20 Retinopathy of Prematurity

20.1 Retinopathy of Prematurity: Pathophysiology of Disease

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Core Messages

- Despite current treatment, retinopathy of prematurity (ROP) continues to be a blinding disease. Understanding the molecular basis of the disease is necessary for prevention and treatment.
- The less developed the retina at birth the worse ROP is likely to be. ROP occurs in two opposite phases. Phase I consists of delayed retinal vascular growth and vessel loss after premature birth resulting in hypoxia. Phase II consists of hypoxia-induced vascular proliferation.
- Both oxygen-regulated and non-oxygen-regulated factors contribute to normal vascular development and retinal neovascularization. Vascular endothelial growth factor (VEGF) is an important oxygen-regulated factor. A critical non-oxygen-regulated growth factor is insulin-like growth factor-I (IGF-I).
- Lack of IGF-I prevents normal retinal vascular growth. Premature infants who develop ROP have low levels of serum IGF-I compared to age-matched infants without disease. Low IGF-I predicts ROP in premature infants. Restoration of IGF-I to normal levels might help prevent ROP.

20.1.1 History of Retinopathy of Prematurity

Retinopathy of prematurity (ROP) was first noted in the late 1940s in preterm infants and described as retrolental fibroplasia, a total retinal detachment seen as white mass behind the lens. The disease was subsequently associated with excessive oxygen use [12, 14, 52]. Oxygen supplementation was curtailed with a decrease in ROP but with an increase in cerebral palsy and death. Supplemental oxygen is now delivered to premature infants to maintain adequate blood levels, but it is monitored carefully [37].

The incidence of ROP has increased further due most likely to factors related to prematurity itself as ever more immature infants are saved after preterm birth. Low gestational age at birth and low birth weight are stronger risk factors than controlled oxygen delivery [22]. ROP is still a major cause of blindness in children in the developed and developing world [67] despite current treatment. Although laser photocoagulation or cryotherapy of the retina reduces the incidence of blindness by about 25%, the visual outcomes after treatment are frequently poor. Prevention and/or medical treatment are urgently required.

To develop such treatments we need to understand the pathogenesis of the disease and develop medical interventions based on this understanding to prevent or treat ROP medically.

20.1.2 ROP: Disruption of Normal Vascular Development

It is necessary to understand normal retinal vascular development to understand the pathology of retinal vascular development in ROP. Retinal blood vessel development in the human fetus begins during the 4th month of gestation [26, 62] and vessels reach the most peripheral temporal aspect of the retina just before term.

Therefore, the retinas of infants born prematurely are incompletely vascularized, with a peripheral avascular zone, the area of which depends on the gestational age at birth. The more premature the infant the less the peripheral retinal vascularization. In the most premature infants to survive (postmenstrual age, PMA, 22–23 weeks) the retinal vessels at birth are found only in the posterior pole.

After premature birth into the relative hypoxia of the extraterine environment the vessels cease growing centripetally from the optic nerve to the periphery and some formed vessels are lost (phase I). In phase II of ROP there is vascular proliferation. It is important to understand these opposite phases of vessel loss and vessel proliferation in ROP.
since the same treatment depending on phase will have opposite effects. Timing of treatment is important.

20.1.3 Pathogenesis: Two Phases of ROP

**Essentials**
- Retinal vascularization is incomplete after premature birth and the degree of vascularization depends on the gestational age. The more immature the infant, the less the retina is vascularized.
- In phase I of ROP vessel growth slows or ceases and some retinal vessels are lost. The retina becomes hypoxic.
- In phase II of ROP vessels proliferate in part in response to hypoxia of non-vascularized retina, which can result in vascular leakage and retinal detachment.

20.1.4 ROP: Phase I

Phase I of ROP is characterized by vessel loss. The normal retinal vascular growth that would occur in utero slows or ceases, and there is loss of some of the developed vessels. Immature vessels are particularly susceptible to oxygen [10, 11, 45, 54, 68], so this phenomenon is thought to be due in part to the influence of supplemental oxygen given to premature infants to overcome poor oxygenation secondary to lung immaturity. However, it may be due also to the relative hyperoxia of the extraterine environment. With maturation of the premature infant, the resulting non-vascularized retina becomes increasingly metabolically active and without a blood supply, increasingly hypoxic [11, 46]. The first phase of vessel loss occurs from birth to PMA about 30 weeks.

20.1.5 ROP: Phase II

Phase II of ROP is characterized by hypoxia-induced vascular proliferation [11, 46] and starts between about 32 and 34 weeks PMA. The neovascularization phase of ROP is similar to other proliferative retinopathies such as diabetic retinopathy. The new blood vessel formation occurs at the junction between the non-vascularized retina and vascularized retina. These new vessels are leaky, and can cause tractional retinal detachments leading to blindness. If the growth of retinal blood vessels after preterm birth were normalized, the second destructive phase would not occur. Alternatively if we could attenuate the rapid proliferation of abnormal blood vessels in the second phase and allow controlled vascularization of the retina, retinal detachments could be prevented.

To accomplish these goals it is necessary to understand the growth factors involved in all aspects of ROP – both in normal retinal vascular development and in the development of neovascularization. The two phases of ROP are mirror images. The first involves growth inhibition of neural retina and the retinal vasculature and the second involves uncontrolled proliferative growth of retinal blood vessels. The controlling growth factors are likely to be deficient in phase I and in excess in phase II. Therefore control of the disease is likely to be complex and will likely require careful timing of any intervention.

20.1.6 Mouse Model of ROP

A disease model is required to study ROP. To take advantage of the genetic manipulations possible in the murine system to study the molecular pathways in retinal vascular development and in the development of ROP, we developed a mouse model of both phases of the disease [68]. The eyes of animals such as mice, rats and cats – though born full term – are incompletely vascularized at birth and are similar to the retinal vascular development of premature infants. When these neonatal animals are exposed to hyperoxia there is induced loss of some vessels and cessation of normal retinal blood vessel development, which mimics phase I of ROP [10, 11, 45, 54, 68].

When mice return to room air, the non-perfused portions of the retina become hypoxic, similar to phase II of ROP and of other retinopathies. The ischemic portions of the retina produce angiogenic factors that result in neovascularization [11, 46]. Hypoxia-inducible factors appear to be common to the proliferative phase of many eye diseases [25, 38] such as retinopathy of prematurity and diabetic retinopathy, as well as in tumor growth and wound healing. This ROP model has been useful to delineate the growth factor changes in both phases of neovascular eye diseases (Fig. 20.1.1).

20.1.7 Oxygen Regulated Factors: Vascular Endothelial Growth Factor in ROP

**Essentials**
- VEGF is an important factor for the development of retinal vascular proliferation in ROP. It is suppressed in phase I of ROP with hyperoxia. VEGF is markedly increased in phase II of ROP and stimulates retinal neovascularization.