**Точка зрения**
**Point of view**

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# К вопросу о патогенезе ретинопатии недоношенных

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**РЕФЕРАТ**

Представлена современная концепция патогенеза ретинопатии недоношенных. Основная причина отводится гипер-оксигенации и незрелой системе зашиты, в связи с чем задерживается созревание ауторегуляции сосудов. Незрелость ауторегуляции сосудов глаза и неадекватная реакция на избыточность кислорода вызывают выраженный спазм сосудов и возникновение циркуляторной гипоксии. Последняя приводит к избыточному выделению фактора роста эндотелия сосудов и стимуляции патологического ангиогенеза.

**Ключевые слова:** *ретинопатия недоношенных, патогенез, ауторегуляция сосудов, патологический ангиогенез, стекловидное тело, сосудистый эндотелиальный фактор роста, циркуляторная гипоксия*

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**ABSTRACT**

*Original article*

**Pathogenesis of retinopathy of prematurity**

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This article presents the modern concept of the pathogenesis of retinopathy of prematurity. The main cause is attributed to hyperoxia and an immature protective system, resulting in delayed maturation of vascular autoregulation. The immaturity of ocular vascular autoregulation and its inadequate response to oxygen lead to significant vasoconstriction and development of circulatory hypoxia. Circulatory hypoxia causes excessive release of vascular endothelial growth factor and stimulates pathological angiogenesis.

**Key words:** *retinopathy of prematurity, pathogenesis, vascular autoregulation, pathological angiogenesis, vitreous body, vascular endothelial growth factor, circulatory hypoxia*

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Retinopathy of prematurity (ROP) is a vasoproliferative disease that affects the ocular tissues of premature infants, especially those with extremely low birth weight and small gestational age. This disease is now considered by scientists to be «a tragedy of life» [1]. Recent advancements in medicine have increased the chances of survival for extremely premature infants, leading to a rise in cases of retinopathy of prematurity. Retinopathy of prematurity is included in screening programs for premature babies in almost every country in the world. Each year, approximately 15 million premature infants are born globally, and more than 30,000 of them suffer from vision loss or blindness due to retinopathy of prematurity [2–6]. ROP is a condition that can cause irreversible blindness in premature infants, if not treated properly.

Researchers around the world have proposed over ten theories on the pathogenesis of ROP, such as the imbalances of factors regulating angiogenesis, oxidative stress and the influence of free radicals, disruptions in the

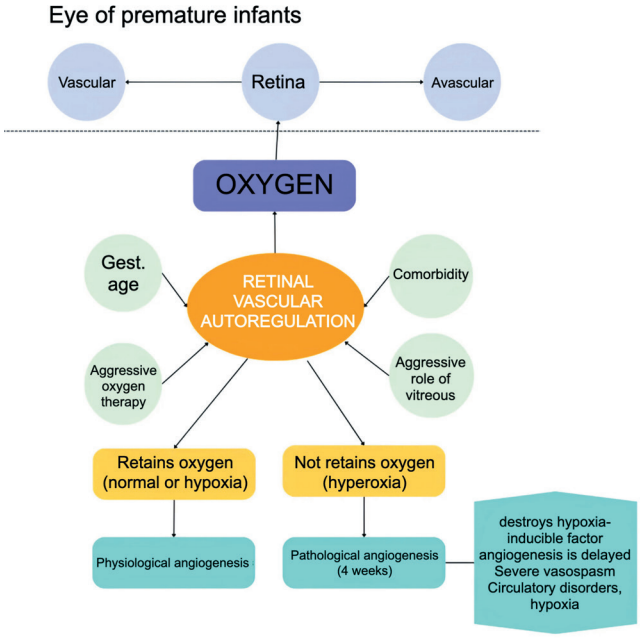


**Fig.** *Diagram of the modern concept of pathogenesis of retinopathy of prematurity (ROP) [15, 16]*

**Рис.** *Современная схема патогенеза ретинопатии недоношенных [15, 16]*

interactions within the inner layers of the retina, the role of oxygen and inflammatory cytokines, disturbances in neurovascular interaction, and alterations in metabolism. However, currently, an increasing number of researchers are focusing on the role of vascular endothelial growth factors in the development of ROP [7–10].

