

Pathophysiology of retinopathy of prematurity

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Abstract:

Retinopathy of prematurity (ROP) is a vasoproliferative disease occurring in premature infants that affects the blood vessels of the developing retina. ROP results in the development of vascular shunts, neovascularization, and in its most severe form tractional retinal detachment. The development of retinal vascular shunts and neovascularization in ROP is related to local ischemia in the immature and incompletely vascularized retina. Understanding the pathophysiology of ROP helps physicians both in the prevention and treatment of ROP and will be discussed in this review article. The role of oxygen in the pathophysiology of ROP will be reviewed with recent studies discussed.

Keywords:

Hypoxia, oxygen, pathophysiology, Retinopathy of prematurity, vascular endothelial growth factor

INTRODUCTION

The original description and first correlation of this disease with prematurity was made by Terry in 1942 and 1943.^[1-3] Terry's initial impressions were based on his observations of a retrolental proliferation of the embryonic hyaloid system, and therefore, the condition was designated as "retrolental fibroplasia (RLF)." As the pathology became more fully appreciated and improved classification systems were developed, the term retinopathy of prematurity (ROP) was adopted. During the 10 years following Terry's observations, ROP was seen in epidemic proportions and became the largest cause of blindness in children in the United States and a major cause of blindness throughout the developed world; approximately 7000 children in the United States alone were blinded by ROP.^[4] In the early 1950's, Dr. Patz from Baltimore made the observation that premature infants receiving vitamins several times a day had less RLF. He noticed that the isolates were opened frequently to administer the vitamins thus reducing the oxygen dose. His theory was hyperoxia was toxic to the premature retina. He was able to verify his theory in an infant animal model creating retinal changes similar to RLF

by administering oxygen. He was one of the first to develop an animal model for ROP.^[5] In the late 1950s and 1960s, oxygen therapy was curtailed because of its incrimination as the principal cause of ROP, and this led to a dramatic decline in the incidence of ROP. This decline in RLF was, however, associated with an increase in premature infant morbidity and mortality as there was no good way to monitor oxygen saturation.^[6,7] Cross estimated that for each case of blindness prevented, approximately 16 babies died as a result of inadequate oxygenation.^[6] The high morbidity and mortality forced an increase in supplemental oxygen. This led to increased survival of very low birth weight preterm infants but severe ROP also increased which is termed the "second epidemic" of ROP.

In the 1980's, pulse oximetry was introduced allowing better monitoring of infant oxygen levels. Despite improvement in oxygen tension monitoring, the "second epidemic" of ROP continued. Lower birth weight and gestational age became recognized as ROP risk factors. In the 1980s and early 1990s, there were numerous clinical trials of treatment with reduced nursery light levels, Vitamin E, cryotherapy, and laser photocoagulation. These studies resulted in no significant improvement in ROP outcomes.

In 2003, a landmark collaborative clinical study from the Wright Foundation and the Cedars-Sinai

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NICU in Los Angeles by Chow, Wright, and Sola showed a dramatic reduction of severe ROP by careful monitoring of O₂ saturations (SpO₂).^[8] Keeping saturations between 83% and 93% from birth and during transport virtually eliminated threshold ROP, with the need for laser treatment 4.5% for high SpO₂ (90%–98%) versus 0% for low SpO₂ (85%–93%).^[8] Subsequent studies from other centers have demonstrated similar results.^[9–14] Vanderveen *et al.* in 2006 showed that changing oximeter alarm parameters to between 83% and 93% reduced the development of prethreshold ROP from 16.7% to 4.2%.^[13] Other clinical studies confirmed that severe ROP can be prevented by careful control of the neonatal environment and maintenance of stable physiologic low oxygen saturations.^[9,12] In the next section, the pathophysiology of ROP and the role of oxygen is explained.

PATHOPHYSIOLOGY OF ROP AND THE ROLE OF OXYGEN

Fundamental to understanding why curtailing supplemental oxygen reduces severe ROP is understanding the pathophysiology. Normally, the fetus *in utero* is in a hypoxic state with a stable partial pressure of oxygen in arterial blood (PaO₂) of 22–24 mmHg. This is in contrast to a full-term baby and a normal adult where the PaO₂ is dramatically higher ranging from 70 mmHg to 90 mmHg. The developing retinal vessels grow from the optic nerve to the peripheral avascular retina. The hypoxic environment is important as it stimulates vascular endothelial growth factor (VEGF) which in turn stimulates retinal vessel growth into the peripheral avascular retina [Figure 1].^[15] Low tissue oxygen levels upregulates VEGF, whereas hyperoxia downregulates VEGF. Premature infants exposed to hyperoxia have reduced retinal VEGF, which stops normal vessel growth resulting in avascular retina. The more immature the infant, the larger the area of avascular retina. Prolonged exposure to high levels of oxygen not only stops vessel growth but will also result in vasoconstriction and, eventually, vaso-obliteration as the vessels involute due to lack of VEGF.^[15] This lack of normal vessel growth leaves the peripheral retina without adequate blood supply. Animal models of oxygen-induced ROP have also demonstrated that hyperoxia downregulates VEGF in both the retina and the brain, inducing global vaso-obliteration of immature vessels as seen in ROP and periventricular leukomalacia (PVL).^[16]

