by the astrocyte (Pierce, Foley, & Smith, 1996; Stone et al., 1995). This down-regulation may delay natural retinal development. When a fetus is delivered prematurely, the normal processes of the developing retinal vascular bed that will nourish the eye are interrupted, due to the change in the infants’ oxygen environment.

Insulin-like growth factor (IGF-1) is another key factor in retinal development. It is believed to regulate retinal neovascularization through control of VEGF activation. Studies have demonstrated a permissive role for IGF-1 in new blood vessel formation, as it allows maximum VEGF stimulation of new vessel growth. Low levels of IGF-1 inhibit vessel growth, despite the presence of VEGF (Hellstrom et al., 2003; Hellstrom et al., 2001; Smith et al., 1999a). IGF-1 is supplied to the fetus from the placenta and amniotic fluid. Premature birth causes IGF-1 levels to fall, due to loss of this environment (Smith, 2003).
Pathogenesis

When an infant is delivered prematurely, retinal development must continue in an altered environment, creating a risk for developing ROP. The infant’s retina becomes hyperoxic relative to the fetal environment (even in room air), leading to decreased levels of VEGF, and, for a time, vasculogenesis is halted between the vascular and avascular retina, increasing the risk for developing ROP (Mintz-Hittner, 2011; Niranjan, Benakappa, Reddy, Nanda, & Kamath, 2012). Additionally, IGF-1 levels fall from in-utero levels after birth, due to the loss of IGF-1, which had been provided by the placenta and amniotic fluid (Smith, 2003). The disease process for the development of ROP is biphasic, with an initial phase of vessel growth retardation, followed by a second phase of vessel proliferation.

Phase I

The first phase of ROP has been described as the hyperoxia-vasocessation phase (Reynolds, 2001). It occurs from birth to postmenstrual age of 30-32 weeks (M. Chen et al., 2011). When a premature infant with very low birth weight is born, the infant has very immature lungs and rapidly becomes cyanotic. The medical response is to provide increased amounts of inspired oxygen, measured as the fraction of inspired oxygen (fiO2). Under conditions of low retinal metabolic demand, this creates relative retinal hyperoxia. Production of VEGF may be inhibited by high levels of supplemental oxygen the infant may receive in the NICU, increasing the arterial paO2, which causes cessation of normal retinal growth and vessel constriction, with a potential for vaso-obliteration of new immature vessels. This may cause subsequent death of vascular endothelia cells (Ashton, Ward, & Serpell, 1953; Chow et al., 2003; Mintz-Hittner, 2011; Patz, Eastham,
Higginbotham, & Kleh, 1953; Patz, Hoeck, & De La Cruz, 1952; Pierce et al., 1996; Reynolds, 2001). Additionally, in utero, the fetus receives insulin-like growth factor (IGF-1) via the placenta, which ceases at the time of birth. After birth, the preterm infant <32 week’s gestation is predisposed to Phase 1 ROP, due to: 1) an inherent lack of normally-developed vessels (Harrell & Brandon, 2007); 2) low IGF-1, which is suppressed by poor nutrition, poor weight gain, sepsis and acidosis; and 3) a low level of VEGF needed for endothelial cell survival, suppressed by the low level of IGF-1 (Hellstrom et al., 2001). In preterm infants with prolonged low serum levels of IGF-1 and slow weight gain, there is also an increased risk of ROP (Hellstrom et al., 2003). As the infant matures, the nonvascularized retina endures increasing metabolic activity, leading to tissue hypoxia. This hypoxia promotes increasing levels of VEGF along with increasing IGF-1 to a critical level, which then triggers retinal neovascularization, progressing to Phase II ROP (Hellstrom et al., 2001).

Phase II

The second phase of ROP is the relative hypoxia-revascularisation phase. It is characterized by a progressive increase in metabolic activity in the nonvascularized retina, resulting in an hypoxia-induced retinal neovascularization. This phase begins around 32-34 weeks postmenstrual age (J. Chen, Stahl, Hellstrom, & Smith, 2011). Prior to 32 weeks gestation, the retina is very immature, with photoreceptors that are not yet fully functional, and the retinal metabolic demand is low (A. T. Johnson et al., 1985). As the retina matures, there is an increased metabolic demand and oxygen consumption, creating relative retinal hypoxia (Reynolds, 2001; Saugstad, 2006). Hypoxia stimulates the up-regulation of pro-angiogenic growth factors, such as vascular endothelial growth
factor (VEGF) and erythropoietin, which, in severe cases, lead to uncontrolled vascular growth in the vitreous (M. Chen et al., 2011; Smith, 2003). The shift in retinal tissue oxygenation may be exacerbated by weaning from oxygen therapy, and potentially worsened by targeting low oxygen saturation levels, although that is not required for initiation of vaso-proliferation. Phase II ROP does not proceed with a gradual transition from avascularized to vascularized retina, but rather, a demarcated ridge line develops along the retina, separating the central vascularized region of the retina from the peripheral avascular region. This structure histologically consists of mesenchymal and endothelial cells (York, Landers, Kirby, Arbogast, & Penn, 2004). Vascular development from this stage may resume without significant disruption, or it may progress to significant ROP, as seen by an abnormal proliferation of retinal vessels into the vitreous and over the surface of the retina (Olitsky, Hug, Plummer, & Stass-Isern, 2011). The new vessel growth is abnormal, producing capillary networks that are fragile, leaky and poorly perfused. These new vessels fail to alleviate tissue hypoxia, leading to persistent growth of these abnormal vessels (Mintz-Hittner, Kennedy, & Chuang, 2011).

The two-phase description of ROP pathophysiology is based on research performed on mouse models using sustained exposure to high levels of inspired oxygen. Their experience is similar to what preterm infants were likely to have received when ROP was first described in the 1940s before the development of the ability to monitor and regulate oxygen levels (Hartnett, 2010b). This model uses high levels of inspired oxygen, exceeding the current management of preterm infants. The mouse is then returned to room air, unlike a premature infant, who is monitored to maintain saturations
in a targeted range with variable oxygen delivery and minute-to-minute fluctuations in transcutaneous oxygen levels (Cunningham, Fleck, Elton, & McIntosh, 1995).

In 1994, John Penn proved that exposure to variable hyperoxia was more likely to produce proliferative retinopathy in newborn rats than exposure to constant hyperoxia. He utilized a model that fluctuates inspired oxygen between 50% and 10% every 24 hours for 14 days (Penn, Henry, & Tolman, 1994). These oxygen extremes in the rat produce rat arterial oxygen levels similar to the transcutaneous oxygen levels measured in today’s preterm infants with severe ROP (Cunningham et al., 1995).

Early exposure of the retina to hypoxia and ischemia exacerbates delayed retinal development in premature infants, in part due to low levels of local and systemic growth factors, including IGF-1. VEGF production within the retina occurs in response to relative hypoxia but is unable to trigger angiogenesis in the absence of adequate IGF-1. Over time, postnatal levels of IGF-1 recover and reach a critical threshold, and VEGF-induced angiogenesis is triggered, contributing to the occurrence of ROP (Kong, Mintz-Hittner, Penland, Kretzer, & Chevez-Barrios, 2008; Mintz-Hittner, 2011; Mintz-Hittner & Kuffel, 2008; Smith, 2003).

The exact etiology of ROP is not completely understood, and many factors appear to contribute to the pathogenesis and progression of the disease. Prematurity, genetic predisposition, oxygen, hypoxia, ischemia, insulin-like growth factor 1 (IGF-1) and VEGF all have proven important in the development of ROP (Hellstrom et al., 2003). Severity of illness, acidosis, blood transfusions and ambient light have also been associated with ROP (Madan & Good, 2005). However, the degree of prematurity itself remains the most significant risk factor, with the avascular retina of premature babies.
creating the highest risk (Akkoyun et al., 2006; Smith, 2003). High oxygen saturations, oxygen fluctuation and hypoxia are known to significantly contribute to the development of ROP (Akkoyun et al., 2006; M. Chen et al., 2011; Chow et al., 2003; Hellstrom et al., 2010; Sapieha et al., 2010; The STOP-ROP Multicenter Study Group, 2000; Vanderveen et al., 2006; Wallace, Veness-Meehan, & Miller, 2007)

**Discovery of the Association of Oxygen Therapy and ROP**

ROP was first associated with prematurity in the 1940s, and then with oxygen supplementation in premature infants in the 1950s (Campbell, 1951; J. Chen et al., 2011; Fisher, 1956; Patz, 1957a). In 1942, Terry, an ophthalmologist from Boston, was the first to recognize and name the previously un-described form of blindness in children born prematurely and of low birth weight, calling it retrolental fibroplasia (Fisher, 1956; James & Lanman, 1976).

In 1951, an Australian pediatrician, Kate Campbell, suggested that ROP, or as it was known at that time, retrolental fibroplasia (RLF), was a result of the toxic effects of uncontrolled oxygen administration given to premature newborns, and suggested avoiding routine administration of oxygen to this population, thereby reserving its use for infants experiencing cyanosis (Reedy, 2004). Subsequent studies in the 1950s demonstrated a causal association between premature newborns exposed to high concentrations of supplemental oxygen therapy and obliterated retinal blood vessels (James & Lanman, 1976).

Following these studies, the use of oxygen was severely curtailed and restricted only to cyanotic infants, at concentrations not to exceed 40% (Reedy, 2004). As a result, the incidence of ROP, or RLF, as it was known at that time, declined in the United States,
from 50% in 1950 to 4% by 1965; however, this decline was accompanied by an increase in neonatal deaths and cerebral palsy in the same time period (Pollan, 2009; Wheatley et al., 2002b). Resurgence in the rates of ROP occurred in the late 1970s and 1980s, despite careful monitoring of oxygen delivery to neonates. This is believed to be due to advances in neonatal care which significantly increased the survival of very preterm infants at greatest risk for developing ROP (J. Chen et al., 2011; Wheatley et al., 2002b).

Today, rather than finding consistently high inspired oxygen at birth as the leading cause of ROP, it is recognized that fluctuations in transcutaneous oxygen levels are also important risks for severe ROP in both clinical and animal studies (Chow et al., 2003; Cunningham et al., 1995; McColm et al., 2004; Penn et al., 1994; Saito et al., 1993; Tin, Milligan, Pennefather, & Hey, 2001b; York et al., 2004). Studies by Penn et al. report that fluctuating oxygen was more damaging than constant exposure, even when the cumulative oxygen delivered to the rat pups measured less. Indeed, the degree of fluctuation positively and strongly correlated with the extent of retinal vascular pathology (Penn et al., 1994; Penn, Henry, Wall, & Tolman, 1995; Penn, Tolman, & Lowery, 1993). These fluctuations in oxygen are proposed to cause fluctuations in retinal oxygenation and may be secondary to changes in both inspired and blood oxygen concentration resulting from episodes of bradycardia and apnea of prematurity (Hartnett, 2010a).

In 1984, an international group of 23 pediatric ophthalmologists from 11 countries formed a consensus statement defining the disease process formerly known as RLF, as the International Classification of Retinopathy of Prematurity (The Committee for the Classification of Retinopathy of Prematurity, 1984). This classification has been updated
two additional times, in 1987 and 2005 (The International Committee for the Classification of the Late Stages of Retinopathy of Prematurity, 1987).

**Classification of ROP**

ROP is classified first, by the location of the lesion of abnormal vascular development relative to the optic nerve (Zone); second, by the degree of abnormality (Stage); third, by the presence or absence of dilated and tortuous posterior pole vessels (plus disease); fourth, by the extent of the disease (clock hours); and fifth, by retinal sequelae as the disease involutes.

**Zones**

There are three zones which describe the extent of retinal vascular development. Zone I is the area immediately surrounding the optic nerve and macula, extending from the disc to twice the distance between the disc and the macula. It has the highest risk for development of scar formation, significant visual impairment, and retinal detachment. Zone II is a ring concentric to Zone I, which extends to the nasal ora serrata (the edge of the retina on the side of the eye toward the nose), and may develop lesions that can progress to the above-mentioned significant sequelae. Zone III is the remaining crescent of retina on the temporal (toward the temple) side, and carries the lowest risk of a poor outcome from severe ROP. (International Committee for the Classification of Retinopathy of Prematurity, 2005).

**Stages**

Five stages of abnormal vessel development have been identified in ROP to describe its severity, ranging from mild (Stage 1) to severe (Stage 5). Stage 1 is
characterized by a line of demarcation between the normal retina nearer the optic nerve and the nonvascularized retina peripherally. Stage 2 includes a ridge of scar tissue with both height and width that arises in the region of the demarcation line. Stage 3 is defined as severely abnormal blood vessel growth when the vessels grow through the ridge toward the center of the eye (intravitreous), instead of following their normal growth pattern along the surface of the retina. This is the stage when most treatments occur. Stage 4 includes severe abnormal vessel development with a partial retinal detachment. Stage 4 is divided between Stage 4A, where the detachment does not include the macula, and the vision may be good, and Stage 4B, with macula detachment and a marked decrease in vision potential. Stage 5 is complete retinal detachment, usually with the retina pulled into a funnel-shaped configuration by the fibrovascular scar tissue. Eyes with Stage 5 ROP usually have no useful vision, even if surgery is performed to repair the detachment (International Committee for the Classification of Retinopathy of Prematurity, 2005; National Eye Institute (NEI), 2009)

Plus Disease

Plus disease implies increased venous dilation and arteriolar tortuosity of the posterior retinal vessels near the optic nerve. It also includes the growth and dilation of abnormal blood vessels on the surface of the iris, the rigidity of the pupil and vitreous haze. The diagnosis of plus disease is usually based on the appearance of the vessels near the optic nerve, as compared with standard retinal photographs. The presence of plus disease indicates a more fulminant or rapidly progressive course. Rush disease is the term used to define Zone I ROP in a patient who also has plus disease. Patients with rush
disease tend to have a poorer prognosis than other patients with ROP (International Committee for the Classification of Retinopathy of Prematurity, 2005).

Extent

The extent of the abnormal vascular involvement of the retina is defined by clock hours. The eye is marked as a clock with a total of 12 hours per eye. The extent of the ROP is described by how many clock hours of the retina are involved.

Involutional Sequelae

Most cases of ROP will regress spontaneously by a process of involution, changing from vasoproliferation to fibrosis. Involutional sequelae include a broad array of peripheral and posterior retinal and vascular changes. The more severe the acute phase of ROP is, the more likely involutional changes will also be severe. Severe changes can ultimately lead to late retinal detachment (International Committee for the Classification of Retinopathy of Prematurity, 2005).

Recommended Screening

Infants born at 32 weeks or less are at risk for developing ROP. Current American Academy of Pediatrics (AAP) guidelines recommend screening all infants born < 1,500 grams or ≤ 30 wks, and those with a birth weight between 1,500 to 2,000 grams, regardless of gestational age, with an associated complicated course (Section on Ophthalmology American Academy of Pediatrics, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology, & Strabismus, 2006; Section on Ophthalmology American Academy of Pediatrics, American Academy of Ophthalmology, Ophthalmology, & Strabismus, 2006). Gestational age refers to the
completed weeks between the first day of the mother’s last menstrual period and the day of delivery (Engle, American Academy of Pediatrics Committee on, & Newborn, 2004). The majority of infants born with a birth weight less than 1,250 grams will develop some degree of ROP (Wright, Anderson, Walker, & Lorch, 1998).

The first exam should be performed at 4 to 6 weeks chronological age, or at 31 to 33 weeks postmenstrual age, whichever occurs later. Postmenstrual age is the infant’s gestational age in weeks plus the time elapsed since birth (Engle et al., 2004) Exams are repeated every 1 to 2 weeks based on the retinal findings, until one of four criteria are met: 1) Zone III retinal vascularization is attained without any evidence of ROP in Zones I or II; 2) there is full retinal vascularization; 3) a postmenstrual age of 45 weeks with zero prethreshold disease (defined as Stage 3 ROP in Zone II or any ROP in Zone I) or worsening ROP is present; 4) regression of ROP with no abnormal vascular tissue capable of reactivation and progression (Section on Ophthalmology American Academy of Pediatrics, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology, et al., 2006).

Clinical experience has shown that very few premature infants develop severe ROP requiring surgical intervention when born at or greater than 29 weeks gestation or greater than 1,250 grams. An unpublished, retrospective IRB-approved review of all infants in the Intermountain medical system born at or less than 32 weeks gestation studied the development of ROP between January 2000 and December 2009. Thirty-five hundred and twenty-two premature infants were included for analysis, and of these infants, 235 (6.6%) developed Stage 3 ROP. One hundred and eight (3.1%) required surgical intervention. Only 2 of the infants (.06%) that developed severe ROP were at
greater than or equal to 29 weeks gestation. These 2 infants had additional risk factors, including prolonged mechanical ventilation, necrotizing enterocolitis (NEC) and exposure to inhaled nitric oxide (Friddle, De Geronimo, Yoder, & Beachy, 2011). In addition to the Intermountain Healthcare population, a study by Lee (2001) examined data collected from 14 Canadian NICUs during 1996 – 1997, and found that only 1/2007 premature babies had severe ROP outside of the < 30 weeks or < 1,200 grams limits. The one patient that fell outside of this standard had a complicated hospital course with prolonged exposure to high inspired oxygen. Based on these findings, the authors concluded that screening only those babies < 1,200 grams would identify all major or severe cases of ROP, resulting in a 46% reduction in infants screened and saving the Canadian healthcare system $1 million annually (S. K. Lee et al., 2001).

As a result of these studies, the current screening guidelines for ROP at Intermountain Healthcare newborn intensive care units are: screen all infants born at less than 29 weeks gestation or less than or equal to 1,250 grams, and screen any infant born at less than 33 weeks gestation with one or more of the following complications: mechanical ventilation greater than 5 days, exposure to iNO, sepsis, NEC or surgery. Based on the Intermountain Healthcare system review, these guidelines would have eliminated eye exams, with the associated stress on the infant and cost, for 585 infants born at 29-33 weeks gestational age, without increasing the risk of missing an infant at risk for developing the disease (Friddle, Yoder, & Di Geronimo, 2013).

Prevention and Intervention

The best prevention for the development of ROP would be to avoid premature births. The March of Dimes reports that 1 in 8 infants are born prematurely, equaling
more than half a million premature babies born each year in the United States alone. Despite research that has helped in our understanding of the risks for premature delivery, the rate of premature birth increased by more than 20% between 1990 and 2006 ("Prematurity Campaign," 2012). Because premature infants continue to be born, we must develop strategies for the provision of intensive medical care to improve outcomes for this population and reduce morbidities, such as ROP.

Additional methods aimed at the prevention of ROP have had variable success. They include: vitamin E and C supplementation, ambient light reduction, increased human milk intake, treatment with inositol, oral D-penicillamine, fish-oil fat emulsion and control of blood oxygen saturations through the use of oxygen targeting.

Because ROP has been related to hyperoxia, there is added concern that reactive oxygen species (chemically reactive molecules containing oxygen) may be involved in this disease, but there is little information to prove or disprove the role of oxidative stress in ROP (Saugstad, 2006). Very high concentrations of the free oxygen radical generator, hypoxanthine, have been found by autopsy in the eyes of babies at risk of developing ROP (Saugstad & Rognum, 1988). It has also been found that those retinas are low in several antioxidants and antioxygen enzymes in the rat model (W. Chen, Hunt, Lu, & Hunt, 1999). Premature human retinas have been found to have relatively low levels of retinal vitamin E but contain an abundance of retinal vitamin C (Nielsen, Naash, & Anderson, 1988).

Vitamin E is a known antioxidant, free radical scavenger. Based on this function, it was suggested that the prophylactic oral administration of vitamin E could reduce the levels of retinal free radicals generated under hyperoxic conditions, which may contribute
to the development of ROP. However, the results of several randomized trials have failed to support the use of pharmacologic dosing of vitamin E to decrease the incidence of ROP (Committee on Fetus and, 1985; Hittner et al., 1981; Phelps, Rosenbaum, Isenberg, Leake, & Dorey, 1987; Puklin, Simon, & Ehrenkranz, 1982; Schaffer, Johnson, Quinn, Weston, & Bowen, 1985). Physiologic vitamin E supplementation is common, but it is not for the intended purpose of ROP prevention (Reynolds, 2001). Additionally, in a multicenter, randomized study of nulliparous women, the use of vitamins C and E doses in women between 14 and 22 weeks gestation did not reduce the risk of preeclampsia or perinatal complications, including ROP (Rumbold, Crowther, Haslam, Dekker, & Robinson, 2006).

Light reduction has also been proposed for the prevention of ROP. In theory, light, like oxygen, generates retinal free radicals, which might be involved in the pathogenesis of ROP (Reynolds, 2001). Yet the LIGHT-ROP study, a randomized, multicenter trial of light reduction in very low birth weight infants, did not demonstrate any effect of light reduction on the incidence of ROP (Reynolds et al., 1998).

Oral D-penicillamine has been studied for the prevention of ROP, after it was found that use of D-penicillamine in the treatment of neonatal jaundice decreased the incidence of ROP. Theoretical modes of action include oxygen-free radical scavenger, facilitation of synthesis and protection of peroxidation of biomembranes by enhancing the action of heme-containing anti-oxidant enzymes (Tandon, Dutta, Dogra, & Gupta, 2010). Despite the theoretical background, a recent double-blind, single-center, randomized, placebo-controlled trial on 88 infants failed to show a difference in the development of ROP (Tandon et al., 2010).
Inositol is a component of membrane phospholipids, and compounds containing inositol are important in signal transduction (Majerus et al., 1990). Breast milk, especially colostrum, has a high concentration of inositol (Bromberger & Hallman, 1986). Inositol supplementation in premature infants with respiratory distress was found to significantly decrease mortality and survival without bronchopulmonary dysplasia. The study also showed the group receiving inositol had decreased ROP (Hallman, Bry, Hoppu, Lappi, & Pohjavuori, 1992). Friedman et al. (2000) also showed infants receiving higher doses of inositol had higher serum inositol concentrations, which was associated with a decreased ROP risk (Friedman et al., 2000). Still, a study on the relationship of human milk intake and ROP did not find a decreased risk of severe ROP (Heller et al., 2007). Thus, this did not change the preference for infants to receive human milk. Inositol supplementation is not current practice.