Based on long-term scientific research, Professor E.I. Sidorenko, at the Department of Ophthalmology of the Pediatric Faculty of the N.I. Pirogov Russian National Research Medical University, proposed the pathogenesis of ROP in 2000. According to this theory, the main cause is attributed to hyperoxia and the immature protective system, leading to delayed maturation of vascular autoregulation. The autoregulation of ocular vessels matures closer to the 30th post-conceptual week. Due to the immaturity of ocular vascular autoregulation and its inadequate, there is pronounced vasoconstriction and the development of circulatory hypoxia occurs.

Professor E.I. Sidorenko emphasizes that oxygen diffusion is limited, and its distribution is strongly dependent on the ocular hemodynamics, which, in turn, is influenced by vascular autoregulation. This process is capable of altering the caliber of vessels, until vascular autoregulation is completed, to maintain a constant partial pressure of oxygen in the tissues.

Excessive oxygen delivery to the tissues, driven by hyperoxia, causes vasoconstriction, reduces the density of vessels, and decreases oxygen supply to the tissues [1]. Inadequate autoregulation fails to maintain a normal level of oxygen in the blood and tissues, and excess oxygen destroys hypoxia-inducible factor-1 (HIF-1), which is unstable and rapidly degraded by oxygen. HIF-1 is an important factor in activating the system against circulatory hypoxia, and its low levels cannot stimulate the production of vascular endothelial growth factor (VEGF). As a result, angiogenesis is delayed. In addition, this process is further influenced by the role of the vitreous. The vitreous is also an oxygen reservoir, which maintains the attack of hyperoxia on the retina for another 6 hours after oxidation stops [11].

Normally, during circulatory hypoxia, factors of the system that counteract circulatory hypoxia are activated. The roles of hypoxia-inducible factors (HIF-1α, 1β), vascular endothelial growth factors (VEGF), insulin-like growth factor-1 (IGF-1), and placental growth factor (PLGF) have been convincingly demonstrated. In circulatory disorders caused by conditions such as myocardial infarction, stroke, and ROP, circulatory hypoxia promotes the accumulation of hypoxia-induced factors, which stimulate the entire circulatory hypoxia response system, primarily leading to the production of VEGF. VEGF binds to receptors on the vascular endothelium and, along with IGF-1 and PLGF, inhibits transaminase and leads to depolarization of the vascular walls, thereby enhancing the activity of endothelial cells, promoting their migration beyond the vessels, and facilitating the formation of new blood vessels [11].

In the first preclinical angiospastic stage of ROP, which occurs during the first 3–4 weeks of life in infants [12, 13], inadequate autoregulation leads to excessive angiospasm, even with normal partial pressure of oxygen in the blood, disrupting hemodynamics and ultimately resulting in total circulatory hypoxia in all parts of the retina. Hypoxia leads to the accumulation of HIF-1, delayed and excessive release of VEGF, and stimulation of pathological angiogenesis. And after that, there is an elevation of VEGF levels to and above 1300 pg/ml, and the effects of VEGF become evident in the form of vessel dilation, tortuosity and increased permeability, which are manifested by transudation, exudation and hemorrhages [14]. Furthermore, the progressive circulatory hypoxia caused by angiospasm stimulates the formation of the Ridge. The ridge arises from the demarcation line and has height and width, which extends above the plane of the retina.

## CONCLUSION

In conclusion, in the modern concept of the pathogenesis of ROP (Figure), the main cause is attributed to hyperoxia and an immature protective system, which delays the maturation of vascular autoregulation. Due to the immaturity of ocular vascular autoregulation and its inadequate, there is pronounced vasoconstriction and

the development of circulatory hypoxia. This hypoxia leads to excessive release of vascular endothelial growth factor (VEGF) and stimulation of pathological angiogenesis. This hypoxia leads to excessive release of vascular endothelial growth factor (VEGF) and stimulation of pathological angiogenesis. The course of ROP is also accompanied by significant biochemical changes in the vitreous body, which exert a toxic effect on the retina.

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