

Retinopathy of Prematurity: What Is New?

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Abstract

Worldwide 50,000 children are blinded by ROP each year. It therefore is important to understand the pathogenesis of this condition. The relation between low gestational age, growth retardation, oxygen dependent growth factors, and hyperoxia are now being understood more clearly. In the first phase of ROP hyperoxia inhibits VEGF. In its second phase VEGF rises and when IGF-1 reaches a threshold at 32-34 weeks of post conceptional age, uncontrolled neovascularization may occur. By avoiding hyperoxia, i.e. $\text{SaO}_2 > 92-93\%$ in very and extremely low birth weight infants and avoiding fluctuations in SaO_2 it is possible to control and prevent severe ROP in most cases.

Introduction

The discovery of the relation between hyperoxia and development of retrolental fibroplasia (RLF, later named retinopathy of prematurity - ROP) represents a watershed in modern neonatology^{1,2,3}. Unfortunately, in spite of the fact oxygen was discovered as a risk factor of RLF 55 years ago we still are not able to control this disease. However, we are perhaps now or in the near future reaching a level where we have a satisfactory and profound knowledge of this disease which may contribute to development of a therapy that prevents ROP. This may be particularly important because there seems to be an explosive increase in severe ROP in low income countries and 50 000 newborn babies are worldwide blinded each year due to ROP. One reason for this is that many countries are now able to get more and more immature babies to survive, however often the

means to control oxygen together with screening programs and therapy are lacking due to financial and personal constraints ⁴.

Risk factors of ROP

In a recent study from New Zealand and Australia ⁵ infants with gestational age < 29 weeks who survived to 36 weeks post-conceptual age was examined. Of these approximately 1/10 developed ROP stage 3 or 4. Gestational age < 25 weeks compared with 28 week gestational age infants represented the most important risk factor, OR 18.6 (95% CI 10.7-32.4). Growth retardation also gave significantly raised odds ratio (< 3rd percentile compared with 25-75th percentile, OR of 3.0 (95% CI 1.7-5.3). Male gender compared with female had odds ratio of 1.7 (95% CI 1.2-2.3).

Among all the risk factors mentioned in the literature low gestational age and birth weight, growth retardation, male gender, hyperoxia, days in oxygen, and septicemia seem to be the most consistent.

Role of oxygen

In 1954 Ashton and Cook were the first to establish that oxygen is important in halting retinal blood vessel development ³. Several investigations have recently shown a relationship between a high oxygen saturation and ROP ⁶⁻⁹. It seems that a SaO₂ > 93% increases the risk for severe ROP as well as need for therapy. Furthermore, some of these studies also demonstrate more lung problems including chronic lung disease in infants nursed in a high oxygen saturation. No difference in death or neuro-psychomotor development has been found so far. These studies have recently been reviewed ¹⁰.

Other studies have shown that fluctuations of SaO₂ may be unfortunate, and exposure to alternating hypoxia and hyperoxia causes severe proliferative retinopathy in the newborn rat ¹¹, and especially when fluctuations occur at a relatively high level¹².

ROP and angiogenic factors

Retinal vessel growth begins during 14-15 weeks of gestation starting from the optic nerve and progresses peripherally and anteriorly. The progressing vasculature is accompanied by astrocytes which sense the oxygen level and secrete vascular endothelial growth factor (VEGF) as a response to hypoxia¹³⁻¹⁵. Today we know that hypoxia stimulates VEGF production which induces neo-vascularization at the border between vascularized and non-vascularized retina, with in the worse case is ending in retinal detachment. Hyperoxia suppresses VEGF. This can be prevented by Placental Growth Factor -1 (PlGF-1) a ligand specific for VEGF-receptor 1^{14, 16-18}.

ROP Phase 1

With premature birth normal vascular development that would occur *in utero* ceases and there is loss of some developing vessels. In utero VEGF is growing at front of vessels. VEGF is, however, dependent on insulin like growth factor-1 (IGF-1) which is transported across the placenta. IGF-1 is therefore a non-hypoxic regulating factor critical to the development of ROP^{19,20}. In ROP phase 1 triggered by premature birth IGF-1 is not maintained at in utero levels, and IGF-1 drops dramatically¹⁹. IGF-1 consequently is low after preterm birth and being initially lowest in those who later develop ROP^{19,20}. Oxygen therapy after birth leading to hyperoxia of the immature retina suppresses VEGF. Because both VEGF and IGF-1 are low in this phase vascular growth ceases.