Overtime, usually several weeks, the avascular retina becomes ischemic which stimulates late VEGF production. If the area of avascular retina is relatively small, physiologic VEGF levels are

produced and stimulate normal retinal vessel growth. If, on the other hand, the area of avascular retina is large and large amounts of VEGF are produced, this induces the immature retinal vessels to sprout arterial venous (AV) shunts at the border between the vascularized and avascular retina (ROP Stages 1 and 2).

Regression occurs if VEGF stimulates normal vascularization past the AV shunt into the avascular retina. Extremely large areas of avascular retina, on the other hand, upregulates VEGF stimulating neovascularization of the AV shunt (ROP Stage 3). Sustained high levels of VEGF can even cause vasodilatation and tortuosity of existing posterior pole vessels (PLUS disease), iris vessel dilatation, and rubeosis iridis. Treatment of Stage 3 ROP is directed to lowering peripheral retinal VEGF levels.^[15] Reducing retinal VEGF levels, either by obliteration of peripheral avascular retina by laser application, or by the use of anti-VEGF agents, will result in regression of neovascularization and reduce the chances of an unfavorable outcome. Extensive neovascularization of the retina can cause retinal fibrovascular proliferation, scarring, and retinal detachment (ROP Stages 4 and 5).

In addition to the role of oxygen and ROP pathogenesis, several inflammatory proteins expressed early in life in extremely preterm infants have been associated with increased risk of ROP, while several angiogenic and neurotrophic growth factors have been associated with a lower risk of ROP. A recent study looking at data from the ELGAN Study (Extremely Low Gestation Age Newborns) reported that placental DNA methylation of 16 CpG sites representing eight genes associated with inflammation, angiogenesis and/or neurotrophic growth factors were associated with prethreshold ROP, after adjusting for gestational age and birth weight as they are independent risk factors for ROP.^[17] This study demonstrates the future potential for improved prediction of ROP development using early epigenetic markers and possible therapeutic targets to reduce incidence and severity of ROP. Future studies to make this a clinical reality will contribute to the prevention of severe ROP. However, the current mainstay to prevent severe ROP remains reducing hyperoxia in premature infants [Figure 1].

IMPORTANCE OF PREVENTION-LOW PHYSIOLOGIC OXYGEN

Many studies have conclusively shown that avoiding hyperoxia in low birth premature infants is associated with a

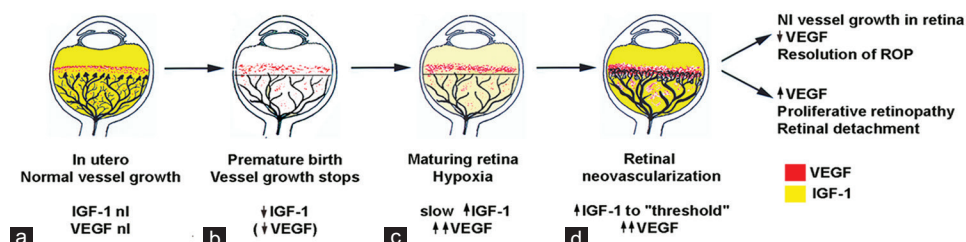


Figure 1: (a-d) Pathophysiology of Retinopathy of Prematurity (Adapted from Hellstrom *et al.* PNAS 2001;98:5804)

significant decrease in neonatal morbidity and does not have a detrimental effect on developmental outcomes at 18 months corrected age.^[10] Chow *et al.* in 2003 demonstrated that after implementation of a new protocol of strict O₂ management, not only was there a significant decrease in severe ROP requiring laser therapy in very low birth weight infants (<1500 g), but also a decreased incidence of cerebral palsy and hearing impairment.^[8] Oxygen saturation was controlled at 83%–93%, with minimal fluctuations and an oxygen blender present in the delivery room and during transport to the NICU. Sola's group at Emory specifically studied neurological outcomes with low versus high oxygen dosing. His group found significantly better outcomes in the physiological low oxygen group.^[10] Kong *et al.*'s study, a collaboration between Baylor and the Wright Foundation, on the effect of hyperoxia on the infant mice brain supports the presumption that hyperoxia causes brain ischemia similar to PVL seen in premature infants.^[16]