Fish-oil fat emulsion is high in docosahexaenoic acid (DHA), which is important for fetal brain development and visual acuity in infants. An observational study was completed in order to compare the safety and efficacy outcomes on an intravenous fat emulsion containing fish-oil from the first day of life. Researchers found a significantly lower risk of laser therapy for ROP among infants who received this emulsion, proposing that it was effective in the prophylaxis of severe retinopathy (Pawlik, Lauterbach, & Turyk, 2011). Fish-oil supplementation may aid in the prevention of severe ROP; however, more rigorous investigation with a blind controlled, multicenter study is warranted.
Oxygen Targeting

The recognition of the role of hyperoxia in the development of ROP has led many NICUs, including those within Intermountain Healthcare, to recommend lower oxygen saturation targets for at-risk premature infants. This strategy has met with the most success in the prevention of ROP. While a number of studies have reported a decreased incidence of ROP with use of lower saturation targets, there is little consensus on the definition of the ideal targeted range, and there is a great deal of cross-over in the oxygen saturation ranges characterized as high versus low saturation targets (Askie, Henderson-Smart, Irwig, & Simpson, 2003; Carlo et al., 2010; Chow et al., 2003; Cryotherapy for Retinopathy of Prematurity Cooperative Group, 2001; Deulofeut, Critz, Adams-Chapman, & Sola, 2006; J. P. Goldsmith & Greenspan, 2007; Greenspan & Goldsmith, 2006; Hagadorn et al., 2006; Hay & Bell, 2000; Johnston et al., 2011; Noori et al., 2009; B. Stenson et al., 2011; S. C. Sun, 2002; The STOP-ROP Multicenter Study Group, 2000; Tokuhiro et al., 2009; Vanderveen et al., 2006). See the Appendix for a summary of these studies. One study, STOP-ROP (2000), showed a decrease in the incidence of severe ROP when higher levels of oxygen were administered to infants with confirmed prethreshold ROP from 46% to 32% (p = .004; The STOP-ROP Multicenter Study Group, 2000). The evidence supporting the appropriate oxygen target is limited, and concern has been raised with the results of the only randomized, multicenter, blinded studies, SUPPORT and BOOST-II. These studies both showed that while risk of severe ROP was less in the lower oxygen saturation group, there was an increased mortality for this group in both studies (Carlo et al., 2010; B. Stenson et al., 2011). This means that for every two to three infants that were spared developing severe ROP, one would die
(Fidler, 2011). This finding has created uncertainty and concern in the oxygen management of this population. The true impact of oxygen targeting on the incidence of ROP, especially when coupled with other changes in NICU care, remains uncertain.

**Challenges in Achieving Oxygen Targets**

Premature infants are known to have immature breathing patterns, with periodic breathing and apneic spells (Abu-Shaweesh, 2011). The literature defines periodic breathing as periods of regular respiration for as long as 20 seconds, followed by apneic periods of 10 seconds or less that occur at least 3 times in succession (Nimavat, 2012). Its absolute prevalence is high in preterm and lower in term infants, approaching 100% in preterm infants weighing less than 1,000 grams (Rigatto, 2003). Periodic breathing is associated with a significant decrease in minute ventilation and is accompanied by a rapid, marked decrease in oxygen saturation in very low birth weight infants, who may also progress to prolonged apnea (Mathew, 2011).

Clinically significant apnea in infants is defined as breathing pauses that last for greater than 20 seconds or less than 20 seconds if associated with bradycardia or oxygen desaturation (Committee on Fetus and Newborn, 2003). Apnea of prematurity (AOP) is felt to be a developmental disorder that self-resolves as the infant matures and develops improved neurologic synaptic connections and myelination of the brainstem (Darnall, Ariagno, & Kinney, 2006). The incidence is inversely related with gestational age and birth weight, with nearly all infants with AOP born at less than 29 weeks gestation and less than 1,000 grams falling to 54% at 30 to 31 weeks and 7% by 34 to 35 weeks (Zhao, Gonzalez, & Mu, 2011). AOP usually ceases by 37 weeks’ postmenstrual age but may persist for several weeks beyond term, especially in infants born before 28 weeks’
gestation (Darnall, Kattwinkel, Nattie, & Robinson, 1997; Eichenwald, Aina, & Stark, 1997; Henderson-Smart, 1981). Recent research suggests that intermittent hypoxia, as defined as brief, repeat episodes of decreased oxygen hemoglobin saturation, may not be clinically apparent without continuous saturation monitoring, but may continue until term-equivalent and beyond for premature infants, even after the resolution of AOP (Rhein, Dobson, Darnall, Corwin, Heeren, Poets, McEntire, Hunt, & Caffeine pilot study, 2014).

The ventilatory response to hypoxia after birth in premature infants is not like an adult with a sustained response to hypoxia. Infants have a biphasic hypoxic response that begins with an initial increase in ventilation lasting 1 to 2 minutes, followed by a decrease that reaches below baseline ventilation in preterm infants. This late decline has been called hypoxic ventilatory depression and may persist in preterm neonates for 4 to 6 weeks (Mathew, 2011; Nock, Difiore, Arko, & Martin, 2004). Such a response to low oxygen in infants appears to result from initial stimulation of peripheral chemoreceptors, then overriding depression of the respiratory center as a result of hypoxemia (Gauda, McLemore, Tolosa, Marston-Nelson, & Kwak, 2004). There is also evidence that hyperoxia results in blunting of peripheral chemoreceptor response, predisposing the preterm infant to apnea following hyperoxia (Cardot et al., 2007; Katz-Salamon, Jonsson, & Lagercrantz, 1995; Ling, Olson, Vidruk, & Mitchell, 1996). Current evidence suggests that both increased and decreased carotid chemoreceptor activity can predispose the preterm infants to apnea.

The chemoreceptor response in preterm neonates to elevated carbon dioxide (CO2) concentration has been shown to be blunted, as compared to term infants (Cohen
& Katz-Salamon, 2005; Koons, Hegyi, Mehta, Hiatt, & Weinberger, 2003). This is thought to be partially due to decreased central chemosensitivity, or mechanical factors that prevent an adequate ventilator response (Carlo & DiFiore, 1990; Noble, Carlo, Miller, DiFiore, & Martin, 1987). In addition to these findings, it has been demonstrated that a progressive decrease in inspired oxygen concentrations causes a significant flattening of CO2 responsiveness in preterm infants (Rigatto, De La Torre Verduzco, & Gates, 1975). This unstable response to low inspired oxygen levels may play an important role in AOP and offers a physiologic rationale for the decrease in incidence of apnea observed when a slightly increased concentration of inspired oxygen is administered to premature infants (Simakajornboon, Beckerman, Mack, Sharon, & Gozal, 2002).

AOP treatment options are fairly limited and include prone positioning, methylxanthine therapy, nasal intermittent positive pressure ventilation (NIPPV), continuous positive airway pressure (CPAP) with either low or high flow through a nasal cannula, and ultimately, endotracheal intubation and mechanical ventilation.

**Oxygen Saturation Variability**

The achieved versus intended pulse oximeter saturation (AVOX) study examined the ability of NICU teams in different facilities to maintain oxygen saturation levels within limits established in their units. It showed that in infants of less than 28 weeks’ gestation, there was marked instability with fluctuations in saturations on both sides of the targets. Overall time within the intended range for all patients combined ranged from 16% to 64% (Hagadorn et al., 2006). This study demonstrates the daunting challenge of
caring for these tiny infants. No data were provided on mode of oxygen delivery or medications that may alter the severity of periodic breathing or AOP.

Compliance with ordered alarm limits has also been identified as challenging, in a study by Clucas et al (2007). The objective of the study was to determine the rate of compliance with hospital alarm limits guidelines for pulse oximetry in preterm infants on oxygen. They found that lower alarm limits were set correctly 91% of the time and upper limits only 76.5% of the time.

Barriers to implementation of oxygen saturation targeting, and strategies for overcoming these barriers, have been identified and addressed in several studies. Barriers include staff buy-in, unclear population limits and targeted saturation values, default alarm limits on monitors and inappropriate nurse-patient ratios for adequate response to alarms (Ford et al., 2006). Strategies for overcoming these barriers have also been identified through staff education, standardized oximeter alarm orders, targeted saturation defaults set on monitors, nursing protocols in response to changes in oxygen management, bedside signs and staff contracts for compliance (Chow et al., 2003; Ellsbury & Ursprung, 2010; Ford et al., 2006).

Measurement Devices

In July of 2009, the NICU at PCH changed its patient monitoring to the Phillips IntelliVue MP70 patient monitor®. As part of the package, Massimo Signal Extraction Technology pulse oximeters (Masimo SET™, Irvine, CA) were installed at every bedside. Pulse oximetry is painless, relatively easy to apply, causes minimal agitation and allows for continuous monitoring. Multiple studies on premature infants at risk for ROP have attempted to define the optimal range for infants’ saturation levels in order to
predict outcomes for vision. However, these have come at the cost of increased mortality and a concern that in our efforts to avoid hyperoxemia, we have subjected infants to increased hypoxia, contributing to morbidity and mortality.

Masimo Signal Extraction Technology (SET) has been shown to dramatically decrease the rate of false alarms due to motion and low perfusion (Masimo). A pulse oximeter is a medical device and must meet regulatory requirements for assuring safety and effectiveness. Requirements for safety include assessing the device’s basic safety and essential performance and for effectiveness in having an adequate design process that can identify hazardous situations. These regulations are set by the International Electrotechnical Commission (IEC) and the Food and Drug Administration (FDA) (Weininger, 2007). Specifications of the Masimo SET™ monitor include saturation ranges from 1-100%, and saturation accuracy from 70% to 100% ± 3% in neonates with motion, no motion, and low perfusion states (Masimo, 2007).

There are multiple studies in the literature that have utilized arterial blood oxygen levels (paO2) and arterial blood saturation (SaO2) as the gold standard to establish the validity of the SpO2 readings. Correlations studies on pulse oximetry for newborns have been reported at high levels of correlation, between r = 0.895 to r = 0.987, p< .0001. These studies also found SpO2 to be a more reliable measure, as compared to transcutaneous oxygen measures (Bohnhorst, Peter, & Poets, 2002; Bucher, Fanconi, Baeckert, & Duc, 1989; Castillo et al., 2008; Deckardt, Schneider, & Graeff, 1987; Durand & Ramanathan, 1986; Hay, Brockway, & Eyzaguirre, 1989; Holmes et al., 1998; Jennis & Peabody, 1987; Nickerson, Sarkisian, & Tremper, 1988; Ramanathan, Durand,
A study of effectiveness of 20 different pulse oximeters during motion, found the Masimo to have the highest sensitivity (98%) and specificity (93%), with the smallest dropout rate (0.2%) of any of the monitors studied, when compared to the SpO2 reading on a stationary hand (Barker, 2002).

Along with the monitoring system came a trend option to look at reports of oxygen saturations in the form of histograms. The histogram can record saturation data for 24 hours, with one saturation point recorded every 5 minutes. If the monitor is unable to record more than 70% of the saturation values, the report will be printed with a question mark to identify it as a less reliable representation of the patient’s saturations.

Despite the recognition that excessive oxygen administration to premature infants has a high association with ROP, and the institution of tighter controls and oxygen monitoring, the incidence of ROP has continued to be high. This is likely due to the increased survival of very low birth weight infants, who are at greatest risk for developing the disease. Poor weight gain, the presence of a patent ductus arteriosus, intraventricular hemorrhage (IVH), necrotizing enterocolitis and sepsis have been identified as potential risk factors for developing ROP (M. Chen et al., 2011; Wheatley et al., 2002b). Other factors reflecting the overall health of the baby, such as sepsis, anemia and chronic lung disease, have been shown to have a positive association with the development of ROP as well (Flynn, 1983; Smith, 2003; Tasman et al., 2006). Recently, postnatal weight gain, hyperglycemia and insulin-like growth factor 1 (IGF-1) levels were identified as important predictors for ROP risk (Blanco, Baillargeon, Morrison, & Gong,
2006; Ertl, Gyarmati, Gaal, & Szabo, 2006; Garg, Agthe, Donohue, & Lehmann, 2003; Hellstrom et al., 2003). Poor early weight gain, as well as low serum levels of IGF-1 during the first weeks/months after birth, are strongly correlated with the development of severe ROP (Hellstrom et al., 2003; Lofqvist et al., 2007; Lofqvist et al., 2006; Wallace, Kylstra, Phillips, & Hall, 2000).

**Treatment**

Fortunately, despite the number of infants who develop some degree of ROP, only 6% to 9% require treatment (Early Treatment For Retinopathy Of Prematurity Cooperative Group, 2003). Surgical intervention is available in two forms: cryotherapy or laser photocoagulation.

**Cryotherapy**

Cryotherapy first became the standard of care in 1988 (Harrell & Brandon, 2007). Cryosurgery involves repeated applications of an extremely cold probe to the outside of the eye, thus cauterizing the avascularized areas of the retina in an attempt to stop secretion of factors that promote the progression of ROP, such as vascular endothelial growth factor (Harrell & Brandon, 2007). The CRYO-ROP study recommended treatment of ROP as indicated by a 50% risk for retinal detachment. This degree of severity was termed the *threshold* for treatment of ROP and was defined as at least 5 contiguous or 8 cumulative clock hours of Stage 3 ROP in Zone I or II with the presence of plus disease (Cryotherapy for Retinopathy of Prematurity Cooperative, 2001). The procedure limits some peripheral vision while preserving central vision. Following the adoption of cryosurgery, unfavorable ROP structural outcomes decreased by over 40%,
and visual acuity outcomes improved by 30% (Cryotherapy for Retinopathy of Prematurity Cooperative Group, 1990). Visual acuity outcomes for eyes with threshold ROP are favorable in slightly more than half of the eyes treated in the CRYO-ROP study (Tasman, 2001). Cryotherapy is associated with many complications, including, but not limited to: pain, increased risk of infection, edema of the periorbital region, retinal scarring, lacerations of the conjunctiva, arrhythmias, increased oxygen needs, seizures and even death (De Roo-Merritt, 2000). Because this procedure required direct contact with the area of the eye being treated, it is problematic if the ROP is in the posterior part of the eye where the probe cannot reach.

Laser

Laser photocoagulation for the treatment of ROP has demonstrated promising outcomes, although in smaller studies than the cryosurgery studies. An argon or diode laser is directed through the lens directly to the retina in order to destroy the unvascularized tissue by a process called photocoagulation (DeJonge, Ferrone, & Trese, 2000). Photocoagulation results when the ray of the laser causes the protein material in the eye to condense and therefore stop the development of new vessels from growing (De Roo-Merritt, 2000). Laser photocoagulation has become the standard treatment modality because the laser is believed to have the advantage of causing less pain, less inflammation, greater portability and the improved ability to treat posterior disease (Cyber-Sight, 2003; De Roo-Merritt, 2000). Disadvantages of laser therapy have been reported because of increased risk of cataract developments, scarring, hemorrhage and burns of the cornea, iris or lens of the eye (De Roo-Merritt, 2000).
The acceptance of more aggressive surgical intervention for the treatment of ROP in those babies identified as having prethreshold disease is a change in clinical care that has occurred in the past decade. In 2003, the results of the Early Treatment for ROP (ET-ROP) study were published, supporting the surgical management of type I ROP and resulting in improved visual acuity and structural outcomes (Early Treatment For Retinopathy Of Prematurity Cooperative Group, 2003). Type I disease, or high risk “prethreshold ROP,” is defined as ROP in Zone I at any Stage with plus, Zone I Stage 3 without plus or Zone II Stage 2 or 3 with plus. Following the publication of the ET-ROP study, most centers adopted the revised recommendations to treat babies with early prethreshold disease, as opposed to waiting until traditional threshold criteria occurred (Cryotherapy for Retinopathy of Prematurity Cooperative Group, 1988). One ongoing concern following the adoption of this more aggressive treatment strategy is that more premature babies may potentially end up with surgical intervention for ROP disease that would have otherwise regressed spontaneously. Historical data from the original cryotherapy study (Cyro-ROP) found that 6% of premature infants < 1,250 grams had threshold ROP requiring surgery (Cryotherapy for Retinopathy of Prematurity Cooperative Group, 1988). In ET-ROP, surgical intervention increased, so that 9% of babies screened were found to have prethreshold disease and were surgically treated (Early Treatment For Retinopathy Of Prematurity Cooperative Group, 2003). Also of interest, in ET-ROP, a significantly higher percentage of babies were found to have Zone I prethreshold disease, as compared to the original Cryo-ROP data (22.7% vs 9.6%, respectively). The impact on the incidence of surgical intervention for ROP, since the adoption of the ET-ROP guidelines at many centers has not been described in detail. In a
small study out of the University of Nebraska looking at their own population, Alme (2008) found that surgical intervention increased from 5% to 11% after adopting the revised ET-ROP guidelines. This was also associated with a significant reduction in Stage 5 retinal detachment (Alme et al., 2008).

New Directions in Treatment

The newest investigational option for the treatment of ROP is based on the role of vascular endothelial growth factor (VEGF) in retinal neovascularization. Intravitreous infusion of bevacizumab, a vascular endothelial growth factor inhibitor, has been used for the treatment of ROP (Lalwani et al., 2008; Mintz-Hittner, 2011). Short-term effects have demonstrated a positive effect on the regression of retinal neovascularization in Zone I but not Zone II disease, as well as improved vision in the form of less myopia at the 1 year follow-up, as compared to those infants treated by laser coagulation (Harder, von Baltz, Jonas, & Schlichtenbrede, 2011). Concern has been raised on the exact dosage required for optimal effect; too much stops growth into the avascular retina permanently; too little allows new abnormal vessel growth into the vitreous. The ideal dose would stop vitreous growth permanently, allowing new vessel growth to continue into the avascular retina (Mintz-Hittner, 2012). Additional concern has been raised because VEGF is essential for normal angiogenesis in a growing infant, and there is concern about the unknown potential systemic effects of treatment with an anti-VEGF drug on the developing preterm infant (Hard & Hellstrom, 2011).

The visual prognosis for children who have ROP and reach threshold disease is poor, despite current available medical interventions. The multicentered cryotherapy study showed that approximately 30% of the infants who received cryotherapy for
threshold disease still had unfavorable vision at their 3 month follow-up, persisting into their 1 year, 5.5 year, and 10 year follow-ups (Cryotherapy for Retinopathy of Prematurity Cooperative, 2001; Cryotherapy for Retinopathy of Prematurity Cooperative Group, 1990, 1996). Reducing the incidence of threshold disease is the main goal to avoid unfavorable visual outcomes in premature infants.

Infants who have had laser or cryotherapy for ROP require close observation of the retina by a retinal surgeon for life because the incidence of late retinal detachments continues to be a risk and can sometimes be effectively treated (Tasman, 1979). It has been found that untreated ROP can cause changes in middle-aged adults as well. In a study of 47 former premature patients (86 eyes) now ages 45 to 56 (mean, 49.9 years) with a history of ROP, 88% were found to have had a pathologic posterior segment event, most commonly retinal dragging. Retinal detachments occurred in 26% of the eyes, myopia in 90% of the eyes and cataracts in 84% of the eyes. The study also found that 49% of the patients had visual acuity of 20/200 or greater with the best corrected visual acuity at 20/60 (Tasman et al., 2006).

**Summary Statement**

Retinopathy of prematurity can be a devastating eye disease in premature infants. Developments in treatment have reduced vision-threatening complications but do not offer cures for the problem. The best way to improve visual outcomes for this high-risk population is to prevent the development of abnormal vasculature in the eye.

Despite, or perhaps because, multiple advances in neonatal care have resulted in the improved survival of very immature infants over the past 70 years, ROP continues to pose a problem for hundreds of premature infants each year. Oxygen targeting is a
method used to decrease the incidence and severity of this disease. Oxygen targeting research has failed to recognize the potential impact of time out of targeted range on the development of ROP, despite studies of both animal models and humans that have shown oxygen fluctuations to be a contributor to the development of ROP. Every newborn intensive care (NICU) nurse knows that some infants in this at-risk population have hemoglobin oxygen saturations that fluctuate frequently above or below the targeted range.

No one has looked at the impact of time the infant spends out of targeted saturation range on normal retinal development as well as the development of ROP. Additionally, a number of infants are given respiratory support in the form of nasal cannula flow, continuous positive airway pressure (CPAP) or mechanical ventilation at 21% oxygen, which is the equivalent of room air (RA). No one has defined the optimal oxygen target for this population, and there is concern that high oxygen saturations during treatment with 21% oxygen could contribute to the development of ROP.

This study evaluates whether the development of ROP can be explained by the average time an infant spends out of the targeted oxygen saturation range over 24 hours, in the weeks prior to the development of ROP or retinal maturation. Additionally, the effects of higher oxygen saturation targets while an infant is receiving 21% oxygen were evaluated to determine if this increases the risk of developing ROP. Finally, the potential effects of time out of saturation range on infant survival to discharge were evaluated. This is important in understanding the potential impact of the time the infant spends above or below a targeted saturation range. This study can lead to a better understanding of the application of pulse oximetry and/or variability in preterm infants and may lead to
exploring alternative measures to control saturation levels, provide safer patient care and improve outcomes.
References


CHAPTER 3

METHODOLOGY

Research Design

This is a retrospective, longitudinal, observational study of all infants at risk for ROP at a single NICU over a 3-year period. The study analyzes the relationship between the percentage of time an infant spends outside a target oxygen saturation range and the development of ROP or full maturation of the retinal vasculature. If significant, the time out of targeted saturation range may explain the development of ROP, allowing for measures to be taken to adjust oxygen delivery or to redefine the optimal targeted saturation, ultimately helping to avoid the development of ROP.

