PATHOGENETIC ASPECTS OF FUNDUS CHANGES IN ARTERIAL HYPERTENSION

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Abstract. *The retinal vasculature is primarily derived from the central retinal artery (CRA), the first intraocular branch of the ophthalmic truncus arteriosus. The CAS penetrates the optic nerve and then enters the eye through the central part of the optic disc, where it divides into two main branches. These branches further divide into arterioles, which provide blood supply to the peripheral parts of the retina. Each arteriole supplies the inner nerve layer of one quarter of the retina.*

Keywords: *retinal vessels have distinctive features that distinguish them from other blood vessels.*

The CAS is the terminal vessel, and when it is blocked, sudden blindness occurs. Large vessels are located in the inner part of the retina, closer to the internal limiting membrane. Arterioles form two layers of capillaries: the superficial vasculature, located in the nerve fiber layer and the ganglion cell layer, and the deep capillary network, which is located deeper than the inner nuclear layer. The development of optical coherence tomography angiography (OCTA) has helped to better understand the complexity of the retinal vasculature, with vessels measuring only 100-300 μm in diameter. In addition, an intermediate capillary network, located between the superficial network and the deep capillary network, and a radial peripapillary capillary network, providing blood supply to the retinal nerve fiber layer, were identified. The retinal pigment epithelium (RPE) and outer layers of the retina are nourished by diffusion from the choriocapillary vasculature and are separated from it by the blood-retinal barrier (BRB). The presence of GHR prevents macromolecules and other potentially harmful substances from leaking into the retina. In addition to primary and secondary hypertension, there are other factors that play an important role in the development of GHR. The prevalence of GH is higher among African-Caribbeans than Caucasians and among women compared to men. Genetic factors may also play a role, and certain genotypes are associated with an increased risk of developing GH.

Retinal vessels have distinctive features that distinguish them from other blood vessels: the absence of sympathetic nervous innervation, autoregulation of blood flow and the presence of a blood-retinal barrier. Thus, the increase in blood pressure (BP) is directly transmitted to the vessels, which first narrow. However, a further increase in blood pressure disrupts this compensatory tone and leads to damage to the muscle layer and endothelium. Vascular spasm. Despite the considerable attention paid to hypertension and its complications, the pathogenesis of GH, especially the onset of lesions, is still not fully understood. It is believed that the first changes that occur in response to increased blood pressure in the retinal vessels are vascular spasm and an increase in vasomotor tone, which manifests itself as a general vasoconstriction. This is a consequence of local regulation of blood flow and an attempt to control blood volume in the vascular bed using myogenic and metabolic mechanisms. Since the ARIC (Atherosclerosis Risk in Communities) study, arteriovenous ratio (AVR) has been the most widely used method for

assessing global retinal vasoconstriction. It is based on the diameters of the equivalent CRAE (CRAE) and central retinal vein (CRV), referred to as retinal venous equivalent (CRVE). A study of 223 subjects, of whom 86 were normotensive and 137 had initial hypertension (up to 1 year after first onset), found that those with hypertension had lower CRAE and AVR, while there was no significant difference in CRVE. In addition, patients with hypertension and retinopathy showed higher arterial stiffness, pulse waveform (PWV) and aortic augmentation index (AIx). Also, lower AVR predicted increased 3-year CVD risk in women. Another study proved that a decrease in CRAE and an increase in CRVE correlated with higher mean BP. This indicates a decrease in the light cross-section of blood vessels in hypertension. Inconsistent data regarding the increase or absence of venous diameter in hypertension may suggest that venous dilation is associated with retinal ischemia and hypoperfusion, which appear later in GR. Persistently elevated blood pressure leads to arteriosclerosis. This leads to an increase in blood flow resistance and a decrease in perfusion, and consequently, to retinal ischemia. In addition, arteriosclerotic changes cause several modifications in vascular structure, such as intimal thickening, media wall hyperplasia, and hyaline degeneration. On ophthalmoscopy, these changes appear as focal and diffuse narrowing of the arterial wall (similar to "silver" or "copper" wire symptoms), accompanied by arteriovenous "compression" that results from the increased pressure imposed on the venules by the altered arterioles. “Compression” is associated with both current and previous blood pressure, indicating its persistence and long-term characteristic of hypertension. Observations by Zheng et al showed that increased tortuosity of retinal arterioles and venules is also associated with chronic hypertension. When hypertension is poorly controlled or reaches extremely high levels, the damage progresses. Over time, this can lead to destruction of the blood-retinal barrier, the appearance of hemorrhages, fatty exudates and cotton wool-like lesions, which are signs of ischemia of the retinal nerve fiber layer. Also, people with hypertension have fewer perifoveal arterioles and venules, which may indicate gradual vascular occlusion and necrosis. In the case of an advanced stage of headache, an increase in intracranial pressure (ICP) may occur. When increased cerebrospinal fluid pressure is imposed on the optic nerve head and its vessels, it leads to ischemia and swelling of the optic disc (papilloedema).