ROP Phase 2

With maturation the non-vascularized retina becomes increasingly metabolic active and therefore hypoxic. As mentioned above, hypoxia leads to high VEGF which induces neo-vascularization. This is similar to other proliferative retinopathies. This leads to ROP phase 2, occurring around 32-34 weeks post conception²⁰. However, simultaneously as the infant matures IGF-1 rises slowly. When IGF-1 reaches the threshold needed for VEGF to trigger neo-vascularization, ROP phase 2 is initiated. IGF-1 level reaches this threshold at

around 34 weeks post conceptional weeks and if VEGF is high, neo-vascularization proliferation proceeds^{18, 20}.

Growth hormone (GH) seems to be a factor non-related to oxygen that plays a role in regulation of neo-vascularization. GH suppressed neo-vascularization is mediated through inhibition of IGF-1^{18, 19}.

Transforming growth factor β (TGF- β) inhibits hyperoxia induced VEGFR reduction. TGF- β 1 protects retinal capillaries from hyperoxia-induced loss. TGF- β 1 and the VEGFR ligand PIGF-1 further increases protection from hyperoxia induced degeneration²¹.

Consequences for treatment

Present therapy for severe ROP is mainly based on laser retinal ablation of the avascular retina. Such therapy reduces incidence of blindness 25 %. However, treatment does not improve the chance of good visual acuity (>20/40). Such therapy therefore still is insufficient .

A number of antioxidants and nutrients have or may be tested out. Vitamin A and C supplementation do not seem to reduce the rate of severe ROP^{22, 23}. In fact, a high ascorbic acid level at the end of 1st week of life indicates worse outcome. A meta-analyses including limited number of studies and patients found a significant reduction in stage 3+ (5.3% to 2.4%) with vitamin E (15-100 mg/kg/d)²⁴. D-penicillamine is a powerful antioxidant and vasomodulator²⁵. Some promising data strongly indicate that this drug may reduce severe ROP²⁵.

In the future a control of vasoactive substances may be of interest. In ROP phase 1, the hyperoxic phase, it may be important to elevate VEGF and IGF-1, and in phase 2, the hypoxic phase, VEGF should be lowered. One target in phase 1 could be to enhance VEGF receptor-1 (VEGFR 1) by PIGF-1 or TGF- β 1. Growth hormone (GH) inhibits IGF-1 and consequently VEGF. In phase 2 growth hormone could reduce IGF-1, direct blockers of VEGFR 1 could also be of interest in this phase. However, in order to be successful with such an approach it is utmost important to know exactly in which ROP phase each baby is. To induce VEGF if the baby is in phase 2 could be disastrous. Another problem is

that these growth factors mentioned also play a role in other tissues and organs as well, and the global consequences by adding for instance growth factors or growth hormone is as yet not overseen. This therapeutic approach therefore belongs to the future if it ever can be realized.

The most important tool at hand to day is therefore control of oxygen saturation. Chow et al⁷ have shown it is possible to dramatically reduce ROP by strictly controlling SaO₂ lower than 93% in the nursery. This requires an intense daily effort teaching the whole staff how important it may be to keep the SaO₂ for instance between 85-92%. It is also important to avoid fluctuations in SaO₂ especially at high levels. Bagging of the infants following apneas or suctioning often leads to high SaO₂ peaks. This should be avoided and the staff should be taught to do such bagging not with 100% O₂ if not absolutely needed. Blended oxygen using the appropriate FiO₂ therefore is of importance.

Conclusion

It seems to be possible to drastically reduce severe cases of ROP by careful control of SaO₂ to < 93% and also by avoiding fluctuations in SaO₂. The understanding of the relation between oxygen associated vascular growth factors and oxidative stress may give us new insight into pathogenesis of ROP. Whether antioxidants as D-penicillamine, vitamin E, or other, will become part of future therapy is not known. If one is able to control vascular growth factors at the right time a possible new and powerful tool to eradicate this feared condition would be at hand. There apparently is, however, a long way to go before such therapy can be tried out. In spite of a tremendous progress in this field the last decade or so there are, however, still several unanswered questions we hopefully will penetrate in the nearest future.

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