Additionally, the effects of higher oxygen saturation targets while an infant is receiving respiratory support with 21% oxygen will be evaluated to determine if this increases the risk of developing ROP. This can lead to a better understanding of the effect of hemoglobin oxygen saturation values over time, and whether alternative measures to control saturation levels may be needed, such as the use of a nitrogen blend to provide subambient oxygen or servo control of oxygen delivery to provide immediate adjustments in oxygen, according to pulse oximetry measurements.
Theoretical Model

Oxygen has been identified as a key element in the delay in retinal maturation and in the development of ROP. Vascular endothelial growth factor (VEGF) is an oxygen-mediated factor essential for normal retinal vessel growth. As the retina develops anterior to retinal vessels, there is an increase in oxygen demand from the developing neural tissue that creates localized tissue hypoxia. VEGF is expressed in response to this hypoxia, and blood vessels grow toward the VEGF stimulus. When an infant is born prematurely, the oxygen environment is altered from the levels existing in the uterus. The retina becomes relatively hyperoxic, causing vasoconstriction, vaso-obliteration and inhibiting new blood vessel formation by down-regulating VEGF expression (Mintz-Hittner, 2011). This may cause a delay in the natural retinal development or increase the risk of developing ROP. Insulin-like growth factor-1 (IGF-1) has also been associated with ROP as a necessary factor in the function of VEGF. The infant’s supply of IGF-1 from the placenta and amniotic fluid is removed at the time of birth, contributing to reduced VEGF activity and slow growth of the retinal vasculature. As the infant matures, IGF-1 levels may be slow to increase and must reach a threshold for VEGF activation. This leads to phase 2 ROP.

Oxygen targeting was developed in an attempt to avoid hyperoxia in the newly-born infant at risk for ROP. The maintenance of lower oxygen saturations attempts to avoid the down-regulation of VEGF expression in order to avoid phase 1 and phase 2ROP. Oxygen targeting research has shown a decrease in the incidence of ROP through the use of lower oxygen saturations, but has failed to recognize the potential impact that time out of targeted range has on the development of ROP.
Methods of Procedure

Sample

This retrospective study includes all infants admitted to Primary Children's Medical Center newborn intensive care unit January 2010 through December 2012 who were determined to be at risk for the development of ROP. The guidelines for determining which infants are at risk for ROP include all infants born at less than 29 weeks gestation or less than or equal to 1,250 grams. Inclusion criteria also includes any infant born at less than 33 weeks gestation with one or more of the following complications: mechanical ventilation greater than 5 days, exposure to inhaled nitric oxide, sepsis, necrotizing enterocolitis, or undergoing any surgery. Institutional review board approval was obtained from the University of Utah for the study. Exclusion criteria included the use of extracorporeal membrane oxygenation (ECMO), infants admitted after the development of ROP and infants that died or were discharged without documentation of retinal examination.

Data Collection

In 2010, a decision was made to adopt oxygen targeting in the NICU population identified as at risk for ROP through the use of the “Oxygen with Love” (OWL) protocol (J. Goldsmith, 2009). As part of this process, a mandatory computerized education program was developed and distributed to all staff in the NICU, discussing the pathophysiology of ROP and the risks and benefits of oxygen use in premature infants. Education was provided on the targeted oxygen management practices described by Chow and coworkers associated with improved outcomes due to avoiding hyperoxia and repeated episodes of hypoxia-hyperoxia. A policy for response to significant events was
introduced, with a commitment statement from staff to ensure compliance with the policy.

The patient monitors were reprogrammed, with profiles established for each of the established target ranges for the patients. On admission, the nurse would select the appropriate profile, based on gestational age or diagnosis, which would then set the monitor alarms in the identified range. OWL cards with the ordered saturation range were also placed on each monitor to provide additional visual reminders. Admission and respiratory order sets were standardized to reflect the agreed-upon saturation ranges: 1) infant < 33 weeks 85% -93%, 2) infants > 33 weeks, 85% -95%.

As part of this quality improvement project, I (the author/investigator) conducted weekly rounds in my role as the clinical nurse specialist to verify that infant alarms were set correctly and educating staff/ correcting the limits if alarms were found to be set incorrectly. I answered staff questions promoted nurse buy-in, despite the increase in monitor alarms. A 24-hour histogram for each individual patient’s saturation was printed and reviewed, in order to evaluate the success in achieving the targeted saturation range. Over time, alarm compliance improved. However, many infants were found to have highly variable times out of targeted range.

In June 2011, an updated mandatory computer education program was introduced, with an adjustment to the saturation targeting range for gestational age. This was in response to concerns raised in the SUPPORT and BOOST II studies with regards to increased infant mortality (Carlo et al., 2010; B. Stenson et al., 2011). Monitor profiles and patient order sets were changed to reflect the new oxygen ranges based on postmenstrual age: 1) infant < 29 weeks, 85% -93%, 2) infants 29-32 6/7 weeks, 88% -
94%, 3) infants $\geq$ 33 weeks, 92% -98%, if on oxygen. A daily histogram review was also added as part of patient rounds, to ensure that the entire team was aware of the infant’s ability to be maintained in the targeted saturation range. Over a 4-year period, the overall incidence of ROP decreased, and the need for ROP treatment also decreased (see Table 1).

Saturation Histogram

Weekly histograms were collected on all infants at-risk for ROP per the above guidelines, as part of a quality improvement project to increase nursing awareness of individual patient saturation targeting. Therefore, all infants at-risk for ROP contributed data to the analysis. These histograms represent the 24 hours of time with a 1 second sample of data recorded every 5 minutes. The horizontal axis shows the range of 2% units of saturation from 79-100%. The vertical axis shows the percentage of time the patient spent in each 2% unit. The histogram data represents the 288 (1440 min/24hr ÷ 5 min)

<table>
<thead>
<tr>
<th>Year</th>
<th>2008</th>
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<th>2011</th>
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<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
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<td>532</td>
<td>473</td>
<td>521</td>
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<td>24%</td>
<td>103</td>
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<td>34%</td>
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</tr>
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<td>12%</td>
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<td>30%</td>
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<td>18%</td>
</tr>
<tr>
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<td>5</td>
<td>6%</td>
</tr>
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<td>2</td>
<td>1%</td>
<td>4</td>
<td>5%</td>
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</tr>
</tbody>
</table>
saturations 1 to 2 days prior to the weekly eye exam. The majority of histograms were collected on Monday, and the majority of eye exams were performed on Wednesday. Not every patient had an eye exam every week. Histograms were collected weekly on every patient as long as the patient was present in the NICU, though occasionally histograms would not be available, due to patient travel away from the bedside on the day of collection. Additional data collected includes the ordered targeted range for saturations, the infants’ weekly weight, the current treatment with supplemental oxygen and the mode of oxygen delivery (ventilator, continuous positive airway pressure, high flow nasal cannula, nasal cannula).

**Procedure**

IRB approval was obtained prior to accessing the patient record. This study has minimal patient risk since it is a retrospective review of de-identified data. All data were collected by the primary investigator (PI) and were stored in a password-protected, encrypted database at the site of the study. Data from the medical record for each infant were obtained to identify gestational age and birth weight, as well as risk factors for ROP to determine eligibility criteria. Eye exam results were recorded. All infants were examined by the same board-certified pediatric ophthalmology service (Moran Eye Center, University of Utah), which followed the ROP international classification and guidelines. Exams were reported with information on severity of the disease (Stage), location (Zone), presence or absence of dilated and tortuous posterior vessels (plus disease), the extent of the disease (clock hours) and finally, by retinal sequelae as the disease involutes. Eye exams began at 31 weeks postmenstrual age or 4 weeks after
delivery, whichever came later. Exams continued every 1 to 2 weeks until the infant’s discharge/death or retinal vessel maturity was obtained.

Additional information collected from the infant’s chart included admitting diagnosis for transfer to Primary Children’s Hospital (PCH) NICU and survival to discharge. The infant’s exposure to methylxanthines, specifically caffeine and/or theophylline, was collected as a treatment modality for periodic breathing and apnea. Weekly weights were obtained to identify growth characteristics of each infant as a marker of adequate nutrition and IGF-1 availability.

Preparing Data for Analysis

Each individual patient was given a study ID number, and individual data were recorded by this ID. Individual histogram data were evaluated for each infant’s ordered saturation range. For each week the infant was in the NICU, I analyzed and recorded the percentage of time each infant was above, within, and below the ordered saturation range within 24 hours, based on the histogram. Additionally, because the targeted saturation for each individual varied, the percentage of time each infant was below fixed limits of ≤ 85%, and above > 93% was recorded. Because there was a great deal of variability in the ordered saturation range, final analysis used the fixed points of 85% and 93% to evaluate the effects of saturations out of this range. Weekly data were also collected, including the infants’ mode of ventilation by category, weekly weight and weekly postmenstrual age. Missing histograms were left as missing data for that discrete time period.

A chart review of each individual patient was conducted to identify the use of methylxanthines to treat periodic breathing. Any history of sepsis, surgery, intraventricular hemorrhage and necrotizing enterocolitis was identified, all of which
have been associated with the development of ROP. These variables were coded as a “yes” or “no” during the course of the hospitalization. They were later left out of the analysis because there was not an onset time associated with these variables to identify whether they occurred before or after the onset of ROP.

Eye exam data upon Stage, Zone, and completed maturity were entered, as recorded by the ophthalmology examination. Stage was ultimately used to define the presence of ROP and was listed by severity, ranging from no ROP at Stage 0 to complete retinal detachment at Stage 5. To avoid the problem of reciprocal causation, infants were censored at the time ROP was first identified and removed from further analysis. The development of ROP, retinal maturity or death/discharge was used to define the endpoint for the study period. When the eye was deemed mature, no further data were analyzed.

Data Analysis

Descriptive statistics were used to evaluate the demographics of the study group. Aim 1. Hierarchical linear modeling (HLM) was originally intended to evaluate the relationship that time out of targeted saturation range had on the development of ROP. Longitudinal data with repeated measures of oxygen variability from the weekly histograms was used. Due to concerns for reciprocal causation, the method was later changed.

Survival analysis using a discrete-time hazard model was determined the best model to predict the risk of developing ROP, due to the time out of the saturation targeted range. This was controlled for birth weight and the postmenstrual age at which the infant entered the study using logistic regression. Reciprocal causation gives the interpretive difficulty of trying to determine if X causes Y, or if it is possible that Y causes X. To
address this, the time-varying predictor had to be defined, and the values had to be predetermined for each patient involved in the study. The targeted saturation values of 85-93% as the accepted standard for ROP prevention for infants at risk for the development of ROP were used throughout the study. Data were collected in the days prior to the exam by censoring infants once an ROP status was known. This removed the possibility that time out of range could have been influenced by an individual’s ROP status.

Data using a discrete-time hazard model required relatively evenly matched events. If there were > 10 days between data points on an individual identification number, an additional data point (week) was added to the data. Known data were entered; missing data were left as missing. If there were < 3 days between data points, the additional data were eliminated. The goal was to have as close to 7-day spacing between data points as possible, so that each week the subject was in the study was equally represented. Discrete-time survival analysis treats time as if it were divided into discrete units or chunks. This method allows one to examine event occurrence sequentially among infants at risk for ROP at each discrete point in time (Singer & Willet, 2003).

The hypothesis was that the infants with the greatest saturation variability out of targeted range would have the greatest risk for developing ROP. The percentage of time with high and low saturations was also individually evaluated to determine which had a greater effect on developing ROP. This aided in predicting the risk for infants in order to guide decision-making about the best saturation ranges to target. I expected to see that infants who spent more time out of range over time would have a greater risk for the development of ROP. I assumed that infants with low saturation variability would not
have ROP, and that moderate variability might have mild ROP. Known risk factors of birth weight and postmenstrual age at the time of study entry were considered in the analysis.

**Aim 2.** The effect of allowing higher oxygen saturation targets when an infant is breathing 21% oxygen on the development of ROP, as compared to lower targeted saturations while breathing greater than 21% oxygen was evaluated. Descriptive statistics were used to compare the ROP time out of targeted saturation range for the two groups. A logistic regression equation was used to evaluate breathing 21% oxygen for significance, controlling for birth weight, postmenstrual age and oxygen saturation variability, with the development of ROP as the outcome variable.

The hypothesis was that the 21% oxygen group with higher saturation limits was equivalent to the > 21% oxygen group with lower targeted saturations. I expected the groups to have equivalent rates of ROP, with the RA group having no difference in outcomes.

**Aim 3.** To evaluate the relationship that time out of targeted saturation range has on the risk of death before discharge. Survival analysis using a discrete-time hazard model was used to explain the risk of death before discharge due to the time out of saturation targeted range, controlling for birth weight and the corrected gestational age when the infant entered the study by using logistic regression. Death before discharge was used as the outcome variable. This concern was raised, due to the results of the SUPPORT and BOOST-II trials showing an increased mortality in infants maintained with lower oxygen saturations (Carlo et al., 2010; B. Stenson et al., 2011).
All statistics were run on SPSS® 20 statistical software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM CORP) with a significance level set at p < 0.05. Data are displayed graphically and in tables.

Logistic Regression

Logistic regression can be used to develop a model that will successfully predict categorical outcome variables such as no ROP, mild ROP and significant ROP. It is used to estimate the probability of an event occurring to a given individual (Munro, 2005). Logistic regression has the benefit of reporting information as odds ratios that help in the interpretation of the data. Odds ratio is the probability of an occurrence over the probability of nonoccurrence. The discrete-time event occurrence is based on period-by-period data, and in this case, week-by-week data. Utilizing this model allows the sequential examination of event occurrence among individuals who are eligible to experience the event at each discrete point in time. The term hazard is used to denote the risk of the event occurrence for an individual in each discrete time period (Singer & Willet, 2003).

Assumptions of logistic regression and discrete-time hazard model:

1. Dichotomous or continuous independent variable: This study looked at the independent variables of birth weight, postmenstrual age and time out of saturation range, all of which are continuous variables.
   a. The population variances of the dependent variable are the same for all levels of the independent variable: This held true for the variables of weight and gestational age. When time out of range was separated into the time less than or equal to 85 or greater than
the assumption no longer held for time ≤ 85, with a large number never having low saturations. Because of this, the inverse transformation of the percentage of time the infant was ≤ 85% was used to achieve normality.

b. Discrete-time hazard function required that there be a separate record for each time period when an individual is at risk, and that censoring occurs at the time of event occurrence (Singer & Willet, 2003). Data were coded to ensure each weekly time period was represented.

2. Categorical dependent variable: Most commonly, logistic regression utilizes dichotomous outcome variables, known as binary logistic regression. It is also possible to use multinomial logistic regression for outcome variables with two or more values, as was used in this study.

a. Each categorical level is independent of the previous variable. Each case in this study is mutually exclusive, belonging to only one group, and every case present is a member of one of the groups.

b. Discrete-time hazard function requires that an individual can experience the event in a given time period only if he or she did not already experience it at any prior period. Conditionality was used to ensure that only eligible individuals were in the data set, and as individuals experienced the event, they were censored and dropped out of the risk set, becoming ineligible to experience the
event in a later period. This conditionality ensured that the hazard probability for an individual in a given time period assessed his or her unique risk of event occurrence in that period (Singer & Willet, 2003).

c. The categories are exhaustive. Each case was a member of only one of the categories, and all cases were represented by a category

3. No perfect collinearity: This means that a predictor is so related to another predictor that one can be determined by another (Menard, 2008). Often the variables of birth weight and gestational age at birth can be collinear—as gestational age increases, the weight of the infant increases. This was not an issue because gestational age at birth was not used. Postmenstrual age upon admission was used to account for the infant’s adjusted age at the time of study entry.

4. Relevant predictors are included in the analysis, and irrelevant predictors are excluded. A hierarchical method was used by entering key variables into the equation in blocks. Three blocks were used in this study. The blocks were based on past research and the theory being tested in this study. Initially, the time variable by week was entered. This led to a cubic model, indicating that there is increased risk over time to a point, after which the risk diminishes, only to potentially increase again for more severe ROP. For the outcome of death, a quadratic model was significant. Next entered were the basic infant covariates known to be high risk factors for the development of ROP. The infant’s birth weight and postmenstrual
age were entered first at the time of study entry. Finally, the saturation values were entered for the total time out of range, as well as the time at or below 85% and above 93%.

**Equipment Validity and Reliability**

Pulse oximetry has become the standard of care in NICUs to monitor systemic oxygenation in sick neonates and thereby avoid hypoxia and hyperoxia (Laptook, Salhab, Allen, Saha, & Walsh, 2006; Weininger, 2007). Hypoxia is associated with central nervous system damage, multi-organ damage, increased pulmonary vasculature resistance, patent ductus arterious, impaired development and increased mortality (Bancalari, 2011). Hyperoxia is a concern for premature infants at risk for bronchopulmonary dysplasia (A. H. Jobe & Ikegami, 1998; A. J. Jobe, 1999) and retinopathy of prematurity (Akkoyun et al., 2006; M. Chen et al., 2011; Kinsey, 1956; Kinsey et al., 1977).

Pulse oximeters measure the ratio of oxyhemoglobin (Hbo2) to reduced hemoglobin (Hb) in arterial blood and display this value as oxyhemoglobin saturation (SpO2). The Beer-Lambert law states that the amount of light emerging from a substance in solution is determined by three physical properties: the concentration of the absorbing material, the distance that the light must travel through the sample, and the probability that a photon at that particular frequency will be absorbed by the material (Wagner & Ruskin, 2007). Pulse oximetry is based on the premise that different types of hemoglobin absorb light at different wavelengths, and that the color and concentration of blood varies with oxygen saturation (Wagner & Ruskin, 2007). Light is measured through the Masimo SET Low noise optical probe (LNOP®). The probe is designed to enhance performance
by minimizing direct interference from ambient light and stabilizing the sensor on the patient’s skin though a mild adhesive (Goldman, Petterson, Kopotic, & Barker, 2000). The peak absorption frequency of Hb is known to be 660 nm (red light), and the peak absorption frequency of HbO2 is 940 nm (near infrared light); these frequencies readily penetrate tissues other than blood, but Hb and HbO2 are the only substances in the blood with absorption peaks at those frequencies, allowing them to be used for determining oxygen saturation. The probe uses two light-emitting diodes (LEDs) that illuminate the vascular bed with a red and near infrared light (Wagner & Ruskin, 2007).

The pulse oximeter combines the two technologies of spectrophotometry (the detection and quantification of compounds in solution) to quantify hemoglobin oxygen saturation, and optical plethysmography, which measures pulsatile changes in arterial blood volume at the sensor site (Kamat, 2002). A conventional pulse oximeter (CPO) measures the ratio of the absorption of light in red light and near infrared light for hemoglobin and oxyhemoglobin (Salyer, 2003). The pulsatile (AC) signal represents the light absorption by arterial blood, while the unchanging (DC) signal results from absorption by venous blood and tissues, such as skin and bone. The signal is measured several hundred times per second and is “normalized” by dividing the AC signal by the DC signal at each wavelength. This isolates the arterial signal and creates a plethysmographic waveform that resembles that of the arterial waveform. The assumption is made with conventional oximetry that arterial blood is the only light-absorbing pulsatile component being read (Goldman et al., 2000).

The accuracy of pulse oximetry is also limited by assumptions made during calibration of the device. Calculations based solely on the Beer-Lambert law overestimate
oxygen saturation because of reflection and scattering of the incident light (Wagner & Ruskin, 2007). Calibration tables were developed from experiments with volunteers, by simultaneous light absorption readings and blood oxygen values. The reference values are obtained from desaturation studies, in which absorption ratios and arterial oxygen content are measured in healthy adult human volunteers who inhale hypoxic gas mixtures. Studies are limited to values that can be safely induced in healthy subjects, with SaO2 typically falling between 75% and 80% (Severinghaus & Naifeh, 1987). The shape of the absorption curve below 75% is extrapolated. It would be unethical to conduct similar studies in infants or at lower saturation levels. The calibration is performed in the factory before the device is distributed.

In 1995, Masimo released a version of oxymetry with signal extraction technology (SET) that dramatically decreased the rate of false alarms due to motion and low perfusion. The SET technology functions as a CPO, but then identifies the venous blood signal, which has a lower oxygen saturation level than arterial blood, isolates it, and uses adaptive filters (DST, SST, FST and MST) to cancel the noise and extract the arterial signal in order to report accurate arterial oxygen saturation and pulse rate. These filters are used in a patented parallel processing mode, along with the conventional red over infrared algorithm, to improve sensitivity and specificity along with fidelity (Barker, 2002).

Masimo SET™ technology is commonly used in Intermountain Healthcare facilities. A pulse oximeter, as a medical device, must meet regulatory requirements for assuring safety and effectiveness. Requirements for safety include assessing the device’s basic safety and essential performance and having an adequate design process that can
identify hazardous situations. These regulations are set by the International Electrotechnical Commission (IEC) and the Food and Drug Administration (FDA) (Weininger, 2007). Specifications of the Masimo SET™ monitor include saturation ranges from 1-100%, saturation accuracy from 70% to 100% ± 3% in neonates with motion, no motion, and low perfusion states (Masimo, 2007).

The Massimo Signal Extraction Technology pulse oximeter (Masimo SET™, Irvine, CA) is the brand of oximetry used at the study site. This technology was used to monitor and record 24-hour saturations at 1-week intervals for all infants born at < 33 weeks gestation, thus at risk for the development of retinopathy of prematurity, for the course of their hospitalization. These monitors are available at every bedside and are already in use on every infant admitted into the NICU as the standard of care. Pulse oximetry is a noninvasive means of obtaining information regarding saturation of blood hemoglobin with oxygen (SaO2) continuously. This has the advantage not only of being noninvasive, but of providing a rapid response time, low risk of skin injury, and self-calibration of the monitor. Monitoring pulse oximetry saturations (SpO2) is used as an index of arterial oxygenation (Durand & Ramanathan, 1986).

Validity

Face validity. Face validity is the most superficial assessment of whether the monitor measures saturation, but often the most important at the bedside. Nurses use face validity every time they respond to a saturation alarm, assessing the color of the patient to make a judgment about whether the alarm was real or false. A study by O’Donnell et al. (2007) evaluated the effectiveness of clinician (doctors and nurses) visual assessment of infants immediately after birth when the infant first looked pink and the pulse oximeter
oxygen saturation at which infants first looked pink. There was disagreement about whether the newborn infant looked pink, with wide variation in the SpO2 when they were considered to become pink. The SpO2 at which individual infants were perceived to turn pink varied from 10% to 100% (O'Donnell, Kamlin, Davis, Carlin, & Morley, 2007). Clearly, the visual color appearance is difficult to judge, compared to SpO2 readings on newly born infants.

