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MODERN IDEAS ABOUT THE DIAGNOSIS OF FUNDUS CHANGES IN HYPERTENSION

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Abstract. *There is some disagreement regarding the correct test method for imaging lesions in GH. For example, conventional fundoscopy has been shown to have limited added value in GR due to significant interobserver variability. Moreover, fundoscopy may not be suitable for detecting subtle changes. Maestri et al. compared the use of direct ophthalmoscopy with microdensitometry in the assessment of vascular vasoconstriction expressed as arteriovenous diameter ratio (AVR). Their study showed that semi-automated microdensitometry is more useful in diagnosing early vascular changes than standard ophthalmoscopy. The high reliability of this method is due to minimal interobserver and intraobserver variability.*
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Recently, significant progress has been made in the field of imaging the internal structures of the eye. Now you can observe not only the large vessels of the retina, but also penetrate deeper to the level of the capillaries. The introduction of retinal adaptive optics (AO) and optical coherence tomography (OCT) has provided scientists with improved data on retinal vascular changes. This is particularly important for monitoring retinal microcirculation to predict cardiovascular risk. With these new imaging techniques, lesion progression can be closely monitored as it allows for in vivo observation of the vessels. Spectral domain OCT (SD-OCT) provided faster scanning, denser examination, and three-dimensional imaging. A study using SD-OCT analysis in a group of 119 patients, of whom 56 had hypertension, showed that in the chronic stage (KWB grades I and II) it is an accurate, reproducible and convenient method for assessing the diameter of the central retinal artery (CRA), diameter of the central retinal vencula (CRV) and the CRA/CRV ratio (AVR). Additionally, SD-OCT demonstrated a stronger correlation of these measurements with worsening visual acuity than the KWB classification due to the presence of subretinal fluid (SRF) in patients with severe hypertension (SBP >180 mmHg or DBP >110 mmHg. Art.). In their study, Ahn et al. also proposed a new classification of hypertensive retinopathy based on OCT data, including 3 grades: mild to moderate, malignant without SRF, and malignant with SRF. SD-OCT is also useful for monitoring retinal nerve fiber layer (RNF) reduction and central macular thickness in grade IV hypertensive retinopathy. Findings from the Singapore Malay Eye Study highlight the association between decreased arteriolar and venular diameters and RNFL thickening, even after excluding patients with glaucoma. Data from another study suggest that SD-OCT assessment should be added to the standard assessment of hypertensive retinopathy in patients with systemic hypertension for the early diagnosis of hypertensive macro- and microorgan damage (HMOD).

OCTA provides a rapid and harmless assessment of the retinal microcirculation. Microvascular changes in the retina and choroid are assessed based on parameters such as vascular density (VD), foveal avascular zone (FAZ) area, and radial peripapillary capillary (RPC) vasculature. Retinal capillary assessment has been effective in diabetic retinopathy, and its use in hypertensive retinopathy may also be effective. This makes it possible to detect even subtle differences in capillary structure, which may be early markers of ischemia and hypoxia, before changes occur in arterioles and venules. Moreover, recent studies using OCTA analysis show that

vessel density in the SVP is reduced in a group of hypertensive patients with inadequate blood pressure control. In addition, decreased retinal and choroidal vascular density is closely associated with stenosis of the coronary arteries and their branches, making OCTA an effective and harmless method for measuring and detecting the early stages of CAD, which may reduce the likelihood of developing myocardial infarction. It is also reasonable to perform simultaneous SD-OCT and OCTA analysis. Unlike SD-OCT, OCTA cannot measure retinal vessel diameter but provides an assessment of hemodynamics and retinal vascular flow density. Takayama et al. expressed the need to implement a new classification system based on the use of OCTA and measurement of choroidal vasculature in proximity to the fovea, which is also reduced in hypertension. They demonstrated that changes in SVP, FAZ area, capillary density, and inner retinal thickness occurred in a group of hypertensive patients without hypertensive retinopathy. As mentioned earlier, subtle changes in the vasculature may develop before the onset of hypertension. This implies that increasing the frequency of OCTA monitoring may be useful for monitoring changes in retinal vasculature and thickness in a group of patients at risk of developing hypertension.

Adaptive optics (AO) retinal imaging is another important tool for precise imaging of the retinal vasculature. With a resolution of less than 2 μm, it has improved the quality of retinal images and aided in the assessment of cellular and subcellular details such as endothelial cell health and subtle fluid leaks [90]. Using this technique, retinal vessel wall thickness (VW) and luminal diameter (LD) can be directly measured. The semi-automated method for measuring vascular parameters has low intraobserver variability. Another useful vascular parameter is the wall-to-lumen ratio (WLR), which can be measured by combining AO with scanning laser ophthalmoscopy. The increase in WLR that occurs in hypertension is due to a decrease in LD and thickening of the arteriolar wall. This is used to detect subtle retinal microvascular changes observed during early remodeling. Its importance is further expanded as increased WLR correlates not only with age and higher body mass index (BMI), but also with early stage hypertensive macro- and microorgan damage (HMOD). Increased use of AO for retinal imaging will be essential in the search for new mechanisms of vascular changes associated with hypertension. It has already improved our understanding of the implications of changes at the capillary level for perfusion.