The sequence of changes presented by pathogenesis appears to reflect the cascade of changes that occur during the development of hypertensive retinopathy. However, recent research suggests that the entire process may be much more complex. Lesions visible at the bottom of the eye may occur in different sequences; for example, the presence of hemorrhages does not always precede general vascular constriction. In addition, arterial stenosis is observed among individuals without hypertension as a result of changes in the caliber of retinal vessels (narrowing of arterioles and dilation of venules). A large meta-analysis on a group of 10,229 subjects indicates that these changes in retinal vessel diameter are associated with an increased risk of developing hypertension, which develops up to 10 years after the onset of these changes. This observation supports the theory that changes in the retinal microcirculation may precede arterial hypertension. Decreased arteriolar caliber also correlates with older age and low birth weight, as well as higher hematocrit, white blood count, and platelet count. A meta-analysis by Chew et al demonstrated that there is a strong association between decreased diameters of both retinal arterioles and the central retinal artery and hypertension, and that each 10 mmHg increase in mean arterial pressure is associated with a decrease in mean retinal arteriolar diameter by 10 mmHg. 3 μm. This decrease occurs because increased blood pressure causes a gradual entropic restructuring of the arterioles, which

leads to a decrease in the outer and inner diameter of the vessel. Several mechanisms are involved in the pathogenesis of GH. One of them is an increased level of oxidative stress, expressed by an increase in plasma markers such as gamma-glutamyl transferase and ferritin. Other important pathomechanisms are low-velocity inflammation (increased high-sensitivity C-reactive protein, which is a marker of systemic low-velocity inflammation and correlates with the prevalence and severity of hypertensive retinopathy) and increased platelet activation (the presence of hypertensive retinopathy is positively correlated with urinary 11-dehydro-TXB2 levels, biochemical marker of platelet activation). Hypertension damages the vascular endothelium, which is located at the border between the blood and the interstitial spaces. Its main role is to control vasoregulation, hemostasis and inflammation. Nitric oxide (NO), important for vasodilation, is produced by endothelial cells. Observation of retinal blood flow after intravenous administration of NG-monomethyl-L-arginine (nitric acid synthase inhibitor) in groups of normotensive and hypertensive patients showed significant changes. In the hypertensive group, blood flow did not change, whereas in the normotensive group, blood flow decreased significantly. This indicates a reduced role of nitric acid-dependent vasodilation in the regulation of blood flow in patients with hypertension and impaired endothelial function. This was further confirmed in the hypertension group by increased levels of von Willebrand factor, a substance that accumulates in endothelial cells, and increased concentrations of angiotensin-converting enzyme (ACE, CD143) bound to their membranes.

Neovascularization may play an important role in the pathogenesis of hypertensive retinopathy. Angiogenesis is primarily controlled by a close balance between progiogenic and antiangiogenic factors. Pathological mechanisms such as ischemia, hypoxia, and inflammation causing endothelial damage may promote neovascularization. It should be emphasized that retinal ischemia and hypoxia are important components of hypertensive retinopathy. A 2012 review highlights the potential role of the vascular endothelial growth factor (VEGF) family in the pathogenesis of hypertensive retinopathy. One of the best-known members of this family, VEGF-A, plays a key role in neovascularization and is a major factor in vascular permeability, the increase of which is correlated with hypertension. VEGF is also an early marker of vascular endothelial damage. Changes in its concentration may be significant for the early diagnosis of patients with microcirculatory complications, such as hypertensive retinopathy. This is further supported by increased plasma VEGF levels in hypertensive patients with retinopathy. VEGF may be released in response to hypoxia caused by damage to the nerve fiber layer and activation of AT1-R. A report from 2016 was the first to describe a patient with proliferative retinopathy during the course of severe uncontrolled hypertension.

Hypertensive retinopathy goes through the following phases:

Vasoconstriction phase. At this stage, local autoregulatory mechanisms begin to operate. This causes vasospasm and constriction of the retinal arterioles, which is manifested by a decrease in the ratio of arterioles to venules (normal value = 2:3). Elderly patients with arteriosclerosis develop focal narrowing of the arterioles, since the affected vascular segments cannot undergo narrowing.

Sclerosis phase. A constant increase in blood pressure causes certain changes in the vessel wall: intima - thickening; media – hyperplasia; arteriole wall - hyaline degeneration.