Nurses will also base their response to saturation monitor alarms on the correlation of the oximeter pulse rate with the ECG monitor heart rate. If the numbers match, they are more likely to investigate the alarm event as a true event, rather than a false event. A study by Malviya et al. (2000) defined false alarms as a decrease in SpO2 < 90% that by expert clinical observation and opinion was considered artifactual, as evidenced by a lack of correlation between the pulse rate and ECG heart rate (Malviya et al., 2000).

Content validity. Content validity asks whether the monitor measures all aspects of saturation. The development of the Masimo SET™ oximeter worked to addresses this issue in its attempts to reduce noise through the use of filters. This improved the sensitivity and specificity of the monitor (Goldman et al., 2000)

Conventional oximeters have a quoted accuracy within ± 2% in adults if HbO2 is between 70% and 100%, because calibrations are based on healthy volunteers at those levels. Accuracy is quoted to be ± 3% between 50% and 70% as extrapolated data (Salyer, 2003). Accuracy is not specified if HbO2 is below 50% (Salyer, 2003). Durand and Ramanathan (1986) did a study with 75 NICU neonates to try to determine the optimal saturation range for infants. He found that 90% of the infants with an SpO2
between 87% and 94% had arterial PO2 between 50 and 80 mm Hg (Durand & Ramanathan, 1986). Another study examined 2 different conventional oximeters in hypoxic pediatric intensive care patients with saturations ranging from 60% to 79%. It concluded that for every 10% decrease < 75% SpO2, the SaO2 decreased by an average of 5% +/- 5% (Carter et al., 1998). The accuracy seems decreased at lower saturations, yet this does not make a large clinical impact, as a saturation of 66% ± 6 would warrant intervention. Conversely, hyperoxia is difficult to predict with pulse oximetry because of the relationship of arterial oxygen to hemoglobin oxygen saturation on the oxygen dissociation curve. The oxygen-hemoglobin dissociation curve is sigmoid, the curve flattens at higher levels of arterial oxygen and an increase in PO2 produces little increase in saturation (Blackburn, 2012). A study by Bohnhorst et al. (2002) defined hyperoxia in neonates as a paO2 > 80. They studied 56 infants by comparing arterial blood oxygen levels (paO2) to SpO2 with three different motion-resistant monitors in a correlation study, the Masimo SET™, Nellcor Oxismart™, and Agilent Viridia™. An upper SpO2 limit of 95% had a sensitivity of 93-95% for a paO2 > 80 for all three monitors. The specificity was better at 56% with the Masimo monitor, slightly lower with the Nellcor and only 26% with the Agilent (Bohnhorst et al., 2002). Poets et al. (2002) have also reported that at an upper alarm limit of 95%, new-generation pulse oximeters are much better than conventional pulse oximetry in detecting hyperoxemia (Poets, Urschitz, & Bohnhorst, 2002).

Dyshemoglobinemia can compromise pulse oximetry readings because conventional pulse oximetry, including the Massimo SET™, are unable to distinguish between oxygenated hemoglobin (functional hemoglobin) and dysfunctional
hemoglobins, such as methemoglobin and carboxyhemoglobin (fractional hemoglobins) that are unable to bind and carry oxygen (Salyer, 2003). In the absence of dyshemoglobinemias, the fractional and functional saturations are equal (Barker, Curry, Redford, & Morgan, 2006). It only becomes problematic for patients with carbon monoxide poisoning or for smokers, an unlikely condition for patients in a NICU. There are newer monitors that examine eight wavelengths of light to measure the concentration of methemoglobin and carboxyhemoglobin, in addition to SPO2. The Masimo Rainbow SET Rad-57 Pulse CO-oximeter is one such monitor studied by Barker et al. in 2006 (Barker et al., 2006).

Hypothermia was evaluated in a study by Iyer et al. (1996). Twenty-five infants < 3 months of age undergoing cardiac surgery were evaluated with a pulse oximeter probe. Skin temperature varied, and SpO2 was compared with SaO2 measures. Pulse oximetry bias increased to > ± 3% in 45.5% of the readings when skin temperature was < 27 degrees C. SpO2 bias remained acceptable in 95% of the readings, with temperatures > 29 degrees C (Iyer et al., 1996). This is important to keep in mind in cases of severe hypothermia. Therapeutic hypothermia for hypoxic-ischemic encephalopathy in a newborn decreases the infant’s temperature to 33.5 degrees C for 72 hours (Thoresen & Whitelaw, 2005). This is generally the lowest temperature target in the NICU and is within the range of acceptable readings for saturation monitoring.

Construct validity. Construct validity has to do with the monitor behaving in an expected way. Most clinicians would agree that motion artifacts and the resulting false alarms have been the most significant drawback to using pulse oximetry in critical care settings (Cannesson & Talke, 2009). Homes et al. (1998) studied 18 sick neonates by
comparing a CPO by Nellcor® to both the new Masimo SET™ and the infants’ arterial blood saturation (SaO2). They found that the Masimo SET™ reduced the risk of false alarms when compared with CPO during motion and low perfusion, without a loss in accuracy of the SpO2 display (Holmes et al., 1998). Another study of 75 healthy children aged 1 to 10 years was conducted by comparing a CPO to the Masimo SET™ with staff blinded to the readings on the monitors. Chi square and fishers exact tests were used to compare the incidence of true alarms and false alarms between the two monitors. They reported a positive predictive value (proportion of true alarms divided by the total number of alarms) for Masimo at 87% versus 61% for the COP, with a 50% reduction in false alarms with the Masimo monitor (Malviya et al., 2000). Barker (2002) studied 20 different pulse oximeters in 70 healthy volunteers during motion and hypoxemia. The Masimo SET™ had the best overall performance, with a performance index of 94% and a precision of 2.98%. The worst-functioning oximeter studied had a performance index of 28% and a precision of 6.44% (Barker, 2002).

Sahni et al. (2003) studied the performance of two saturation monitors, the Masimo SET™ and Nellcor, simultaneously in 15 healthy male newborns undergoing circumcision. The infants’ behavioral states ranged from quiet sleep to crying. Analysis of the reported percentage of saturation and heart rate showed the Masimo monitor to have greater accuracy in all behavioral states (Sahni, Gupta, Ohira-Kist, & Rosen, 2003).

**Concurrent validity.** Concurrent validity asks, does the score obtained predict the level of oxygen saturation or oxygen level in arterial blood? There are multiple studies in the literature that have utilized arterial blood oxygen levels (paO2) and arterial blood saturation (SaO2) as the gold standard to ensure the validity of the SpO2 readings.
Correlations for newborn studies have shown high levels of correlation, between $r = 0.895$ to $r = 0.987$, $p < .0001$ (Bohnhorst et al., 2002; Bucher et al., 1989; Castillo et al., 2008; Deckardt et al., 1987; Durand & Ramanathan, 1986; Hay et al., 1989; Holmes et al., 1998; Jennis & Peabody, 1987; Nickerson et al., 1988; Poets & Southall, 1994; Ramanathan et al., 1987; Shiao & Ou, 2007; Solimano et al., 1986; Southall et al., 1987)

Reliability

Reliability is the ability of the tool to measure arterial hemoglobin saturations in a repeatable and predictable way, with individual patients and across multiple patients and studies. Reliability is confirmed every time a study demonstrates a high correlation between the construct validity and sensitivity, and specificity of saturation monitoring.

Alternate forms of oximetry have been used in multiple studies to compare effectiveness between various saturation monitors placed on the same patient simultaneously. Correlations were run between the different monitors and frequently against the gold standard arterial blood measurements. In each case, the Masimo SET™ monitor performed in a reliable, predictable way (Barker, 2002; Bohnhorst et al., 2002; Carter et al., 1998; Castillo, Deulofeut, Critz, & Sola, 2011; Hay et al., 2002; Holmes et al., 1998; Malviya et al., 2000; Workie, Rais-Bahrami, & Short, 2005).

In the early days of pulse oximetry, CPO was frequently evaluated against an alternative form of oxygen measurement commonly used in the early 1980s, known as transcutaneous oxygen tension (tcPO2). TcPO2 was the most commonly used, non-invasive method of monitoring an infant’s oxygen status. It provided continuous information but required calibration for use, used a heated probe that could potentially burn and was found to significantly underestimate PaO2 in infants (Durand &
Ramanathan, 1986). These studies used regression analysis to compare SpO2 to TcPO2 and PaO2. SpO2 was consistently found to be a more reliable measure of arterial saturation when compared to TcPO2 (Baeckert et al., 1987; Durand & Ramanathan, 1986; Hay et al., 1989; Sendak, Harris, & Donham, 1986; Southall et al., 1987; Wimberley, Helledie, Friis-Hansen, Fogh-Andersen, & Olesen, 1987).

Other methods of assessing reliability for instruments are not appropriate for the evaluation of saturation monitors. Pulse oximeters are used for continuous measurement and measure a dynamic construct of oxygenation, particularly in infants receiving supplemental oxygen. Test/retest is not an option for continuous measurement. There is no way to conduct a split-half test to show reliability of saturation monitoring, as it is an all or nothing prospect. Interrater and intrarater reliability are also methods used to assess observational and/or coding of data.

Sensitivity and Specificity

Sensitivity and specificity are statistical measures of the saturation monitor performance. Sensitivity measures the proportion of true measurements out of saturation range that are correctly identified. Specificity measures the proportion of false alarms that are correctly identified. Sensitivity and specificity depend on the alarm limit set on the monitor. Sensitivity may be increased by narrowing the alarm limit, but specificity is then decreased, resulting in a higher risk of false alarms. A study by Bucher et al. (1989) found that if the goal is to avoid hyperoxemia, then a high sensitivity is more important than a high specificity. It maintained that a minimum sensitivity of 95% is required so that no more than 1 instance of hyperoxemia in 20 will be missed by the monitor. This level of sensitivity resulted in a 38% to 57% specificity in the monitors studied (Bucher
et al., 1989). The rate of false alarms was not studied in this study. Other studies would argue that the single most important characteristic of a pulse oximeter is to identify all episodes of hypoxemia, in order to permit intervention before the development of clinically significant hypoxemia (Malviya et al., 2000). The NICU has the unique challenge of monitoring infants for both hyperoxemia and hypoxemia with narrow alarm limits, making them subject to high rates of false alarms. Paky and Koeck (1995) attempted to define a saturation alarm setting that would be reliable in detecting both hyperoxemia and hypoxemia. They studied SpO2, as compared with arterial PaO2 levels. They concluded that they could not establish a sensitivity level of 90% to maintain arterial PaO2s of 40 to 90 mmHg. At a sensitivity of 85%, the alarm range on the pulse oximeter was 92.5 to 95%. They then concluded that the sensitivity level at this range was too low to avoid both hyperoxemia and hypoxemia (Paky & Koeck, 1995). Specificity was not reported but was likely quite low, given the narrow range. This study was prior to the development of motion sensitive monitors that have better sensitivity and specificity ratings.

A study regarding the effectiveness of 20 different pulse oximeters during motion found the Masimo to have the highest sensitivity (98%) and specificity (93%), with the smallest dropout rate (0.2%) of any of the monitors studied, when compared to the SpO2 reading on a stationary hand. Data on the averaging time and alarm limits (discussed below) were not provided (Barker, 2002).

Sensitivity and specificity can be influenced by averaging the time for the saturation reading. The Masimo SET™ can be adjusted from 2 to 16 seconds. A study by Ahmed et al. (2009) evaluated the difference between monitoring at a 2 second and a 16
second averaging period, based on the frequency of events when all other clinical responses were the same. The shorter averaging time increases the saturation fidelity, making it more sensitive to small changes in saturation. Conversely, the longer averaging time slowed the oximeter’s reaction to rapidly changing values, thereby improving specificity with fewer false alarms. There was not a significant difference seen in the amount of time spent within different saturation ranges (Ahmed, Rich, & Finer, 2010). This may be an option to consider in trying to find the balance in evaluating clinically significant events that need nursing intervention for the safety of the patient.

The monitor alarm selection for patients in critical care areas are expected to have high sensitivity to detecting signs of deterioration (Burgess, Herdman, Berg, Feaster, & Hebsur, 2009; Chambrin, 2001; Graham & Cvach, 2010). This, however, creates high false positive alarm rates, which are managed in part by low patient to nurse ratios. The concern is that when alarm frequency is high, nurses are at risk for becoming desensitized to the alarms (Burgess et al., 2009; Graham & Cvach, 2010). Further investigation is needed in this area.

**Summary**

This study looked at the effects of the time infants spend out of the targeted oxygen hemoglobin saturation range on the development of ROP. It used a retrospective, observational study design, tracking standard practice. Weekly 24-hour histogram reports of individual patient oxygen saturation values were coded for the time the infant spent above and/or below the ordered targeted saturation. It is known that it can be difficult to maintain a narrow targeted saturation range in premature infants prone to periodic breathing and apnea. What is not known is the impact saturation variability may have on
the risk for developing ROP. Given the current practice of targeting oxygen saturations, it would be of significant interest to those caring for these infants to define the impact of the time spent out of the targeted saturation range on the development of ROP and the risk of death. Understanding the impact of time out of targeted range, due to hypoxia and/or hyperoxia, on the development of ROP or death, can help develop strategies for managing these infants. Additionally, defining the impact of higher oxygen ranges for infants receiving 21% oxygen will be important in future management decisions for this population of patients. The results of this study will help guide in the management of patients at risk for ROP by identifying or allaying concerns about additional risk factors for the development of this disease.
References


CHAPTER 4
PATHOGENESIS OF RETINOPATHY OF PREMATURITY:
DOES INFLAMMATION PLAY A ROLE?²

Abstract

Retinopathy of prematurity (ROP) is a disorder of retinal blood vessel development that is potentially blinding. ROP is the number one cause of blindness in infancy and the second leading cause of childhood blindness in the United States. The exact etiology is not completely understood, and many factors appear to contribute to the pathogenesis and progression of the disease. These factors may include prematurity, low birth weight, genetic predisposition, oxygen, hypoxia, ischemia, insulin-like growth factor, vascular endothelial growth factor and sepsis. This article reviews the process of retinal development, the pathogenesis of ROP and how oxidative stress, infection and inflammation may contribute to this pathogenesis.

Introduction

Retinopathy of prematurity (ROP) is a disorder of retinal blood vessel development and is the second leading cause of childhood blindness in the United States behind cortical visual impairment (Steinkuller et al., 1999). The National Center for Health Statistics report has listed the incidence of infants born at risk for developing this

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eye disease (≤32 weeks gestation) to be at 2% of all live births. In 2008, 84,224 babies were born at or less than 32 weeks gestation in the United States (Peristats, 2012). The National Eye Institute has estimated that 14,000-16,000 of these infants are affected by some degree of ROP, and that 1,100-1,500 infants in the US develop ROP severe enough to require medical treatment on an annual basis. Of these, 400-600 become legally blind from ROP each year (National Eye Institute (NEI), 2010).

Retinopathy of Prematurity (ROP) is a potentially blinding disorder caused as abnormal new blood vessels develop in the immature retina. In 1942, an ophthalmologist from Boston named Theodore Terry was the first to recognize a previously undescribed form of blindness in children born prematurely and of low birth weight. He named the condition based on the eye examination finding that showed a white fibrous mass behind the lens which obliterated the retinal vessels which he named "retrolental fibroplasia" (Terry, 1944). The name was later changed in 1984 by consensus of an international group of pediatric ophthalmologists to retinopathy of prematurity (The Committee for the Classification of Retinopathy of Prematurity, 1984).

Despite efforts to avoid the development of ROP since it was first recognized in the 1940s by Terry, ROP continues to be a challenging problem in the care of premature infants. The exact etiology of ROP is not completely understood and many factors appear to contribute to the pathogenesis and progression of the disease. Prematurity, genetic predisposition, oxygen, hypoxia, ischemia, insulin-like growth factor 1 (IGF-1) and VEGF all have been shown to be important in the development of ROP (Hellstrom et al., 2003). Severity of illness, sepsis, acidosis, blood transfusions and light have also been associated with ROP (Madan & Good, 2005). The degree of prematurity itself remains
the most significant risk factor, with the avascular retina of premature babies being at the highest risk (Akkoyun et al., 2006; Smith, 2003). High oxygen saturations, oxygen fluctuation and hypoxia are known to significantly contribute to the development of ROP (Akkoyun et al., 2006; M. Chen et al., 2011; Chow et al., 2003; Hellstrom et al., 2010; Sapieha et al., 2010; The STOP-ROP Multicenter Study, 2000; Vanderveen et al., 2006; Wallace et al., 2007).

Normal Retinal Development

The vascular supply for the retina consists of two main parts: 1) the choroidal vessels that underlie the retina and 2) the retinal vessels that serve the inner retina. Vascular development for the choroid is complete by 22 weeks of gestation (McLeod et al., 2006). The choroid provides nutrition through diffusion to the early retina. The choroidal vessels are more permeable and have a high venous partial pressure of oxygen (PaO2). They lack the ability to autoregulate in response to hyperoxia. Therefore, during times of hyperoxia, PaO2 levels are raised across the thickness of the retina, and the retinal vessels respond by constricting (Madan & Good, 2005). As the retina matures, there is little change in the choroid blood supply, despite the high rate of growth and development in the retina during mid- to late gestation. As a result, the retina requires its own vascular supply for adequate nutrition (Quinn, 2004). Normal retinal vascular development begins at the optic disc at about 16 weeks gestation, through a process of vasculogenesis. Vasculogenesis is the *de novo* development of vasculature that involves, the proliferation, differentiation, and organization of blood vessels from endothelial progenitors known as angioblasts (McLeod et al., 2006). To accomplish vasculogenesis, circulating angioblasts develop early retinal vessels in the region surrounding the optic
nerve. Angiogenesis then proceeds to extend the retinal vasculature to the periphery by 36-40 weeks gestation, through formation of new blood vessels from existing vessels (Harrell & Brandon, 2007; Mintz-Hittner, 2011).

The developing retinal vessels reach only 70% of the distance from the optic disc to the periphery by 27 weeks of gestation (Madan & Good, 2005). Retinal vascular development is ideally accomplished while the fetus is in the uterus in a relatively hypoxic environment where the average PaO2 is 25-35, which is supported by the infant’s fetal hemoglobin and lower metabolic demands (Quinn, 2004).

The retinal vasculature is comprised of two laminar, but interconnected, layers: the primary superficial layer and the ganglion cell layer, which lies deeper in the retina. The layers are joined by fine capillaries (Hughes et al., 2000). Vasculogenesis in the retina is believed to be responsible for early vessel formation in the inner plexus, but is not responsible for vessel formation in the temporal and peripheral regions of the human retina (Hughes et al., 2000). The formation of the primary vascular layer in the retina is intimately associated with the development of cells in the nerve fiber/ganglion region, known as astrocytes (Gariano, 2010; Stone et al., 1995). Astrocytes are glial cells that give biochemical support to endothelial cells, sense physiologic hypoxia and express vascular endothelial growth factor (VEGF); (Hartnett, 2010b). VEGF is one of the most important factors in vascular development and is associated with pathologic angiogenesis (Hartnett, 2010b; Mintz-Hittner, 2011; Smith, 2003). Astrocytes emerge from the optic nerve and migrate just ahead of the developing vascular network (Dorrell et al., 2002). This places them in a position to respond to physiologic levels of hypoxia in the avascular areas of retina (Chan-Ling et al., 1995; Quinn, 2004; Stone et al., 1995).
Astrocytes are present only in retinas in which retinal vasculature forms, and are restricted to the inner layer of retina that allows them to respond to hypoxia of the inner layers by expressing VEGF, which is essential to induce the formation of the superficial layer of blood vessels (Raghuveer & Bloom, 2011; Stone et al., 1995). The normal formation of retinal vessels depends on a period of physiologic hypoxia to stimulate the release of VEGF by the astrocytes (Chan-Ling et al., 1995; Forsythe et al., 1996; Levy et al., 1995; Quinn, 2004). Hyperoxia, will inhibit new blood vessel formation by downregulating VEGF expression by the astrocyte, limiting the hypoxic stimulus (Pierce et al., 1996; Stone et al., 1995). This down regulation may cause a delay in the natural retinal development. When a fetus is delivered prematurely, the normal processes for the developing retinal vascular bed that will nourish the eye are interrupted.

Insulin-like growth factor (IGF-1) is another key factor in retinal development. IGF-1 is hypothesized to regulate retinal neovascularization through control of VEGF activation. Studies have demonstrated a permissive role for IGF-1 in new blood vessel formation, as it allows maximum VEGF stimulation of new vessel growth. Low levels of IGF-1 will inhibit vessel growth, despite the presence of VEGF (Hellstrom et al., 2003; Hellstrom et al., 2001; Smith et al., 1999b). IGF-1 is supplied to the fetus from the placenta and the amniotic fluid. Premature birth cause IGF-1 levels to fall through loss of the amniotic fluid and placental supply in the fetal environment (Smith, 2003).

**Pathogenesis**

When an infant is delivered prematurely, the retinal development must continue in an altered environment, creating the risk for developing ROP. The infant’s retina becomes hyperoxic (even in room air), leading to decreased levels of VEGF, and, for a
time, vasculogenesis is halted between the vascular and avascular retina, increasing the risk for developing ROP (Mintz-Hittner, 2011; Niranjan et al., 2012). Additionally, IGF-1 levels fall from in utero levels after birth, due to the loss of IGF-1, which is provided by the placenta and the amniotic fluid (Smith, 2003). The disease process for the development of ROP is biphasic, with an initial phase of vessel growth retardation followed by a second phase of vessel proliferation (Smith, 2003).

Phase I

The first phase of ROP has been described as the hyperoxia-vasocessation phase (Reynolds, 2001). It occurs from birth to postmenstrual age of 30-32 weeks (M. Chen et al., 2011). When a very low birth weight premature infant is born, the infant’s immature lung places them at high risk for hypoxemia. The medical response is to provide increased amounts of fraction of inspired oxygen (FIO2). Under conditions of low retinal metabolic demand this creates relative retinal hyperoxia. Production of VEGF may be inhibited by the high levels of supplemental oxygen the infant may receive in the NICU, which causes cessation of normal retinal growth, and vessel constriction with a potential for vaso-obliteration of new immature vessels. This may cause subsequent death of vascular endothelia cells (Ashton et al., 1953; Chow et al., 2003; Mintz-Hittner, 2011; Patz et al., 1953; Patz et al., 1952; Pierce et al., 1996; Reynolds, 2001).