A recent study by Liu *et al.* compared the rates of severe ROP related to SpO₂ targets at 21 hospitals in North America, comparing the effect of increasing SpO₂ targets between the two time periods 2006–2012 and 2015–2017.^[18] During these two time periods, five clinical trials were conducted in extremely preterm infants to compare the effects of 85%–89% versus 91%–95% SpO₂ targets within 24 h of birth on the relative risk of death or major disability at the corrected age of 18–24 months. The combined data from these studies reported in the Neonatal Oxygen Prospective Meta-analysis (NeOProM) Collaboration found there was no difference between these two SpO₂ targets on death or disability at the corrected age of 18–24 months.^[19] Their secondary outcome analysis confirmed prior data that lower SpO₂ targets resulted in lower rates of treated ROP but also suggested these lower SpO₂ targets resulted in increased death rates.^[19] The NeOProM Collaboration has many study limitations, acknowledged by the publication, and nicely outlined by Schmidt and Whyte.^[20] These limitations include less separation in oxygen exposure between treatment groups, with the lower SpO₂ target groups having higher than intended saturation levels, and the potential for false-positive results based on multiple subgroup analyses. Importantly, caregivers' compliance with the recommended alarm settings and responses to alarms, placement of the oximeter probes or transfusion policies were not reported, all factors that can influence the infant's true SpO₂ and confound the study conclusions. In addition, the oximeter masking algorithm used by the studies, as well as the variability in the alarm limits between the studies, resulted in significant overlap of the saturations between the high and low oxygen groups thereby limiting the validity of their conclusions.

Notably, the rates of treated ROP in the high oxygen groups were variable across the five trials ranging between 9% and 22%; these rates are 2–6 times higher than the rates of treated ROP reported by other centers that compared their rates of treated ROP on high oxygen protocols before switching to low oxygen protocols.^[8,9,11] The conclusions related to the effect of lower SpO₂ targets on death rates from these studies

and the validity of these conclusions is disputed by many neonatologists and pediatric ophthalmologists, reflected by the variable SpO₂ targets adopted by NICUs across North America. Despite this, many NICUs have increased their SpO₂ target levels in response to this meta-analysis, which has resulted in increased severe ROP without apparent decreases in mortality.^[21,22]

The results from Liu's recent study unfortunately, yet predictably, showed that the 14 hospitals that increased their lower or upper SpO₂ target limits had a significant 3% increase in severe ROP (from 12% to 15%). In comparison, the seven hospitals that did not increase their lower or upper SpO₂ target levels had a 2% decrease in severe ROP (from 11% to 9%); the difference in change of severe ROP between these two hospital groups was statistically significant. The rate of severe ROP for infants with an associated SpO₂ target lower limit between 88% and 95% had a higher rate of developing severe ROP than infants with an associated SpO₂ target lower limit between 82% and 87% (rate of severe ROP was 14.7% versus 9.7%). This study clearly demonstrates that increasing SpO₂ targets causes increased severe ROP incidence contributing to increased infant morbidity due to the burden of increased ROP screening, treatment, and long-term follow-up required for these infants.

Maintaining SpO₂ within the recommended target range to reduce severe ROP is challenging and compliance with intended target ranges is variable.^[23,24] It requires a concerted team effort in the NICU and commitment and education around its importance in reducing the risk for severe ROP. Described challenges include low nurse-to-patient ratios, inadequate nurse education, alarm fatigue, incorrect alarm limit settings,^[25] or infants not spending time within the recommended target limits,^[23] and concerns that hypoxia is more detrimental than hyperoxia.^[26,27] A commitment to improved education in the NICU and policy changes that focus on maintaining accurate SpO₂ target limits is key to reducing the burden of ROP.

A premature infant is in reality a fetus out of the womb. Looking to the future, our treatment of premature infants should be to recreate the natural fetal environment of stable physiologic hypoxia. This must be implemented at birth before there is damage to the developing vascular system. Low oxygen protocols have made great strides improving outcomes, but it is extremely difficult to achieve stable physiologic hypoxia using standard ventilation of the lungs. Perhaps one day, the NICU will use a form of ECMO (extracorporeal membrane oxygenation) to bypass the lungs and keep systemic oxygen levels low and stable. Finding reliable and valid ways to monitor tissue oxygen in preterm infants will be key to preventing the devastating long-term effects of severe ROP. The risks and benefits of policy changes with regard to oxygen therapy in extremely premature infants needs to be carefully evaluated to ensure we are providing the best care for these vulnerable patients.

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Conflicts of interest

There are no conflicts of interest.

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