This results in severe arteriolar narrowing, changes in vascular-venous junctions, and dilation and increased light reflection (silver and copper wires). Changes in vascular-venous

junctions occur when a thickened arteriole crosses a vein and therefore compresses it, since the vessels share a common lining. The vein, in turn, appears dilated and tortuous beyond the AV junction.

Exudative phase. Observed in patients with a strong increase in blood pressure; characterized by a violation of the blood-head barrier and the flow of blood and plasma in the vessel wall, which disrupts autoregulatory mechanisms. At this stage, signs of retinal damage occur, such as retinal hemorrhages (flame-shaped and pinpoint spots), hard exudates, smooth muscle necrosis, and retinal ischemia (flaky spots).

Malignant hypertension. Severe intracranial hypertension leads to ischemia and swelling of the optic nerve (papilloedema). Fibrinous necrosis of choroidal arterioles also occurs, leading to segmental infarction of the choroidal capillaries. This results in: Elschnig spots: When overlying the yellow pigmented retinal epithelium (RPE); Siegrist's stripe: RPE hyperplasia over choroidal infarcts; detachment of the neurosensory RPE. These features are called choriodopathy. Pontremoli et al examined genetic factors associated with GH and found that a deletion allele for angiotensin converting enzyme was associated with an increased risk of developing GH. Smoking is considered to be strongly associated with severe or malignant GH, as studied by Poulter et al. Renal dysfunction (persistent microalbuminuria and low creatinine clearance) in patients has shown to be informative as a marker of GH and target organ damage. Ukkaya et al found an association with plasma leptin. It was noted that plasma leptin levels were higher in patients with GH and suggested that this was associated with damage to the vascular endothelium. McDonald presented evidence arguing that in the case of GH, ETA receptors associated with arterial smooth muscle serve as mediators of vasoconstriction in the microvasculature of the retina. Two receptor subtypes for endothelin (ET) have been defined: endothelin receptor A (ETA) and endothelin receptor B (ETB), classified based on their different affinities for ET molecules and their tissue distribution. In the capillary layers of the retina, ET-1 has been implicated as a potential endothelial-to-pericyte signaling molecule, but the precise mechanisms underlying the regulation of pericyte function remain unclear. ET receptor antagonists play a key role in determining the cellular activity and pathological consequences of these vasoactive peptides. Bosentan, a recently developed non-selective ET receptor antagonist, blocks both ET-A and ET-B receptors.

Studies using Bosentan have shown a reduction in blood pressure in animals with hypertension, as well as in patients suffering from hypertension and congestive heart failure. Thus, retinal microcirculation in HD is mainly regulated by local molecules capable of constricting or dilating blood vessels, which are produced by the vascular endothelium, neurons and glia. Among these regulatory factors, the family of endothelial (ET) peptides, which have vasoconstrictor properties, plays an important role in the autoregulation of retinal microvessels in hypertension and in the systemic regulation of blood pressure. Marek-Trzonkowska et al. studied the development of GR, focusing on determining the imbalance between pro- and antiangiogenic factors in the context of hypertension. Their research concerns the relationship between hypertension and GH with low levels of proangiogenic factors in the blood and a simultaneous increase in the production of angiogenesis inhibitors.

The role of endothelial factor in the formation of GH in hypertension is known, in particular, in its effect on endothelial function and changes in the structure of blood vessels. A characteristic feature of GR is thickening and restructuring of arterial walls, as well as an increase in the vascular wall-lumen ratio of blood vessels. The process of loss of precapillary arterioles and

capillaries, known as “microvascular or capillary rarefaction,” is characteristic of GR. Studies also indicate an important role of angiogenesis in the development of microcirculatory changes in hypertension. Disturbances in angiogenesis during the development of the embryonic period can cause underdevelopment of the microvasculature and contribute to the occurrence of hypertension. It is also worth noting that hypertension can be caused by antiangiogenic therapy aimed at suppressing tumor vascular growth, which leads to a decrease in vascular density in tissues, which in turn increases resistance in peripheral vessels, leading to increased blood pressure and vascular damage. and also causes inflammatory processes. Based on this, it can be assumed that hypertension is associated with a decrease in the level of physiological pro-angiogenic factors in the blood and an increase in the concentration of angiogenesis inhibitors. In another study conducted by Chen et al, elevated levels of uric acid in the blood were found to be key in the development of GH. A 1 mg/dL increase in uric acid concentration significantly increased the risk of developing GH, which was confirmed by statistical analyzes assessing the correlation between serum uric acid levels and the prevalence and severity of GH. An increase in uric acid levels of 1 mg/dL significantly increased the risk of GH by 6%.

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