In utero, the fetus receives insulin-like growth factor (IGF-1) via the placenta, which ceases at the time of birth. The infant is predisposed to Phase I ROP due to an inherent lack of normally-developed vessels (Harrell & Brandon, 2007).

After premature birth, IGF-1 is suppressed by poor nutrition, sepsis, and acidosis. Preterm infants with prolonged low serum levels of IGF-1 and slow weight gain, have an
increased risk of ROP (Hellstrom et al., 2003). A low level of IGF-1 decreases retinal vascular growth by suppressing the VEGF activation necessary for endothelial cell survival (Hellstrom et al., 2001). As the infant matures, the nonvascularized retina has increasing metabolic activity leading to tissue hypoxia. This hypoxia promotes increasing levels of VEGF along with increasing IGF-1 to a critical level, which then triggers retinal neovascularization that moves to Phase II ROP (Hellstrom et al., 2001).

Phase II

The second phase of ROP is the relative hypoxia-revascularization phase. It is characterized by a progressive increase in metabolic activity in the nonvascularized retina, resulting in a hypoxia-induced retinal neovascularization. This phase begins around 32-34 weeks postmenstrual age (J. Chen et al., 2011). Prior to 32 weeks gestation, the retina is very immature, with photoreceptors that are not yet fully functional, and the retinal metabolic demand is low (A. T. Johnson et al., 1985). As the retina matures, there is an increased metabolic demand and oxygen consumption, creating a relative retinal hypoxia (Reynolds, 2001; Saugstad, 2006). Hypoxia stimulates the up-regulation of pro-angiogenic growth factors, such as vascular endothelial growth factor (VEGF) and erythropoietin, which, in severe cases, leads to uncontrolled vascular growth in the vitreous (M. Chen et al., 2011; Smith, 2003). The changes in retinal tissue oxygenation can be exacerbated by weaning the infant from oxygen therapy and potentially by targeting low oxygen saturation levels. Phase II ROP does not proceed with a gradual transition from avascularized to vascularized retina but rather a demarcated ridge line develops along the retina that separates the central vascularized region of the retina from the peripheral avascular region. This structure histologically consists of mesenchymal
and endothelial cells (York et al., 2004). Vascular development from this stage may resume without significant disruption, or it may progress to significant ROP, as seen by an abnormal proliferation of retinal vessels into the vitreous and over the surface of the retina (Olitsky et al., 2011). The new vessel growth is abnormal, producing capillary networks that are fragile, leaky and poorly perfused. These new vessels fail to alleviate tissue hypoxia, leading to persistent growth of these abnormal vessels (Mintz-Hittner et al., 2011).

Early exposure of the retina to hypoxia and ischemia exacerbates delayed retinal development in premature infants, in part due to low levels of local and systemic growth factors, including IGF-1. VEGF production within the retina occurs in response to relative hypoxia but is unable to trigger angiogenesis in the absence of adequate IGF-1. Over time, postnatal levels of IGF-1 recover and reach a critical threshold, and VEGF induced angiogenesis is triggered, contributing to the occurrence of ROP (Kong et al., 2008; Mintz-Hittner et al., 2011; Mintz-Hittner & Kuffel, 2008; Smith, 2003).

**Classification of ROP**

ROP is classified 1) by the location of the lesion of abnormal vascular development relative to the optic nerve (Zone); 2) by the degree of abnormality (Stage); 3) by the presence or absence of dilated and tortuous posterior pole vessels (plus disease); 4) by the extent of the disease (clock hours) and 5) by retinal sequelae as the disease involutes. Severity of disease is based on the Zone, Stage and presence of plus disease.
Zones

There are three zones which describe the extent of retinal vascular development. Zone I is the area immediately surrounding the optic nerve and macula, extending from the disc to twice the distance between the disc and the macula, and has the highest risk for the development of scar formation, significant visual impairment and retinal detachment. Zone II is a ring concentric to Zone I, which extends to the nasal ora serrata (the edge of the retina on the side of the eye toward the nose) and may develop lesions that can progress to the above-mentioned significant sequelae. Zone III is the remaining crescent of retina on the temporal (toward the temple) side and carries the lowest risk of a poor outcome from severe ROP (International Committee for the Classification of Retinopathy of Prematurity, 2005). See Figure 1.

Figure 1. Scheme of retina of the right eye, showing zone borders used to describe the location of retinopathy of prematurity.
Stages

Five stages of abnormal vessel development have been identified in ROP to describe its severity, ranging from mild (Stage 1) to severe (Stage 5). Table 2 describes the characteristics of the different stages.

Plus Disease

Plus disease implies increased venous dilatation and arteriolar tortuosity of the posterior retinal vessels near the optic nerve. It also includes the growth and dilatation of abnormal blood vessels on the surface of the iris, rigidity of the pupil, and vitreous haze. The diagnosis of plus disease is usually made on the appearance of the vessels near the optic nerve, as compared with standard retinal photographs. The presence of plus disease suggest a more fulminant or rapidly progressive course. Rush disease is the term used to define Zone I ROP that also has plus disease. Patients with rush disease tend to have a poorer prognosis than other eyes with ROP (International Committee for the Classification of Retinopathy of Prematurity, 2005).

Oxidative Stress and ROP

ROP was first associated with oxygen supplementation in premature infants in the 1940s. Higher oxygenation is associated with the development of abnormal vascular growth in the eye (Campbell, 1951). Because ROP has been related to hyperoxia, there is concern that reactive oxygen species (ROS) may be involved in this disease, but there is limited information to prove or disprove the role of oxidative stress in ROP (Saugstad, 2006). Very high concentrations of the free oxygen radical generator, hypoxanthine, have
<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>Stage 1</td>
<td>A line of demarcation between the normal retina nearer the optic nerve and the nonvascularized retina peripherally.</td>
</tr>
<tr>
<td>Stage 2</td>
<td>A ridge of scar tissue that arises in the region of the demarcation line that has both height and width.</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Severely abnormal blood vessel growth when the vessels grow through the ridge toward the center of the eye (intravitreous) instead of following their normal growth pattern along the surface of the retina. This is the most common stage to begin treatment.</td>
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<tr>
<td>Stage 4</td>
<td>Severely abnormal vessel development with a partial retinal detachment. Stage four is divided into two parts:</td>
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<tr>
<td></td>
<td>• Stage 4A, where the detachment does not include the macula, and the vision may be good.</td>
</tr>
<tr>
<td></td>
<td>• Stage 4B, with macula detachment and a marked decrease in vision potential.</td>
</tr>
<tr>
<td>Stage 5</td>
<td>Complete retinal detachment, usually with the retina pulled into a funnel-shaped configuration by the fibrovascular scar tissue.</td>
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been found, by autopsy, in the eyes of babies at risk of developing ROP (Saugstad & Rognum, 1988). It has also been found that those retinas are low in several antioxidants and antioxygenzymes in the rat model (W. Chen et al., 1999). Premature human retinas have been found to have relatively low levels of retinal vitamin E but contain an abundance of retinal vitamin C (Nielsen et al., 1988). The premature infant has inadequate concentrations of antioxidants at birth, as well as an impaired ability to synthesize antioxidants in response to hyperoxia, making them susceptible to ROS-induced damage that may lead to ROP (J. Lee & Dammann, 2012).

Oxygen has been identified as a key element in the delay in retinal maturation and in the development of ROP. Vascular endothelial growth factor (VEGF) is an oxygen-mediated factor that is essential for normal retinal vessel growth. As the retina develops anterior to retinal vessels, there is an increase in oxygen demand from the developing neural tissue that creates localized hypoxia. VEGF is expressed in response to this hypoxia and blood vessels grow toward the VEGF stimulus. When an infant is born prematurely, the oxygen environment is altered from levels in the uterus. The retina becomes relatively hyperoxic which will cause vasoconstriction, vaso-obliteration and will inhibit new blood vessel formation by downregulating VEGF expression (Sola, Chow, & Rogido, 2005). This may cause a delay in the natural retinal development or increase the risk of developing ROP. Insulin-like growth factor-1 (IGF-1) has also been associated with ROP as a necessary factor for the function of VEGF. The infant supply of IGF-1 from the placenta and amniotic fluid is removed at the time of birth, contributing to the retinal vasculature going dormant. As the infant matures, IGF-1 levels may be slow
to elevate and must reach a threshold for VEGF activation. This leads to Phase II ROP.

This process is demonstrated in Figure 2.

Oxidative stress has long been implicated as a cause of ROP. Oxidative stress can be a consequence of inflammation, as well as hypoxia/ischemia, hyperoxia, and reperfusion (Saugstad, 2005b). Preterm infants have higher levels of oxidative stress compared to term infants, which is further complicated by an immature antioxidant system (Moore, Berger, & Wilson, 2012).

Hypoxia alone can stimulate the production of tumor necrosis factor-alpha (TNF-α), a proinflammatory cytokine, which results in the breakdown of the retinal-blood barrier. Increased levels of TNF-α have been found in the retina of rats for up to 3 days after hypoxic exposure, inducing retinal ganglion cell death (Sivakumar, Foulds, Luu, Ling, & Kaur, 2011).

**Infection and ROP**

All neonates are susceptible to infection because of immature immune systems, particularly the premature neonate, due to a delay or decrease in immune response to foreign antigens (Blackburn, 2012). There is evidence that the exposure of the preterm

*Figure 2. Pathogenesis of ROP. (Reprinted with permission from Smith, L. (2003))*
neonate to infection and inflammatory mediators is associated with an increased risk for ROP (M. Chen et al., 2011; Tolsma et al., 2011). Candida sepsis has been independently associated with both an increase in the severity of ROP, as well as the need for surgical intervention. A meta-analysis of eight studies found that systemic fungal infection in very low birth weight infants was significantly associated with ROP and severe ROP (Bharwani & Dhanireddy, 2008).

**Systemic Inflammation**

Studies looking at maternal chorioamnionitis as an independent risk factor for ROP have not found a clear association (J. Lee & Dammann, 2012). Infants born to mothers with clinical chorioamnionitis with signs of systemic inflammation have been reported to have an increased risk for ROP (Woo et al., 2012a). Maternal systemic inflammation has been shown to decrease levels of IGF-1 (Woo et al., 2012a), which inhibits vascular growth by suppressing VEGF.

Oxidative stress has long been implicated as a cause of ROP. Oxidative stress can be a consequence of inflammation as well as hypoxia/ischemia, hyperoxia and reperfusion (Saugstad, 2005b). Preterm infants have higher levels of oxidative stress compared to term infants, a condition which is further complicated by an immature antioxidant system (Moore et al., 2012).

Hypoxia alone can stimulate the production of tumor necrosis factor-alpha (TNF-α), a proinflammatory cytokine, which results in the breakdown of the retinal-blood barrier. Increased levels of TNF-α have been found in the retina of rats for up to 3 days after hypoxic exposure, inducing retinal ganglion cell death (Sivakumar et al., 2011).
Lee and Dammann (2012) reported that their series of epidemiologic studies support the hypothesis that prenatal, perinatal and postnatal systemic inflammation is an additional risk factor for ROP beyond immaturity and/or hyperoxemia (J. Lee & Dammann, 2012). They found that prenatal combined exposure to systemic inflammation (SIRS) and chorioamnionitis (CAM) added to the risk of severe ROP (Dammann et al., 2009) and that neonatal sepsis, oxygen exposure, and low gestational age were not only independent risk factors for ROP but also interact beyond additive and even multiplicative patterns (M. Chen et al., 2011). They propose a possible prephase in the pathogenesis of ROP, beginning prior to birth due to fetal inflammation as well as possible influences of neonatal inflammation due to early and late onset sepsis during Phase I and II.

**Nursing Implications**

Nurses play a key role in the monitoring and management of the premature infant. Nurses must be educated in the need to maintain infant’s oxygen saturations in an optimal range. It can be very difficult to maintain premature infants prone to periodic breathing and apnea of prematurity in a narrow oxygen saturation range. The nurse plays a vital role in infant positioning, activity, and oxygen titration to help maintain the infant in the defined range.

The bedside nurse is responsible for the prevention and detection of infection in the neonate. Infection prevention begins with appropriate hand hygiene. Hand washing has been identified as the most important action to avoid the spread of germs. Central line associated blood stream infection (CLABSI) precautions are also important in the prevention of infection (Stevens & Schulman, 2012). The nurse is responsible for the
monitoring and detection of early signs of sepsis with prompt notification, so the appropriate identification and treatment can be given.

The best prevention for the development of ROP would be to avoid premature birth. Because premature infants continue to be born, we must develop strategies for the provision of intensive medical care necessary to improve outcomes for this population. Nursing actions that monitor oxygen saturations and oxygen delivery, as well as prevent and detect infection, can aid in the prevention of ROP.

In summary, ROP is a vision-threatening disease that occurs only in premature infants. The process has been best described as occurring in phases, with a suppression of vascular growth followed by a rapid proliferation. Although likely multifactorial, low birth weight, prematurity and oxygen use are strongly associated with an increased risk of the disease. There is increasing evidence that inflammatory processes related to perinatal infection and inflammation as well as postnatal sepsis, also play a role in the pathogenesis of the disease, warranting further investigation.
References


CHAPTER 5

RETINOPATHY OF PREMATURITY (ROP) RISK RELATED TO TARGETED OXYGEN SATURATION RANGE

Abstract

ROP is known to be associated with prematurity, low birth weight and oxygen. Many facilities have adopted a targeted oxygen saturation range of 85-93% in order to maintain infants at optimal oxygen levels. The ability to maintain premature infants within this targeted range can be difficult. Many infants spend significant amounts of time both above 93% and below 85%. The potential effect of this time out of targeted range on the development of ROP is unknown. A 24-hour histogram of saturation levels was collected weekly for each infant at risk for ROP from the time of admission and coded for the % of time spent > 93% or ≤ 85% over a period of 3 years. Data were entered longitudinally until retinal maturity occurred or until death/discharge. Survival analysis, using a discrete-time hazard model, was used to predict the risk of developing ROP at Stage 1 or at ≥ Stage 2, due to the total time above and below the targeted range. The study controlled for the effects of gestational age and birth weight using logistic regression. All models included a cubic time trend to reflect the average change in probability of developing ROP. Two hundred and forty-one infants were included in the

3 Article to be submitted to Pediatric Research
analysis after exclusion of 46 infants due to the presence of ROP prior to admission (26),
death (12) or discharge (8) before an eye exam. The total time the infant was out of the
targeted saturation range had no effect on the development of ROP, but the % of time the
infant spent \( \leq 85\% \) predicted the development of \( \geq \) Stage 2 ROP (p<.01). For every 2.7% of the time the infant spent \( \leq 85\% \), their risk for ROP increased by 1.5 times.
Unexpectedly, the % of time the infant spent > 93% decreased the risk for ROP \( \geq \) Stage 2 ROP (p<.01). For every 10% of the time the saturation is >93%, the risk of developing ROP decreases by 0.794 times. These data raise concerns that the time an infant spends \( \leq 85\% \) increases the risk for the development of Stage 2 or greater ROP, whereas the time the infant spends at > 93% decreases this risk. The upper limit for saturations >93% to be beneficial remains unknown.

**Introduction**

Oxygen has been identified as a key element in the development of ROP. Vascular endothelial growth factor (VEGF) is an oxygen-mediated factor that is essential to normal retinal vessel growth. As the retina develops anterior to retinal vessels, there is an increased oxygen demand from the developing neural tissue that creates localized hypoxia. VEGF is expressed in response to this hypoxia, and blood vessels grow toward the VEGF stimulus.

When an infant is born prematurely, the oxygen environment is altered from levels in utero. The retina becomes relatively hyperoxic, causing vasoconstriction, vaso-obliteration and the inhibition of new blood vessel formation, due to down-regulating VEGF expression (Chow et al., 2003). This has been described as Phase I ROP, occurs from birth to a postmenstrual age of 30-32 weeks (M. Chen et al., 2011) and may cause a
delay in the natural retinal development, thereby increasing the risk of developing ROP. Insulin-like growth factor-1 (IGF-1) has also been associated with ROP, as it is an essential factor for the function of VEGF. An infant’s supply of IGF-1 from the placenta and amniotic fluid is removed at the time of birth, contributing to the delay in retinal growth. As the infant matures, IGF-1 levels may be slow to rise, and the levels must reach a threshold for VEGF activation. The nonvascularized retina increases its metabolic activity, leading to relative retinal hypoxia, which promotes increasing concentrations of VEGF. High concentrations of VEGF, along with increasing IGF-1, can trigger retinal neovascularization that moves ROP to Phase II (Hellstrom et al., 2001).

Phase II ROP is believed to begin between 31-34 weeks postmenstrual age. Hypoxia stimulates the up-regulation of pro-angiogenic growth factors, such as VEGF, that can lead to uncontrolled vascular growth and progression of ROP (Smith, 2003). Hemoglobin oxygen saturation targeting was developed as an attempt to avoid hypoxia and hyperoxia in the premature neonate at risk for ROP. Maintenance of lower hemoglobin oxygen saturations avoid the down-regulation of VEGF expression in order to avoid Phases I and II ROP. Studies have shown a decrease in the incidence of ROP through the use of lower oxygen saturations, but have failed to evaluate the potential impact that time out of targeted range has on the development of ROP.

The recognition of oxygen’s role in the development of ROP has led to clinical management of infants by using lower and tighter oxygen saturation ranges to decrease the development of ROP. The evidence supporting the appropriate hemoglobin oxygen saturation target is limited; a targeted saturation range of 85-93% is commonly used for infants at risk for the development of ROP (Castillo et al., 2008; Chow et al., 2003;
Deulofeut et al., 2006; Vanderveen et al., 2006). While a number of studies have reported a decreased incidence of ROP with use of lower saturation targets, the evidence supporting this strategy is limited, and two large, multicenter, randomized control trials, SUPPORT and BOOST II, raised concerns about this management. Both of these studies showed that while the risk of severe ROP was less in the lower saturation group (85% to 89%), mortality increased in this group, as compared to those in the higher saturation range (91% to 94%; Carlo et al., 2010; B. Stenson et al., 2011). These findings emphasize our uncertainty and the need to determine the optimal target saturation range, in order to provide the best overall outcome for at-risk infants.

Hemoglobin oxygen saturation targeting assumes that an individual infant can be maintained within a set target range. Maintaining an infant within a narrow range of saturations can be very challenging because some infants vary rapidly between saturations that are above or below the targeted range. The achieved versus intended pulse oximeter saturation (AVOX) study examined the ability of NICU teams in different facilities to maintain oxygen saturation levels within the limits established in their units. This study showed that in infants of less than 28 weeks’ gestation, saturations frequently fluctuated into both sides of the target. For all patients, the overall time within the intended range varied from 16% to 64% (Hagadorn et al., 2006). The impact on ROP of the time the infant spends out of the targeted range has not been reported.

Additionally, a number of infants are given respiratory support in the form of nasal cannula flow, continuous positive airway pressure or mechanical ventilation at 21% oxygen, the equivalent of room air. The optimal target saturation during these treatments
has not been defined, and there is concern that a high hemoglobin oxygen saturation while on 21% oxygen could contribute to the development of ROP.

The purpose of this retrospective, longitudinal, observational study was to evaluate if the average time over a 24-hour period that the infant spends out of the targeted oxygen saturation range in the weeks prior to the development of ROP can predict the development of ROP. Additionally, the effect of higher hemoglobin oxygen saturation targets while the infant is receiving 21% oxygen was evaluated to determine if this increases the risk of developing ROP.

Methods

Study Sample

All infants admitted to Primary Children’s Hospital newborn intensive care unit in Salt Lake City, Utah, from January 2010 through December 2012, who met AAP guidelines for ROP risk were eligible for the study. Gestational age at birth was determined by maternal dates from the last menstrual period (LMP) and the infant’s examination. The age by examination was used if it differed by more than 2 weeks from the age based on maternal LMP. Exclusion criteria included infants with ROP at the time of admission, and infants that died or were discharged without documentation of retinal examination. Study approval was obtained from the University of Utah Institutional Review Board with oversight for the Children’s Hospital.

Monitoring Equipment

Every infant was monitored by the Phillips IntelliVue MP70 patient monitor® for heart rate, respiratory rate and oxygen saturation. The Massimo signal extraction
technology pulse oximeters (Masimo SET™, Irvine, CA) were part of this package and were used on every patient throughout the course of hospitalization. Phillips monitors provided trend reports of hemoglobin oxygen saturation histograms, recorded every 5 minutes for 24 hours. A 24-hour histogram was collected weekly 1 to 2 days prior to the weekly eye exam on every infant at risk for ROP. Not every patient had an eye exam every week, but saturation data were collected weekly as long as the infant was in the NICU. Occasionally histograms would not be available, due to patient travel away from the bedside on the day of collection. The data were coded for the percentage of time the infant spent \( \leq 85\% \) and \( > 93\% \) in a 24-hour period. Additional data collected weekly included the infant’s weight, the current treatment with supplemental oxygen, mode of oxygen delivery, day of life, postmenstrual age, and eye exam results.

**Ophthalmology Examination**

Current AAP guidelines recommend screening all infants born \(< 1500 \text{ grams} \) or \( \leq 30 \) weeks gestation or with a birth weight \( 1500 \) to \( 2000 \) grams, and regardless of gestational age, any infants with an associated complicated course (Section on Ophthalmology American Academy of Pediatrics, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology, et al., 2006). Data were collected about the incidence of sepsis, intraventricular hemorrhage, necrotizing enterocolitis and surgery as markers of a complicated course. All infants were examined by one of three board-certified pediatric ophthalmologists from the same ophthalmology service (Moran Eye Center, University of Utah). They used the ROP international classification and guidelines, including the Stage, Zone, presence of plus disease, extent of the disease and any sequelae as the disease involutes with each exam. Eye exams
began at 31 weeks postmenstrual age or 4 weeks after delivery, whichever came later. Eye exams continued every 1 to 2 weeks until infant discharge/death/ or retinal vessel maturity occurred.

Statistical Analysis

Descriptive statistics were used to evaluate the demographics of the study group and were reported as mean ± standard deviation for continuous measures and as frequency and percentage for categorical data. A t-test was used for demographic comparisons between infant groups. Kaplan-Meier survival plots portrayed the times to retinal maturity by Phase of ROP, with a log-rank test of equality of cumulative survival functions.

A discrete-time survival model was used to predict the hazard of developing Stage 1 ROP or ROP at ≥ Stage 2, due to the time out of the targeted saturation range, while controlling for the effects of birth weight and postmenstrual age. The discrete time model was implemented as logistic regression, with repeated weekly observations coded as “no event” (event=0) until an ROP occurrence (event=1) occurred, or the patient developed retinal maturity. The terminal data record for each patient thus occurred with the initial development of ROP or at the censoring point of retinal maturity (Singer & Willet, 2003). All models included a cubic time trend to reflect the average change in probability of developing ROP. Three separate logistic regression equations were run to evaluate the effects of saturations less than or equal to 85%, greater than 93%, and the total time the infant was out of targeted range, on the development of ROP. A logarithmic transformation was applied when the original data were skewed. All statistics were run on SPSS® 20 statistical software (IBM Corp. Released 2011. IBM SPSS Statistics for
Results

Data were collected over the course of 3 years for a total of 287 infants admitted to Primary Children’s Hospital (PCH), a quaternary referral center in a free-stand children’s hospital. A total of 241 infants ≤ 33 weeks gestation at the time of birth who were considered to be at risk for ROP and received eye examinations, were included in the analysis. Forty-six infants were excluded, due either to the presence of ROP prior to admission (26), death (12) or discharge (8) before the ROP eye exams. Of the 241 infants included in the analysis, 140 (58%) developed some degree of ROP, of which 81 (58%) had Stage 1 ROP on the first exam and 59 (42%) had Stage 2 or greater on the first ROP exam.

Infant demographics and clinical characteristics of the study population are described in Table 3. Because PCH is a referral center, the infants were admitted with an average postmenstrual age of 31 weeks, having been born at an outside hospital at an average gestational age of 27 weeks and birth weight of 1050 grams. When compared with infants who did not develop ROP, the infants who developed ROP were more immature (gestational age at 26±2 weeks) with a lower birth weight (870±293 grams). Infants who developed ROP were admitted at a younger postmenstrual age (31 ± 4.9SD vs 32 ± 3.7 weeks). The group which developed ROP had significantly more sepsis, IVH and surgery. Gender and incidence of NEC remained the same between the two groups.

Kaplan-Meier analyses (Figure 3) showed a significant ($p<.001$) difference in the distribution function of time to retinal maturity (as defined by examination) by ROP. The
Table 3. Demographics of the ROP Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n=241)</th>
<th>No ROP (n=101)</th>
<th>Any ROP (n=140)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Weight [mean(SD)]</td>
<td>1056 g (411)</td>
<td>1309 (419)</td>
<td>873 (293)*</td>
</tr>
<tr>
<td>Gestational Age wks [mean(SD)]</td>
<td>27.5 wk (2.6)</td>
<td>29.1 wk (2.4)</td>
<td>26.4 wk (2.1)*</td>
</tr>
<tr>
<td>23 weeks [n (%)]</td>
<td>8 (3.3)</td>
<td>1 (12.5)</td>
<td>7 (87.5)</td>
</tr>
<tr>
<td>24 weeks [n (%)]</td>
<td>18 (7.5)</td>
<td>1 (5.6)</td>
<td>17 (94.4)</td>
</tr>
<tr>
<td>25 Weeks [n (%)]</td>
<td>39 (16.2)</td>
<td>4 (10.3)</td>
<td>35 (89.7)</td>
</tr>
<tr>
<td>26 weeks [n (%)]</td>
<td>32 (13.3)</td>
<td>9 (28.1)</td>
<td>23 (71.9)</td>
</tr>
<tr>
<td>27 weeks [n (%)]</td>
<td>33 (13.7)</td>
<td>13 (39.4)</td>
<td>20 (60.6)</td>
</tr>
<tr>
<td>28 weeks [n (%)]</td>
<td>23 (9.5)</td>
<td>12 (52.2)</td>
<td>11 (47.8)</td>
</tr>
<tr>
<td>29 weeks [n (%)]</td>
<td>27 (11.2)</td>
<td>14 (51.9)</td>
<td>13 (48.1)</td>
</tr>
<tr>
<td>30 weeks [n (%)]</td>
<td>22 (9.1)</td>
<td>14 (63.6)</td>
<td>8 (36.4)</td>
</tr>
<tr>
<td>31 weeks [n (%)]</td>
<td>17 (7.1)</td>
<td>12 (70.6)</td>
<td>5 (29.4)</td>
</tr>
<tr>
<td>32 weeks [n (%)]</td>
<td>16 (6.6)</td>
<td>16 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>33 weeks [n (%)]</td>
<td>6 (2.5)</td>
<td>5 (83.7)</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>PMA admission [mean(SD)]</td>
<td>31.0 (4.5)</td>
<td>32.0 (3.7)</td>
<td>31.0 (4.9)*</td>
</tr>
<tr>
<td>Percent of Time ≤ 85% [mean(SD)]</td>
<td>7.91 (11.06)</td>
<td>7.7 (14.5)</td>
<td>8.05 (7.68)</td>
</tr>
<tr>
<td>Percent of Time &gt; 93% [mean(SD)]</td>
<td>47.67 (23.9)</td>
<td>54.6 (27.34)</td>
<td>42.7 (19.77)*</td>
</tr>
<tr>
<td>Total % of Time out of Target [mean(SD)]</td>
<td>55.56 (19.4)</td>
<td>62.4 (21.9)</td>
<td>50.7 (15.75)*</td>
</tr>
<tr>
<td>Male [n (%)]</td>
<td>152 (63.1)</td>
<td>64 (63.4)</td>
<td>88 (62.9)</td>
</tr>
<tr>
<td>Sepsis [n (%)]</td>
<td>214 (88.8)</td>
<td>83 (82.2)</td>
<td>131 (93.6)*</td>
</tr>
<tr>
<td>IVH [n (%)]</td>
<td>109 (45.2)</td>
<td>32 (31.7)</td>
<td>51 (36.4)*</td>
</tr>
<tr>
<td>NEC [n (%)]</td>
<td>84 (34.9)</td>
<td>33 (32.7)</td>
<td>51 (36.4)</td>
</tr>
<tr>
<td>Surgery [n (%)]</td>
<td>160 (66.4)</td>
<td>57 (56.4)</td>
<td>103 (73.6)*</td>
</tr>
</tbody>
</table>

Table 3 shows the mean and standard deviations (SD) for the gestational age and birth weight of each group. Differences between the groups was assessed using an independent samples t-test *=p<.05 when comparing no ROP to any ROP. Of the 241 infants, 58% developed some degree of ROP; SD, standard deviation; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis as defined by pneumatosis on x-ray; sepsis, confirmed culture or a clinical course requiring a minimum of 7 days of treatment.
combined logistic regression coefficients for all infants developing Stage 2 or greater ROP are displayed in Table 4. Time predictors were entered by week to examine event occurrence sequentially among infants at risk for ROP at each discrete point in time. A cubic time trend was used to reflect the average change in probability of developing ROP. Next, birth weight and postmenstrual age were entered to account for the infant’s birth weight risk, as well as to adjust for their age at study entry. Finally, the variables related to time out of targeted saturation range were entered to determine significance. The total time the infant was out of the targeted saturation range, conditional on birth

*Figure 3. Kaplain-Meier Curve*
Table 4. Combined Logistic Regression Coefficients for the Development of ≥ Stage 2 ROP Based on Time out of Targeted Range (85-93%)

<table>
<thead>
<tr>
<th></th>
<th>The effects of saturations ≤ 85%</th>
<th>The effects of saturations &gt; 93%</th>
<th>The effects of Total Time out of Target</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Infants with ROP OR (95% CI)</td>
<td>Infants with ROP OR (95% CI)</td>
<td>Infants with ROP OR (95% CI)</td>
</tr>
<tr>
<td>Linier</td>
<td>0.378 (0.147-0.969)</td>
<td>0.395 (0.15-1.01)</td>
<td>5.00 (0.466-53.72)</td>
</tr>
<tr>
<td>Quadratic</td>
<td>1.26 (1.042-1.524)</td>
<td>.257 (1.04-1.52)</td>
<td>0.804 (0.54-1.207)</td>
</tr>
<tr>
<td>Cubic</td>
<td>0.987 (0.976-0.998)</td>
<td>0.987 (0.98-0.99)</td>
<td>1.008 (0.987-1.03)</td>
</tr>
<tr>
<td>Birth Weight</td>
<td>0.998 (.9998-0.999)</td>
<td>0.999 (0.99-1.00)</td>
<td>1.00 (0.998-1.001)</td>
</tr>
<tr>
<td>Postmenstrual age at Entry</td>
<td>1.110 (1.054-1.168)</td>
<td>&lt;.001</td>
<td>0.980 (0.892-1.08)</td>
</tr>
<tr>
<td>Log of Time ≤ 85%</td>
<td>1.48 (1.113-1.971)*</td>
<td>1.143 (1.08-1.21)</td>
<td>0.977 (0.96-0.99)‡</td>
</tr>
<tr>
<td>Time &gt; 93%</td>
<td></td>
<td>0.977 (0.96-0.99)‡</td>
<td>0.001</td>
</tr>
<tr>
<td>Total Time Out of Range</td>
<td></td>
<td></td>
<td>1.007 (0.985-1.03)</td>
</tr>
<tr>
<td>21% oxygen †</td>
<td>0.50 (0.186-1.344)</td>
<td>0.427 (0.16-1.17)</td>
<td>0.704 (0.24-2.063)</td>
</tr>
</tbody>
</table>

†RA was added to the regression equation for each model. When it was not significant, it was removed from the final result. * Increase in OR for each 2.7% of the time ≤ 85%. The odds ratio per one unit increase the (logged) predictor. Because of nonlinearity, the odds ratios vary with the untransformed original percent score. The first, second (median), and third quartiles of percent of time less than 85% saturation are 1%, 4%, and 10%, respectively. At these values, the approximate odds ratios are 1.24, 1.08, and 1.04, respectively, for a one-unit increase in the percentage of time with saturation under 85%. For example, the approximate odds ratio for a change of 3.5% to 4.5% in percentage of time under 85% saturation is 1.08. The other predictors can be interpreted directly, as their distributions did not require transformation. ‡Decrease in OR for every 1% of the time > 93%. OR, odds ratio; CI, confidence interval.
weight, study entry age, and cubic elapsed time, had no effect on the development of ROP ($p=0.54$). On the other hand, the percentage of time the infant spent $\leq 85\%$ predicted the development of ROP ($p<0.01$). For every 2.7\% of the time the infant spent $\leq 85\%$, their risk for ROP increased by 48\%\(^4\). Unexpectedly, the percentage of time the infant spent $> 93\%$ decreased the risk for ROP ($p<0.01$). For every 10\% of the time the saturation was $>93\%$, the risk of developing ROP decreased by 21\%.

The impact of an infant’s breathing 21\% oxygen by cannula or ventilator on the development of ROP was evaluated. Infants breathing 21\% oxygen were found to spend, on average, 70.4\% (SD 28.3) of their time with hemoglobin oxygen saturations $> 93\%$ versus infants breathing $> 21\%$ oxygen who spent, on average, 36.9\% (SD 24.0) of the time $> 93\%$ ($p<0.001$). The time with hemoglobin oxygen saturations $\leq 85\%$ for infants breathing 21\% oxygen was, on average, 3.3\% (SD 8.8), versus an average time of 8.7\% (SD 11.6) for infants breathing $> 21\%$ oxygen ($p<0.001$). The total time out of the targeted saturation range for infants breathing 21\% oxygen was, on average, 68.3\% (SD 26.3), versus the average total time out of range for infants breathing $> 21\%$ oxygen: 46.2\% (SD 22.2; $p<0.001$). When time breathing 21\% oxygen or time breathing room air was added into the regression equation at all levels, it was not found to be significant for the prediction of ROP (last row on Table 3).

\(^4\) The odds ratio per one unit increase the (logged) predictor. Because of nonlinearity, the odds ratios vary with the untransformed original percentage score. The first, second (median), and third quartiles of percent of time less than 85\% saturation are 1\%, 4\%, and 10\%, respectively. At these values, the approximate odds ratios are 1.24, 1.08, and 1.04, respectively, for a one unit increase in the percentage of time with saturation under 85\%. For example, the approximate odds ratio for a change of 3.5\% to 4.5\% in the percentage of time under 85\% saturation is 1.08. The other predictors can be interpreted directly, as their distributions did not require transformation.
Discussion

The optimal hemoglobin oxygen saturation range for infants at risk for ROP is not known (Saugstad & Aune, 2014). While a number of studies have demonstrated decreased incidence of ROP using a lower saturation as compared to a higher saturation, there has been little consensus on the definition of the ideal targeted range. Unfortunately, lower hemoglobin oxygen saturation ranges were associated with increased mortality in the SUPPORT Study (Carlo et al., 2010). There is a great deal of ambiguity in the desired hemoglobin oxygen saturation ranges, with different definitions for high versus low saturation targets (Askie et al., 2003; Carlo et al., 2010; Chow et al., 2003; Deulofeut et al., 2006; J. P. Goldsmith & Greenspan, 2007; Greenspan & Goldsmith, 2006; Hagadorn et al., 2006; Hay & Bell, 2000; Johnston et al., 2011; Noori et al., 2009; B. Stenson et al., 2011; S. C. Sun, 2002; The STOP-ROP Multicenter Study, 2000; Tin, Milligan, Pennefather, & Hey, 2001a; Tokuhiro et al., 2009; Vanderveen et al., 2006). Achieving the desired saturation range is difficult overall and is even more difficult with narrow targeted ranges. Infants can spend a wide variety of time either above or below the desired target (Armbruster, Schmidt, Poets, & Bassler, 2010; Clucas, Doyle, Dawson, Donath, & Davis, 2007; Deuber, Abbasi, Schwoebel, & Terhaar, 2013; Hagadorn et al., 2006; Lim et al., 2014; Sink, Hope, & Hagadorn, 2011).

This study is the first to look at the effects of the time an infant spends out of the targeted saturation range of 85-93% in the weeks prior to the development of ROP on the development of ROP. The time spent \( \leq 85\% \) increased the risk for developing Stage 2 or greater ROP. While unexpected, this finding has been supported by three studies published by Di Fiore et al., derived from a subset of patients in the SUPPORT study.
The SUPPORT study showed that lower saturations decreased the incidence of ROP (Carlo et al., 2010). The first study published by Di Fiore et al. showed that infants maintained in a saturation target of 85-89%, compared to infants in the 91-95% saturation group, had an increased rate of intermittent hypoxemia events ($\leq 80\%$ for $\geq 10$ seconds and $\leq 3$ minutes) prior to 12 days and beyond 57 days of life ($p<.05$; Di Fiore, Walsh, et al., 2012). They later showed that hypoxemic events increased with postnatal age, and the incidence of hypoxemic events was higher for infants with severe ROP requiring laser therapy, regardless of gestational age, race, multiple births, sex or severity of early systemic illness (Di Fiore et al., 2010). A final study looked at the intermittent hypoxemic events’ duration, severity and time interval between events. Severe ROP was associated with more variable, longer, and less severe hypoxemic events, as defined by a higher nadir, after 14 days of life (Di Fiore, Kaffashi, et al., 2012).

In contrast to the studies showing that the risk of ROP increased with higher hemoglobin oxygen saturations (Askie et al., 2003; Chow et al., 2003; Deulofeut et al., 2006; Noori et al., 2009; B. Stenson et al., 2011; Tin et al., 2001b; Tokuhiro et al., 2009; Vanderveen et al., 2006), the time above hemoglobin oxygen saturation of 93% was associated with a decrease in the risk for developing Stage 2 or greater ROP. The only randomized, multicenter, blinded study that supports the use of higher saturations is the STOP-ROP trial published in 2000 (The STOP-ROP Multicenter Study Group, 2000). This study was unique in its design, evaluating the effects of high (96-99%) versus low (89-94%) saturations on infants with prethreshold ROP, as well as the progression to threshold ROP and the need for laser treatment. They found that 48% of the lower saturation group versus 41% of the higher saturation group developed more severe ROP.
that needed laser treatment. Interestingly, the average postmenstrual age for all study participants was 35 weeks, well into the timing for Phase II ROP.

Both of the findings for low and high saturations required complex analyses and statistical modeling. The surprising trends regarding the amount of time ≤ 85% and > 93% were evident in the basic data themselves, and did not depend on complex data manipulation. These results are consistent with the theoretical model for the pathogenesis of ROP. Phase I ROP (22-30 weeks PMA) is identified as an oxygen sensitive time when the retina requires relative hypoxia for normal vascular development to progress. With relative hyperoxia, VEGF levels decrease, halting retinal vessel growth. Stage 2 Phase II ROP (31-44 weeks PMA) is a time when relative hypoxia in the retina leads to increased VEGF concentrations that may lead to over-proliferation of retinal vasculature and ROP (Mintz-Hittner et al., 2011). The average age for entry into the current study was 31 weeks PMA, which fits the timing of Phase II ROP. The results show that the time an infant spends ≤ 85% saturation increases the risk for the development of ROP, and that having a saturation > 93% lessens this risk. It may be that having higher saturations during Phase II will attenuate the production of VEGF, thereby decreasing the risk for ROP, while lower saturations perpetuate the relative retinal hypoxia and increase the risk for vasculature proliferation, leading to the development of ROP.

This study did not demonstrate that higher saturation levels while an infant is breathing 21% oxygen increased the development of ROP. The literature supports the idea that part of the injury that occurs with ROP may be due to oxidative stress experienced by a premature infant who lacks appropriate anti-oxidant defense mechanisms (J. Lee & Dammann, 2012; Saugstad, 2006). It is not clear whether high
saturation levels can be interpreted as a marker for increased risk of oxidative stress. A study by Nagatomo et al. (2012) in a rat model found that oxidative stress, measured by reactive oxygen metabolites, only occurred after exposure to oxygen concentrations greater than 40% for 24 hours. Rats exposed to 14.4%, 21% and 35.5% oxygen did not show signs of oxidative stress (Nagatomo et al., 2012). Vento et al. (2001) reported a study in term infants resuscitated with 21% oxygen instead of 100% oxygen. They found that infants resuscitated with 100% oxygen exhibited findings reflective of prolonged oxidative stress that did not appear in the 21% oxygen group (Vento et al., 2001). The current study found no increased risk of ROP for infants having high saturation levels while breathing 21% oxygen.

To address the problem of causal ambiguity with the varying covariates, the time-varying predictors were defined, and the targeted values of 85-93% were used as the accepted standard for ROP prevention for infants at risk for the development of ROP. Data were collected in the days prior to the ophthalmologic examination, with censoring of infants once ROP status was known. This gave a natural lag to the data. When the data were evaluated by additional lagging, the results remained similar. This removed the possibility that time out of range could have been influenced by an individual’s ROP status.

**Limitations of This Study**

This study does not address time out of oxygen saturation targets during the first days or weeks of life. While the average age of entry into the study was 31 weeks PMA, infants were enrolled as early as 25 weeks PMA. Only 27% of the study group was < 30 weeks gestation on entry into the study, thereby placing them in Phase I ROP. Additional
study, ideally in a birth facility, will help to determine if these results are consistent for infants entering the study during Phase I ROP.

This study was unable to identify the frequency of saturation fluctuation between high and low saturations. The histogram report only indicates the total percentage of time the infant was above or below the targeted saturation range, without giving any indication of the frequency of the fluctuations. Fluctuations in transcutaneous oxygen levels have been shown to be important risks for severe ROP in both clinical and animal studies (Chow et al., 2003; Cunningham et al., 1995; McColm et al., 2004; Penn et al., 1994; Tin et al., 2001b; York et al., 2004). The variations in oxygen are proposed to cause fluctuations in retinal oxygenation and may be secondary to changes in both inspired and blood oxygen concentration, the result of episodes of apnea and bradycardia (Hartnett, 2010a). Unfortunately, the recording device used in this clinical setting could not measure the number of fluctuations in hemoglobin oxygen saturation.

The group with ROP had significantly more sepsis, IVH and surgery. These variables were not included in the analysis because these data were collected as markers of a complicated course and were not time-stamped. The power of this study is in the use of a discrete-time model that allows for the sequential examination of event occurrence. Further investigation of the timing of these co-morbidities in the trajectory leading toward ROP analyzed with the discrete-time model, would allow evaluation of their potential impact on the development of ROP.

Uncontrolled oxygen administration to premature newborns was the first recognized cause of ROP (Campbell, 1951). Today, with the use of saturation technology and targeted saturations, uncontrolled oxygen administration is no longer the issue in the
development of ROP. However, the upper limit for saturations >93% to be beneficial remains unknown and requires further investigation.

Despite these limitations, the present study is the first to report the impact of time out of targeted range due to hypoxia and/or hyperoxia on the development of ROP. This study has demonstrated the importance of looking at the time the infant spends out of a targeted saturations range. A saturation level ≤ 85% will increase the likelihood of developing Stage 2 or greater ROP, and saturation levels > 93% will reduce the risk of ROP in the same population. This seems to be particularly true for infants during Phase II ROP.

These findings are timely, given the continued debate on what the optimal saturation targets are, and the growing interest in the development of PMA-adjusted saturation levels for infants at risk for the development of ROP. Perhaps the oxygen target for Phase I ROP is different than the optimal target for Phase II ROP. This study would support the use of a higher saturation range for infants, especially by 31 weeks PMA. This study also indicated that allowing infants breathing 21% oxygen to have high oxygen saturations does not contribute to their risk for developing ROP.
References


CHAPTER 6

TARGETED OXYGEN SATURATION RANGE AND INFANT SURVIVAL

Abstract

ROP was first recognized in the 1940s as associated with prematurity, and then, in the 1950s, with oxygen. Current management to decrease the incidence of ROP involves targeting oxygen saturation levels to avoid hyperoxia (>93%) and hypoxia (<85%). The ability to maintain premature infants within the targeted range can be difficult, with saturations frequently above and below these targeted values. The potential effect of this time out of targeted range on the risk of death has not been reported. A 24-hours histogram of saturation levels was collected weekly from the time of admission for each infant ≤ 33 weeks gestation felt to be at-risk for ROP over a 3-year period. Data were entered longitudinally on infants who remained in the PCH NICU until death or discharge. Survival analysis using a discrete-time hazard model was used to predict the risk of death, due to the time above or below the targeted range, while controlling for the effects of gestational age, birth weight and time using a quadratic time trend. Logistic regression was used, with a deviance statistic to determine significance. Two hundred and fifty infants were included in the analysis after exclusion of 37 infants, due to the presence of ROP prior to admission (26), death (3) or discharge without an eye exam (8).

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The percentage of time the infant had hemoglobin oxygen saturation ≤ 85% predicted the risk of death \((p<.001)\). For every 2.7% of the time the infant spent ≤ 85%, the risk for death increased by 1.11 times. The percentage of time an infant spent >93% decreased the risk of death \((p<.001)\). For every 10% of time the infant spent with saturations > 93%, the risk of death decreased by 0.89 times. These data indicate that survival can potentially be improved by reducing the time spent with saturations ≤85%. Although time with saturations above 93% improved survival, these data do not allow determination of how much above 93%, or for how long, it is advantageous because of study monitoring limitations and because saturations were not routinely maintained in this higher range.

**Introduction**

Retinopathy of prematurity (ROP) was first associated with prematurity in the 1940s, and later with oxygen supplementation for premature infants in the 1950s (Campbell, 1951; J. Chen et al., 2011; Fisher, 1956; Patz, 1957b). In 1951, Dr. Kate Campbell suggested that ROP, or as it was known at that time, retrolental fibroplasia (RLF), was a result of the toxic effects of uncontrolled oxygen administration given to premature newborns, and suggested avoiding routine use of oxygen in this population, reserving its use solely for infants experiencing cyanosis (Reedy, 2004). Subsequent studies in the 1950s demonstrated a causal association between premature newborns exposed to high concentrations of supplemental oxygen therapy and obliterated retinal blood vessels (James & Lanman, 1976).

Following these studies, the use of oxygen was severely curtailed and restricted only to cyanotic infants at concentrations not to exceed 40% (Reedy, 2004). The
incidence of ROP, or RLF as it was then known, declined in the United States, dropping from 50% in at risk infants in 1950 to 4% by 1965; however, this decline was accompanied by an increase in neonatal deaths and cerebral palsy within the same time period (Pollan, 2009; Wheatley, Dickinson, Mackey, Craig, & Sale, 2002a). Resurgence in the rates of ROP occurred in the late 1970s and 1980s, despite careful monitoring of oxygen delivery to neonates. This is believed to be due to the fact that advances in neonatal care significantly increased the survival of very preterm infants at high risk for developing ROP (J. Chen et al., 2011; Wheatley et al., 2002a).

The recognition of oxygen’s role in the development of ROP has led to the clinical management of lower and tighter oxygen saturation ranges in order to decrease the risk of the development of ROP. The evidence supporting the appropriate hemoglobin oxygen saturation target is limited; a targeted saturation range of 85-93% is commonly used with infants at risk for the development of ROP (Castillo et al., 2008; Chow et al., 2003; Deulofeut et al., 2006; Vanderveen et al., 2006). While a number of studies have reported a decreased incidence of ROP when using lower saturation targets, the evidence supporting this strategy is limited, and concern has been raised with the results of two large, multicenter, randomized control trials, SUPPORT and BOOST II. These studies both showed that while the risk of severe ROP was less in the lower saturation group (85% to 89%), there was an increased mortality in this group when compared to the higher saturation group (91% to 94%) (Carlo et al., 2010; B. Stenson et al., 2011). This finding has created uncertainty and concern as to the optimal target saturation to provide the best overall outcome for at-risk infants.

Hemoglobin oxygen saturation targeting was developed in an attempt to avoid
hypoxia and hyperoxia in the premature infant at risk for ROP. Oxygen saturation targeting research has resulted in a decrease in the incidence of ROP through the use of lower saturations, but has failed to recognize the potential impact that time out of the targeted range has on the development of ROP and, more significantly, infant survival.

Oxygen targeting assumes that an individual infant can be maintained within the set hemoglobin oxygen saturation range. However, every newborn intensive care (NICU) nurse knows that this can be very challenging, resulting in some infants experiencing saturation frequently above and/or below the targeted range. The achieved versus intended pulse oximetry saturation (AVOX) multicenter study showed that for infants less than 28 weeks’ gestation, there was marked instability with regards to fluctuation in saturations into both sides of the target. Overall, time outside of the intended range (for all patients combined) ranged from 36% to 84% (Hagadorn et al., 2006). A study by Deuber et al. (2013) examined the average amount of time infants spent >92% in 2 separate cohorts. The average time infants had saturations 93-100% in cohort 1 (31 infants) was 42.6% (SD 19.3) and 54.5% (SD 24.3) in cohort 2 (24 infants) (Deuber et al., 2013).

No one has reported the impact of the time an infant spends out of the targeted range has on infant survival. The purpose of this retrospective, longitudinal, observational study was to evaluate if the average time over a 24-hour period that a premature infant spends out of the targeted oxygen saturation range of 85-93% can predict survival.
Methods

Study Sample

All infants admitted to Primary Children’s Hospital newborn intensive care unit in Salt Lake City, Utah, from January 2010 through December 2012, who met AAP guidelines for ROP risk, were eligible for the study (Fierson, American Academy of Pediatrics Section on Ophthalmology, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology and Strabismus, & American Association of Certified Orthoptists, 2013). Exclusion criteria included the use of extracorporeal membrane oxygenation (ECMO), infants with ROP at the time of admission, and infants that died or were discharged without collection of any saturation data. Study approval was obtained from the University of Utah Institutional Review Board providing oversight for the children’s hospital.

Monitoring Equipment

Every infant was monitored by the Phillips IntelliVue MP70 patient monitor® for heart rate, respiratory rate and oxygen saturation. The Massimo Signal Extraction technology pulse oximeter (Masimo SET™, Irvine, Ca) is included in this package and was used to monitor every patient throughout the course of hospitalization. Trend options for reports of oxygen saturation were available as histograms. The histogram recorded 24 hours of saturation data by recording a 1-second sample of data every 5 minutes. A 24-hour histogram was collected weekly for every infant at risk for ROP as long as the infant was in the NICU. Occasionally, histograms were not available, due to patient travel away from the bedside on the day of collection. The data were coded for the percentage of time the infant spent ≤ 85% and > 93% in a 24-hour period of time. Additional data, collected
weekly, included the infant’s weight, current treatment with supplemental oxygen and mode of oxygen delivery, day of life, postmenstrual age and eye exam results.

Statistical Analysis

All statistics were run on SPSS® 20 statistical software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM CORP) to determine the exact p value, with a significance level set at p < 0.05. Descriptive statistics were used to evaluate the demographics of the study group, and were reported as frequencies and percentage for categorical data, or as mean ± standard deviation for continuous measures.

Survival analysis using a discrete-time hazard model was used to predict the hazard of death due to the time out of targeted saturation range, while controlling for the effects of birth weight and postmenstrual age. The discrete-time was implemented as logistic regression, with repeated weekly observations coded as “no event” (event 0) until death occurred (event 1), or the patient was discharged. This model allows for the sequential examination of event occurrence among individuals who are eligible to experience the event at each discrete point in time. All models included a quadratic trend to reflect the average change in probability of death. Two separate logistical regression equations were used to evaluate the effects of saturations less than or equal to 85% or greater than 93% on infant survival. A logarithmic transformation was applied when the original data were not normally distributed.

The Wald statistic has a questionable reliability, particularly for small samples (Bewick, Cheek, & Ball, 2005; Singer & Willet, 2003). Consequently, a deviance-based approach was used, as recommended by Singer and Willett (Singer & Willet, 2003), for
hypothesis testing. This model involved comparing nested models with a calculation of differences in deviances (-2 log likelihood), thereby utilizing a chi squared distribution to determine significance.

**Results**

Data were collected on a total of 287 infants admitted over the course of 3 years to Primary Children’s Hospital (PCH), a quaternary referral center in a free-standing children’s hospital. A total of 250 infants, all \( \leq 33 \) weeks gestation and considered at risk for ROP with evaluable data, were included in the analysis. Thirty-seven infants were excluded, due to the presence of ROP prior to admission (26), discharge before the ROP eye exams (8) or death prior to saturation data collection (3). Of the 250 infants included in the analysis, 17 (6.8%) died prior to discharge.

Infant demographics and clinical characteristics of the study population are described in Table 5. Because PCH is a referral center, the infants were admitted with an average postmenstrual age of 32 weeks, having been born at an outside hospital at an average gestational age of 27 weeks and an average birth weight of 1050 grams. The infants who died had no significant differences in birth weight, gestational age or adjusted gestational age on admission. There were no statistical differences in percentage of time spent greater than 93%, gender, IVH, NEC or surgeries. The two significant differences were a greater percentage of time spent \( \leq 85\% \) and a higher occurrence of sepsis in the nonsurvivors.

The combined logistic regression coefficients are displayed in Table 6. Time predictors were entered first by week as discrete units, in order to examine event occurrence sequentially among infants at risk for ROP at each discrete point in time.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n=250)</th>
<th>Survivors (n=233)</th>
<th>Non Survivors (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Weight grams [mean(SD)]</td>
<td>1056 (417)</td>
<td>1062 (412)</td>
<td>966 (480)</td>
</tr>
<tr>
<td>Gestational Age wks [mean(SD)]</td>
<td>27.5 (2.6)</td>
<td>27.6 (2.6)</td>
<td>26.8 (2.9)</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td>23 weeks [n (%)]</td>
<td>11 (3.3)</td>
<td>8 (72.7)</td>
</tr>
<tr>
<td></td>
<td>24 weeks [n (%)]</td>
<td>19 (7.5)</td>
<td>17 (89.5)</td>
</tr>
<tr>
<td></td>
<td>25 Weeks [n (%)]</td>
<td>39 (16.2)</td>
<td>37 (94.9)</td>
</tr>
<tr>
<td></td>
<td>26 weeks [n (%)]</td>
<td>33 (13.3)</td>
<td>32 (97.0)</td>
</tr>
<tr>
<td></td>
<td>27 weeks [n (%)]</td>
<td>33 (13.7)</td>
<td>30 (90.9)</td>
</tr>
<tr>
<td></td>
<td>28 weeks [n (%)]</td>
<td>23 (9.5)</td>
<td>23 (100)</td>
</tr>
<tr>
<td></td>
<td>29 weeks [n (%)]</td>
<td>29 (11.2)</td>
<td>27 (93.1)</td>
</tr>
<tr>
<td></td>
<td>30 weeks [n (%)]</td>
<td>22 (9.1)</td>
<td>21 (95.5)</td>
</tr>
<tr>
<td></td>
<td>31 weeks [n (%)]</td>
<td>19 (7.1)</td>
<td>16 (84.2)</td>
</tr>
<tr>
<td></td>
<td>32 weeks [n (%)]</td>
<td>16 (6.6)</td>
<td>16 (100)</td>
</tr>
<tr>
<td></td>
<td>33 weeks [n (%)]</td>
<td>6 (2.5)</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Postmenstrual age at admission [mean(SD)]</td>
<td>32. (4.5)</td>
<td>32.1 (4.3)</td>
<td>32.3 (6.2)</td>
</tr>
<tr>
<td>Percent of Time ≤ 85% [mean(SD)]</td>
<td>8.36 (12.6)</td>
<td>7.97 (11.2)</td>
<td>12.6 (25.3)*</td>
</tr>
<tr>
<td>Percent of Time &gt; 93% [mean(SD)]</td>
<td>47.3 (24.0)</td>
<td>48.4 (24.1)</td>
<td>40.8 (22.8)</td>
</tr>
<tr>
<td>Total % of Time out of Target [mean(SD)]</td>
<td>55.6 (19.5)</td>
<td>55.7 (19.4)</td>
<td>54.4 (20.7)</td>
</tr>
<tr>
<td>Male [n (%)]</td>
<td>157 (62.8)</td>
<td>147 (63.1)</td>
<td>10 (58.8)</td>
</tr>
<tr>
<td>Sepsis [n (%)]</td>
<td>206 (82.4)</td>
<td>189 (81.1)</td>
<td>17 (100)*</td>
</tr>
<tr>
<td>IVH [n (%)]</td>
<td>103 (41.2)</td>
<td>97 (41.6)</td>
<td>6 (35.3)</td>
</tr>
<tr>
<td>NEC [n (%)]</td>
<td>79 (31.6)</td>
<td>75 (32.2)</td>
<td>4 (23.5)</td>
</tr>
<tr>
<td>Surgery [n (%)]</td>
<td>151 (60.4)</td>
<td>140 (60.1)</td>
<td>11 (64.7)</td>
</tr>
</tbody>
</table>

Table 5. Demographics of the Survival Study Population.

Of the 250 infants, 6.7% died. Table 5 shows the mean and standard deviations (SD) for the gestational ages and birth weights of each group. There were no differences between the groups as assessed using an independent samples t-test *p<.05, except for sepsis, which occurred in all of the nonsurvivors, and time with saturations ≤ 85%.

SD, Standard deviation; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis, as defined by pneumatosis on x-ray; sepsis, confirmed culture of clinical course requiring a minimum of 7 days of treatment
Table 6. Combined Logistic Regression Coefficients for the Development Death, Based on Time out of Targeted Range

<table>
<thead>
<tr>
<th></th>
<th>The effects of saturations ≤ 85%</th>
<th>The effects of saturations &gt; 93%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Infants who Died OR (95% CI)</td>
<td>p Value</td>
</tr>
<tr>
<td>Linear</td>
<td>0.707 (0.562-0.889)</td>
<td>0.003</td>
</tr>
<tr>
<td>Quadratic</td>
<td>1.01 (1.003-1.017)</td>
<td>0.004</td>
</tr>
<tr>
<td>Birth Weight</td>
<td>1.000 (0.999-1.001)</td>
<td>0.898</td>
</tr>
<tr>
<td>Postmenstrual age at Entry</td>
<td>1.066 (0.977-1.163)</td>
<td>0.151</td>
</tr>
<tr>
<td>Log of Time ≤ 85 %</td>
<td>1.109* (0.68-1.808)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time &gt; 93% Saturation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Increase in OR for each additional 2.7% of time in 24 hours that the infant spends ≤ 85%; OR, odds ratio; CI, confidence interval

Next, birth weight and postmenstrual age were entered to account for the infant’s birth weight risk, as well as to adjust for the age at study entry. Finally, the variables related to time out of targeted saturation range were entered individually, thereby determining their significance as compared to the uncontrolled test without that predictor. Evaluating the effect of the percentage of time with hemoglobin oxygen saturation ≤ to 85% resulted in a difference in deviance statistics of 12.71 (191.78 minus 179.07). As the 0.1% critical value for a $\chi^2$ distribution on one degree of freedom is 10.8, we rejected the null hypothesis at the ($p$<.001). The percentage of time the infant spent with saturations ≤ 85% predicted the development of death. For every 2.7% of the time the infant spent ≤ 85%, their risk of death increased 1.11 times. Evaluating the effect of the percentage of

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6 The odds ratio per one unit increase in the (logged) predictor. Because of nonlinearity, the odds ratios vary with the untransformed original percentage score. The first, second (median), and third quartiles of
time an infant spends with hemoglobin oxygen saturation > 93% resulted in a difference in deviance statistics of 13.9 (191.78 minus 177.85). As the 0.1% critical value for an $\chi^2$ distribution on one degree of freedom is 10.83, we rejected the null hypothesis ($p<.001$). Every 1% of time the infant spent with saturations > 93% decreased the risk of death by 0.99 times.

**Discussion**

The optimal hemoglobin oxygen saturation range for infants at risk for ROP is not known (Saugstad & Aune, 2014). Achieving narrow-targeted saturation ranges is difficult, for infants can spend a large amount of time either above or below the ordered target range (Armbruster et al., 2010; Clucas et al., 2007; Deuber et al., 2013; Hagadorn et al., 2006; Lim et al., 2014; Sink et al., 2011). This study is the first to report the effects on the risk of death of the time an infant spends out of the targeted hemoglobin saturation range of 85-93% in the weeks prior to the development of ROP. The time spent less than or equal to 85% was found to increase the risk of death.

The question of causal ambiguity would ask if the infants who died were impacted by lower saturations or if they were unable to saturate because they were dying? In a week by week review of the data on the 17 nonsurvivors, there was only one of the 17 who was unable to achieve the saturation target. The remaining 16 had variable time both above and below the targeted saturation range.

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percentage of time less than 85% saturation are 1%, 4%, and 10%, respectively. At these values, the approximate odds ratios are 1.058, 1.017, and 1.008, respectively, for a one unit increase in the percentage of time with saturation under 85%. For example, the approximate odds ratio for a change of 3.5% to 4.5% in percentage of time under 85% saturation is 1.017. The other predictors can be interpreted directly, as their distributions did not require transformation.
There are several observational studies that have evaluated various saturation ranges and their effect on ROP; however, none of these demonstrated a difference in mortality, including two systematic reviews and meta-analyses (Askie, Henderson-Smart, & Ko, 2009; Saugstad & Aune, 2011; Tin et al., 2001b). The observations prompted investigation by several multicenter randomized control trials (RCTs) in order to determine the optimal oxygen saturation target in extremely low birth weight infants. These RCTs consist of the SUPPORT trial (Surfactant, Positive Pressure and Pulse Oximetry Randomized Trial) (Carlo et al., 2010), the BOOST II trial (Benefits of Oxygen Saturation Targeting) from the UK, Australia and New Zealand (Boost II United Kingdom Collaborative Group et al., 2013) and the COT trial (B. Schmidt et al., 2013) (Canadian Oxygen Trial). Each of these studies compared two different saturation ranges, low (85-89%) and high (91-95%), for infants with gestational ages of less than 28 weeks.

A recent meta-analysis by Saugstad and Aune combined results of these studies, which encompassed 4,911 infants (Saugstad & Aune, 2014). They found no differences in the outcomes of bronchopulmonary dysplasia, intraventricular hemorrhage or patent ductus arteriosus. There was, however, a decreased risk for severe ROP in the low saturation group, at 10.7% versus 14.5% in the high saturation group (RR 0.74, CI 0.59-0.92). Disturbingly, the low saturation group also showed an increased risk for death before discharge at 19.3% versus 16.2% in the high saturation group (RR 1.18, CI 1.04-1.34), as well as an increased risk for necrotizing enterocolitis at 11.2% versus 9.0% for the high saturation group (RR 1.25, CI 1.05-1.49). In response to the meta-analysis results, Saugstad and Aune, along with several others, have recommended targeting
saturation ranges for infants < 28 weeks gestation at 90-95% (Bancalari & Claure, 2013; Polin & Bateman, 2013; Saugstad & Aune, 2014; Sweet et al., 2013).

While none of these RCTs reported data on the time the infants spent above or below the targeted saturations, Di Fiore et al. (Di Fiore, Walsh, et al., 2012) analyzed a subgroup of the SUPPORT study and showed that infants maintained in the low range (85-89%), as compared to infants in the high range (91-95%), had an increased rate of intermittent hypoxemia events (saturations $\leq 80\%$ for 10 seconds to 3 minutes) before 12 days and beyond 57 days of life ($p<0.05$). The current observational study had variability in the individual patient saturation limits throughout the 3 years of observation. There were three main limits for low saturation alarms: 85%, 88% and 92%. Figure 4 is a histogram of these 3 levels, showing that the lower the saturation alarm limit, the greater the amount of time spent $\leq 85\%$. This finding is consistent with an earlier study by McEvoy et al. (1993) who observed 21 former preterm infants with chronic lung disease (CLD) at two different saturation levels, 87-91% and 94-96%. They found that desaturation episodes $< 85\%$ were significantly greater in the lower saturation group (B. J. Stenson & Orme, 2012). These studies would indicate that a saturation level of 85% may be unsafe and increase the risk of episodes of further desaturation $< 85\%$ with an increased risk for death.

The time spent $> 93\%$ was found to decrease the risk of mortality. It would seem that we have not yet clearly defined the optimal high saturation level, but we have shown evidence that a saturation level $> 93\%$ provides benefit. The STOP-ROP trial (Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity) (The STOP-ROP Multicenter Study Group, 2000) compared saturation ranges of 89-94%
Figure 4. Histogram of the time spent with an SpO2 ≤ 85% at three different monitor alarm levels, 85%, 88%, and 92%.

with 95-99% in preterm infants with prethreshold ROP. Although there was a decrease in the need for laser treatment of ROP in the high saturation group, they also required longer hospitalization, suffered more respiratory morbidity and had a prolonged need for oxygen supplementation. The optimal upper limit for hemoglobin oxygen saturation > 93% to be of benefit remains unknown.

This study was limited by a relatively small sample size. However, even with a mortality rate of less than 7%, there were significant differences, using the deviance-based analysis recommended by Singer and Willet (Singer & Willet, 2003), in survival
of infants with saturations $\leq 85\%$ and $> 93\%$. A larger sample with histogram data showing the percentage of time spent at multiple saturation levels, rather than at a single low or high point, could help to better define the optimal saturation range for this population. This study was also limited by a lack of saturation data in the first days/weeks of life. Data collection began at time of transfer to the study site, without information on the potential impact of saturation levels prior to transport.

Despite these limitations, the present study is the first to report the impact of the time spent out of a targeted saturation range of 85-93\% on the risk of death for premature infants. It has demonstrated the importance of saturation histograms in evaluating the time an infant spends out of a targeted saturation range. A saturation level $\leq 85\%$ will increase the risk of death, while a saturation level $> 93\%$ will decrease this risk in the same population.

These findings are important, given the continued debate on optimal hemoglobin oxygen saturation targets. They support the current recommendation of many,\textsuperscript{19,29-31} that the targeted saturation range for this population should be higher. A low saturation level of 85\% cannot be recommended as safe, given the results of the RCTs (Saugstad & Aune, 2014) and this study. Further studies are needed to determine the optimal upper saturation target and confirm its advantages.
References


Retinopathy of prematurity is known to be associated with prematurity, low birth weight and exposure to supplemental oxygen. An optimal oxygen saturation range of 85-93% is often targeted to minimize the risk of either hypoxia or hyperoxia. Table 7 is a review of the studies published on low versus high saturation targets. Despite attempts to control oxygen targets in this population, ROP continues to be a problem for hundreds of premature infants each year. Oxygen targeting research has failed to recognize the potential impact that the time out of the targeted range has on the development of ROP. Every newborn intensive care nurse knows that it can be very challenging to maintain infants within this narrow range with frequent saturation fluctuations requiring oxygen adjustments. Hagadorn et al. (2006) have shown that the ability to maintain premature infants within the targeted range can be difficult, with many infants spending significant time both above and below the targeted range.

This project began as part of a quality improvement project to evaluate how well a neonatal intensive care unit succeeded in achieving the designated saturation targeted range of 85-93%. Data collection began in 2010, and over time, compliance with the set parameters improved; however, many infants were found to have highly variable times out of targeted range. In 2011, targeted ranges were adjusted to allow for changes as the infant matured. Infants < 29 weeks gestation were maintained at 85-93% with an
adjustment to a saturation range of 88-94% when the infant became 29 weeks postmenstrual age. This was in response to concerns raised in the SUPPORT and BOOST II studies about increased infant mortality among those with a lower saturation range of 85-89%. Daily histogram reports were included in rounds to ensure the entire team was aware of the infants’ ability or inability to be maintained in the targeted saturation range. However, there was a lack of evidence as to what should be done with the information provided by these histograms. When an infant spent 30% of his or her time below and/or 30% of time above the targeted range, it was unknown which was more detrimental (i.e., high or low saturations) in order to guide adjustments in respiratory management.

The effect of the time out of a targeted range, high or low, on the development of ROP is largely unknown. There is limited evidence regarding reference values for pulse oximetry in healthy term neonates during the first 5 days of life. Brockmann et al. (2011) reported an average median saturation of 97.3% ($SD=1.4\%$) in healthy term infants. In this study, infants were found to have saturations > 94% for 95% of the time. Desaturation < 80% occurred infrequently, with a median of 0 times/hour and a 1.7 maximum number of desaturations (Brockmann, Poets, Urschitz, Sokollik, & Poets, 2011). A similar study in healthy preterm infants (born at 29-36 weeks gestation yet monitored by pulse oximetry for 4 hours) had an average median saturation of 95% (range 92-99%). The median duration of time less than 90% was 2%, with a median duration of 1% for saturations < 85% (Harigopal, Satish, Taktak, Southern, & Shaw, 2011). This information suggests that healthy term or preterm infants spend very little time with a SpO2 < 85%.
This is the first study to report the impact of the time a premature infant spends out of the targeted saturation range of 85-93%. It is also the first study to report the effects of high saturations while the infant is breathing 21% oxygen on the development of ROP. The current research study provides important information on the effects of time spent with both low and high oxygen saturations on the development of ROP and death. Infants in this study population largely represent infants in phase 2 ROP (31-44 weeks). It has been shown that low saturations (≤ 85%) are detrimental, with increased outcomes of both ROP and/or death, while high saturations (> 93%) improve both of these outcomes. This study also supports the use of oxygen saturation histogram data in clinical practice to evaluate an infant’s ability to maintain a given saturation target and help guide respiratory management decision-making within this high risk population. These monitoring tools can help answer important clinical questions about the impact and management of low or high saturations.

Limitations

It is important to both qualify the information produced in this study and recognize limitations. This study was at a single study site at a level 4 NICU in a freestanding children’s hospital. The sample was a high-risk population of premature infants, all of whom with complicated clinical courses, making it necessary for transport to this center for further management. The infants who developed ROP had significantly more sepsis, IVH and surgery than did those who did not develop ROP. Because these variables were not time-stamped, they were not included in the discrete-time model analysis. However, the most important known risk factors for the development of ROP are gestational age and birth weight. These were accounted for in this time-based model
by examining the effects of the time an infant spent out of a targeted saturation range of 85-93%.

Because the study site does not provide labor and delivery services, all infants were transferred to the site. The initial saturations in the first hours, days and sometimes weeks of life were thus unknown. The average age at entry into the study was 31 weeks PMA, with only 27% of the study group entering the study at < 30 weeks gestation. While this study supports the use of higher oxygen saturation levels within this population, whether this is true for the first days or weeks of life remains unknown, especially for the highest risk population, those born < 28 weeks gestation. Maternal history can also be incomplete when an infant is transported. Conducting research at a delivery hospital would improve access to maternal history that may help identify potential precursor conditions that could increase or decrease an infant’s risk.

The end point of the study was each infant’s first ophthalmologic exam, which showed the development of either ROP or retinal maturity. This was done to eliminate concerns that nursing behavior in response to saturation alarms might be influenced by knowledge of the presence of ROP. Because of this, the effect of time out of saturation range on the progression of ROP from initial stage to final result is not known, yet would be of interest. It may be just as, or even more, important for infants with known ROP to have higher saturations in order to decrease disease progression, as suggested by the STOP-ROP trial (Hay & Bell, 2000).

Rapid or repeated fluctuations in oxygen may also play a role in the development of ROP. Oxygen fluctuations have been shown to cause ROP in the rat model (Penn et al., 1994; Penn et al., 1993). Infants with more PaO2 fluctuations are at greater risk for
threshold ROP (Hartnett, 2010a; York et al., 2004). The histogram reports recorded the total time the infant was above or below the targeted range. They did not provide information on the frequency or rapidity of the fluctuations from low to high saturations. This likely contributes to the findings that total time an infant was out of range was not a significant finding in the development of ROP. Evaluation of the impact of fluctuations in oxygen would be another important area for further research.

**Implications for Future Research**

The results of this study have several implications for future research. Important questions remain unanswered. First, the impact of the time immediately following birth is unknown. This study needs to be replicated in a center capable of capturing saturation data from the first day of life through retinal maturity or the development of ROP. It would also allow assessment of the impact on infants at earlier gestational ages and in the first phase of ROP (22-30 weeks). Improved access to maternal history to help identify potential precursor conditions that may increase an infant’s risk would be facilitated in such centers. There is some evidence to support maternal chorioamnionitis, with signs of systemic inflammation as increasing the risk of ROP (Dammann et al., 2009; Woo et al., 2012b) as discussed in Chapter 4.

Finer granularity of the saturation data would be beneficial to analyze the risk at different saturation levels. Currently this study gives evidence on the effects of having saturation ≤ 85% or >93%. Finer detail on saturation readings outside of other levels (i.e., <87%, >95%, >97% etc.) may help define a point at which high saturation levels are no longer of impact.
What is the optimal targeted saturation range? That is a question that has gone unanswered for more than 30 years. Current recommendations were largely derived from a study by Bancalari and colleagues (1987) who evaluated the use of transcutaneous oxygen tension (TcPO2) at 50-70 mm Hg to decrease the incidence of ROP. They reported an incidence of ROP at 51% in the continuous-monitoring group, versus 59% in the standard-care group (Bancalari et al., 1987). This study led to clinical practice guidelines for PO2 targets of 50-80% (Myers & American Association for Respiratory Care, 2002). In further review of this study by Fleck and Stenson (2013) mortality was 32% in the continuous-monitoring group, versus 24% in the standard-care group. While statistically insignificant, with an 8% absolute reduction in ROP and an 8% increase in mortality in the continuous-monitoring group, they speculated that had the sample been larger, this study may have provided the first evidence from the era of targeted oxygen therapy that tighter oxygen targets, even while decreasing ROP, increase mortality.

Technology for clinical monitoring of systemic oxygenation changed to pulse oximetry in the late 1980s, and it was soon recognized that saturation monitors are relatively poor at detecting hyperoxia (Bucher et al., 1989). A study by Castillo et al. (2008) evaluated the saturation levels of 85-93% and found a median PaO2 of 54 (±14.7), with 85% of the samples registering PaO2 levels between 40-80 mmHg. When infants were tested with a saturation level > 93%, the median PaO2 of 91 (±59.3) resulted, with 59% of the samples demonstrating a PaO2 level > 80 mmHg. They concluded that targeted saturations of 85-93% would limit the risk of both high and low PaO2 values (Castillo et al., 2008). This information helped develop the randomized controlled trials reviewed in the NeoProm study, (Saugstad & Aune, 2014) which suggested that a higher
saturation level of 90-94% was safer for the infant with regards to improved survival. The current study suggests it may be time to look beyond oxygen to other causes of ROP.

Influences on VEGF Functions other than Oxygen

Anemia can reduce the oxygen content of blood and cause tissue hypoxia, due to reduced transport of oxygen to tissue cells, despite adequate saturation levels. Premature infants are subject to anemia, with hematocrits commonly in the 20s to low 30s (Gaynon, 2006). The role of anemia and blood transfusions in the development of ROP is controversial; many more studies associate ROP with transfusion than anemia (Aggarwal, 1997; Brooks et al., 1999; Dani & Rubaltelli, 2000; Del Vecchio et al., 2013). However, there is evidence that VEGF levels are elevated in the presence of anemia (Dunst et al., 2002; Dunst et al., 1999), which may increase the risk of ROP. It would be very interesting to investigate the combined effects of anemia with saturation. It may be that there is a double-hit process during phase 2 ROP when anemia, in conjunction with low saturations, increases ROP risk through increased tissue hypoxia. Adding serial hematocrit values into the discrete-time model may help determine an association between anemia and ROP or the combined effect of anemia with saturation levels.

Insulin-like growth factor (IGF-1) is believed to regulate retinal neovascularization through control of VEGF activation. Low levels of IFG-1 have been shown to inhibit vessel growth, despite the presence of VEGF (Hellstrom et al., 2003). A major clinical problem in very preterm infants is weight loss and poor weight gain after birth. Poor early weight gain, as well as low IGF-1 levels during the first weeks to months of life, have been found to strongly correlate with the development of severe ROP (Lofqvist et al., 2009; Wu, Vanderveen, Hellstrom, Lofqvist, & Smith, 2010).
Lofqvist et al. (2007) developed the surveillance algorithm WINROP (Weight, IGF-1, Neonatal, ROP) to detect infants at risk for ROP. WINROP was designed for predicting ROP based on weekly weight gain, along with IGF-1 levels with 100% sensitivity (Lofqvist et al., 2009). Wu et al. (2010) evaluated weekly weight measurements alone in 318 infants in the US, using the WINROP algorithm, and successfully predicted all infants who later developed severe ROP at a median of 9 weeks before ROP diagnosis. The WINROP algorithm has been made public, and it would be of interest to apply the algorithm in this study’s population of infants in order to evaluate the effects of weight gain. However, this may only be useful if data is known from the first days to weeks of life.

IGF-1 is produced primarily by the liver. In rat experiments, the amount of IGF-1 in the liver was positively associated with dietary casein and negatively associated with a protein-free diet (Miura, Kato, & Noguchi, 1992). Other areas to study might include looking at not only weight gain, but dietary intake of protein as a predictor of ROP.

**Infection and Inflammation**

Infants in this study who developed ROP were more likely to have a history of sepsis than did those who did not develop ROP. All neonates are susceptible to infection because of immature immune systems. There is evidence that the exposure of the preterm neonate to infection and inflammatory mediators is associated with an increased risk for ROP (M. Chen et al., 2011; Tolsma et al., 2011). Nurses have responsibility for the prevention and detection of infection in the neonate, as discussed in Chapter 4. Reduced infection for this vulnerable population would improve overall outcomes and potentially reduce the risk of ROP.
Inflammation resulting in oxidative stress has also been implicated in the development of ROP (Saugstad, 2005a). It has been hypothesized that inflammation is an additional risk factor for ROP beyond immaturity and/or hyperoxemia, as discussed in Chapter 4. Current early infant nutrition is provided with parenteral lipid emulsions. In the US, soybean oil is the product of choice, but it is known to cause an increase in pro-inflammatory mediators, while investigation of a fish-oil based emulsion has been shown to inhibit the release of inflammatory mediators (Jedrzejczak-Czechowicz & Kowalski, 2011; Waitzberg & Torrinhas, 2009). Early studies utilizing a fish-oil based fat emulsion from the first day of life have demonstrated a reduced risk of ROP requiring laser therapy (Pawlik et al., 2011). More research is needed in this area.

Improved Oxygen Stability

It would be worthwhile to investigate ways of increasing the stability of infant oxygen saturations. In an effort to prevent adverse pulmonary outcomes, there has been a focus on reducing exposure to mechanical ventilation by extubating to continuous positive airway pressure (CPAP) as soon as possible (Claure & Bancalari, 2007). A study by Lim et al. (2014) examined the ability to maintain saturation targets for infants on CPAP. They studied 45 infants < 37 weeks gestation on CPAP and found the infants spent an average of only 31% of the time in an SpO2 range of 88-92%, with a high proportion of time spent outside of the targeted range, both high and low (Lim et al., 2014). There is a need for more study on the risk of time out of the targeted saturation range based on the mode of respiratory support. A possible alternative to improve the time in the targeted range is the use of an automated oxygen controller device to make automatic adjustments to FiO2 in order to maintain SpO2 in the intended range. This
device works off an algorithm for FiO2 adjustments in response to saturation. In studies, automated oxygen controller devices have been shown to deliver less oxygen overall, with an improved time within the targeted saturation (Claure et al., 2011; Claure, D’Ugard, & Bancalari, 2009; Y. Sun, Kohane, & Stark, 1997; Urschitz et al., 2004). With study ongoing, this approach may be feasible in the future to improve the achievement of oxygen targets.

Premature infants are known to have immature breathing patterns, with periodic breathing and apneic spells putting them at risk for hypoxic events. Caffeine is commonly used in premature infants to treat breathing problems. It is believed that caffeine stimulates the respiratory center, decreasing the carbon dioxide threshold and increasing the response to hypercapnea. Caffeine has also been shown to increase skeletal muscle tone and decrease diaphragmatic fatigue, aiding in respiratory effort (Buck, Hofer, & McCarthy, 2008). Caffeine has been found to reduce apnea and chronic lung disease, as well as improve survival without neurodevelopmental disability at the corrected age of 18-21 months (Doyle et al., 2010; P. J. Johnson, 2011; B. Schmidt et al., 2007; Barbara Schmidt et al., 2006). There is new evidence that prolonged caffeine treatment beyond term equivalent reduces the frequency of intermittent hypoxic events (Rhein, Dobson, Darnall, Corwin, Heeren, Poets, McEntire, Hunt, Caffeine Pilot Study, et al., 2014) It would be interesting to examine the caffeine use in the current study population and its effects on the time the infant spent out of desired saturation range.

Implications for Policy and Practice

Changes in practice guidelines in healthcare today must rely on evidence-based literature. The decision to begin oxygen targeting (85-93%) at Primary Children’s
Hospital was based on published evidence that a lower targeted saturation range decreased the incidence of severe ROP without evidence of adverse outcomes. When the SUPPORT and BOOST II studies raised concern for increased infant mortality with lower oxygen targets (85-89%), clinical practice changed to adjust saturation range as the infant matured. This was based on the theory of ROP development as two phases with differing oxygen sensitivity. The results of the meta-analysis and systematic review of the oxygen saturation target studies (Saugstad & Aune, 2014), along with the results of this study showing that a saturation level of $\leq 85\%$ is detrimental to both outcomes of ROP and survival. This would suggest that it is time to re-evaluate current standards and adjust them to improve infant outcomes.

Several authors have already recommended a change in saturation to a higher range of 90-95% (from the current 85-93%) for all infants born at less than 28 weeks gestation (Bancalari & Claure, 2013; Polin & Bateman, 2013; Saugstad & Aune, 2014; Vento, Escobar, Cernada, Escrig, & Aguar, 2012). The European guidelines have adjusted recommendation to a saturation target of 90-95% (Sweet et al., 2013). Vento et al. (2012) have suggested the possibility of keeping saturations targeted 85-90% for the first 7-10 days of life to allow for adaptation to extrauterine life, and then adjusting ranges to 90-95%. There is no clear evidence to support this practice.

On the other hand, NICUs, including PCH, have seen a decline in the rates of severe ROP with the institution of existing oxygen targets, making clinicians reluctant to abandon the current practice. Until these clinicians are convinced of the risk of increased mortality ROP due to time spent at or below 85%, or the safety and value of a higher limit > 93%, it may be very difficult to bring about change.
Nurses are the direct care providers in a neonatal intensive care unit. It is their responsibility to monitor oxygen levels and make adjustments to patient positioning, activity and oxygen delivery in order to help the infants maintain the determined oxygen target. All published studies evaluating nursing compliance with alarms report improved compliance with the lower alarm limit, as opposed to the upper alarm limit, which is frequently found to be set too high (Armbruster et al., 2010; Clucas et al., 2007; Deuber et al., 2013; Mills, Davis, Donath, Clucas, & Doyle, 2010). Nurses seem more concerned with the risk of hypoxia and limit this risk by maintaining the targeted lower alarm limit. The risk for ROP due to hyperoxia remains a concern, however, and will have to be emphasized if saturation levels are adjusted higher. Since we do not know the upper limit for safe oxygen saturation, adjusting to a higher upper limit such as 95% (compared to the current 93%) will require careful monitoring and evaluation of the outcomes.

Current research, including this study, suggests there is a need for a practice change to raise the set oxygen target for infants at risk for ROP based on gestational age, birth weight and perhaps phase of ROP. To accomplish this, patient-care providers will need to understand why a change to our current saturation targets is important to achieve excellent outcomes. The change must be supported at all levels of care management, from the physician to the direct-care nurse. Key stakeholders in medicine, nursing, respiratory therapy and families will need to be involved to help champion this change and help overcome barriers along the way. Changes will need to be made to procedures, guidelines and standard order sets to support the change in saturation ranges. Clinicians will need education on the latest evidence for saturation targets. Working policies will be
needed to facilitate management of the correct saturation target for this vulnerable population.

Such change can be accomplished at a corporate or departmental level to impact the care of infants throughout multiple associated clinical sites. However, it is also important to facilitate the change at the individual infant care level. Outcome measures will have to be identified in order to evaluate the impact of saturation target changes on the development of ROP and death, and the effects of these changes on an infant’s ability to maintain the desired target range. Infants with a higher oxygen target should have fewer desaturation events, which should decrease the number of monitor alarms, as well as decrease the frequency of nursing interventions to rescue the infant. Change can successfully take place when each care team can see the positive effects for the patient and the overall value for the nurse (Gale & Schaffer, 2009).
References


APPENDIX

REVIEW OF OXYGEN TARGETING STUDIES RELATED TO ROP
Table 7. Review of the Studies on Low versus High Saturation Targets.

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>Sample</th>
<th>Saturation Levels</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Low</td>
<td>High</td>
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<tr>
<td>STOP-ROP (2000)</td>
<td>Randomized multicenter, blinded</td>
<td>N=649 with confirmed prethreshold</td>
<td>89-94% (n=325)</td>
<td>96%-99% (n=324)</td>
</tr>
<tr>
<td>Tin et al., (2001)</td>
<td>Observational</td>
<td>N=295 &lt;28 wk (1990-1994)</td>
<td>70%:84%</td>
<td>85%:95%</td>
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<tr>
<td>Sun, SC (2002)</td>
<td>Survey of VON Hospitals</td>
<td>N=1,544 BW 500-1,000 gms (1998-2000)</td>
<td>≤95% (n=802)</td>
<td>&gt;95% (n=742)</td>
</tr>
<tr>
<td>Askie et al., (2003)</td>
<td>Randomized multicenter, blinded</td>
<td>N=358 &lt;30 wks (1996-2000)</td>
<td>91%-94% (n=178)</td>
<td>95%-98% (n=180)</td>
</tr>
<tr>
<td>Chow et al., (2003)</td>
<td>Observational</td>
<td>N=447 BW 500-1,500 gms (1997-2001)</td>
<td>85%-93%</td>
<td>90%-98%</td>
</tr>
<tr>
<td>Vanderveen et al., (2006)</td>
<td>Historical control</td>
<td>N=323 BW ≤ 1,250 grams (2000-2004)</td>
<td>85%-93% (n=72)</td>
<td>87%-97% (n=251)</td>
</tr>
<tr>
<td>Study</td>
<td>Method</td>
<td>Sample</td>
<td>Saturation Levels</td>
<td>Results</td>
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<td>Low</td>
<td>High</td>
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<tr>
<td>Deulofeut, (2006)</td>
<td>Historical control</td>
<td>N=504 ≤ 1,250 gram (2000-2005)</td>
<td>85%-93% (n=202)</td>
<td>92%-100% (n=300)</td>
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<td>4.6%: 7.2%</td>
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<td>35%: 51%</td>
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<tr>
<td>Wallace et al., (2007)</td>
<td>Retrospective cohort study</td>
<td>N=105 (2002-2005)</td>
<td>90%-96% (n=81)</td>
<td>97%-100% (n=55)</td>
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<td></td>
<td></td>
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<td>18%: 14%</td>
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<tr>
<td>Noori et al., (2009)</td>
<td>Historical control</td>
<td>N=323 &lt;1,000 gms (1998-2004)</td>
<td>83%-89% (n=72)</td>
<td>89%-94% (n=251)</td>
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<td>15.7%: 50.7%</td>
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<td>46.6%: 44.9%</td>
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<tr>
<td>Tokuhiro et al., (2009)</td>
<td>Historical control</td>
<td>N=137 &lt;33 weeks (2004-2007)</td>
<td>88%-92% (n=78)</td>
<td>92%-98% (n=59)</td>
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<td></td>
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<td>17.9%: 32.3%</td>
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<tr>
<td>SUPPORT (2010)</td>
<td>Randomized multicenter, blinded</td>
<td>N=1,316 ≤ 28 weeks (2005-2009)</td>
<td>85%-93% (n=654)</td>
<td>91%-95% (n=662)</td>
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<td></td>
<td></td>
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<td>8.6%: 17.9%</td>
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<tr>
<td>BOOST II (2001)</td>
<td>Randomized multicenter, blinded</td>
<td>N=3631 ≤28 weeks</td>
<td>85%-98%</td>
<td>91%-95%%</td>
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<td>19.9%: 16.2%</td>
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<td>21.8%: 13.3%</td>
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