Researchers S. Akbar and colleagues studied the effects of arterial hypertension on the fundus of the eye. They have developed an automated system that can analyze heart rate (HR) and retinal health in hypertension. Particular attention was paid to the arteriovenous ratio and papilledema on retinal images. Hypertension can cause various changes in the retina, such as vascular tortuosity, hard exudates, cotton wool lesions, hemorrhage and papilledema, which can affect visual acuity. Researchers have presented a new automated system for GR classification that uses hybrid functions and is supported by a vector machine used in medical practice.

This system includes two modules: vascular analysis, which determines the arteriovenous ratio, and analysis of the optic nerve head region, which detects papilledema on fundus images. For the first module, a set of hybrid features was used in combination with a vector machine method and a basic radial kernel to estimate the arteriovenous ratio. The second module analyzes the optic nerve head to look for signs of swelling. The first module achieved an average accuracy of 95%, while the second module achieved an average accuracy of 96%. This newest system allows you to analyze the state of the retinal vessels, the state of the vessels of the head of the optic nerve head and link them with heart rate (HR).

In 2014, A. Triantafyllou and co-authors conducted a study of angioretinopathy caused by high blood pressure and its relationship with vascular wall stiffness in patients with normal blood pressure and early manifestations of hypertension. This is explained by the fact that changes in micro- and macrocirculation are characteristic of long-term hypertension, but not enough studies

have analyzed these changes in the early stages of GH. Non-dilated fundus photographs were used to assess retinal vascular diameters, including the central retinal artery (CRA), venular equivalent, and arteriovenous ratio (AVR). Arterial stiffness was determined by measuring pulse wave velocity (PWV) and aortic augmentation index (AIx). This study is the first to show an association between quantitative changes in the retina and increased arterial stiffness in the early stages of HD. Violation of micro- and macrocirculation in hypertension is a dynamic and interconnected process that manifests itself at the earliest stages. Given the importance of both retinal arteriolar constriction and arterial stiffness in cardiovascular risk, identifying associated micro- and macrovascular changes may be important in assessing cardiovascular health in patients with hypertension.

Guedri et al., studying the diameter of blood vessels during GR, used a modern computer method. The essence of this method is to measure the diameter of a blood vessel in an image of the retina. The proposed method includes thresholding and rarefaction segmentation steps, followed by retinal feature point detection according to the Douglas-Puker algorithm. Then the contours of the vessel are determined, and Heron's formula is used to calculate the diameter.

McDonald proposed a new approach to the study of GH by studying mRNA, endothelin receptors and their antagonists. This work noted clinical and histological changes in the retina, such as hyalinization of the retinal arteries, increased thickness of the vascular basement membrane, narrowing of the retinal arterioles, necrosis of the arteriolar walls, closure of the retinal capillaries, the appearance of cotton wool spots on the retina, smooth muscle degeneration, and disruption of the blood-retinal barrier. Despite the association between systemic hypertension and GH, the exact pathogenesis of this disease remains poorly understood.

Zou and colleagues performed an extensive study of the fundus vessels in GH in cases of hypertension, despite the fact that the symptoms of hypertension have been described in the medical literature since 1859. To assess changes in the fundus in patients with hypertension, in 1939 Keith, Wagener and Barker proposed a classification that included 4 stages: 1) moderate general narrowing of the retinal arteries; 2) stage 1 plus abnormal arrangement of vessels and their narrow constrictions; 3) stage 2 plus the presence of exudates, cotton wool spots and flame-shaped hemorrhages; 4) stage 3 plus papilledema.

Currently, interest in the clinical aspects of hypertension continues, and Zou et al introduced a new arterial-venous classification (AVC), emphasizing the central line of the vessel. The vessel centerline is extracted after pre-processing vessel segmentation and determining the location of the optical disc in the fundus image. A region of interest (ROI) of the retinal vessels is then analyzed. Each pixel on the centerline is treated as a local feature and the analysis is performed using Gray Level Co-occurrence Matrix (GLCM) and Adaptive Local Binary Pattern (A-LBP) using a Maximum Relevance Minimum Redundancy (mRMR) scheme. For arterial-venous classification, an algorithm with functional K-nearest neighbor (FW-KNN) estimation is used. Experimental studies on the DRIVE and INSPIRE-AVR databases showed high classification accuracy - 88.65% and 88.51%, respectively.

In parallel to this study, Spanish scientists in the same year presented data on the micro- and macrocirculation of the retina obtained using automatic retinography during GR. These data correlate with the results of ultrasound examination of the carotid arteries. Based on these data, a new medical technology called “web integration” (Wivern) was developed, which can be used in multidisciplinary medical centers to analyze micro- and macrocirculation. This tool allows you to manage clinical information in several medical specialties such as neurology and ophthalmology. Each study provides automated analysis, including retinography, carotid ultrasound, and blood

pressure monitoring, and provides automated calculations to assess cardiovascular risk. The Wivern application enables interdisciplinary research into the vasculature.

The significance of hypertensive chorioretinopathy. Hypertensive retinopathy and chorioretinopathy serve as indicators of hypertensive changes in other parts of the body. Features of mild hypertensive retinopathy, including global and focal arteriolar narrowing, copper hoops, and arteriovenous junction narrowing, have been associated with coronary artery disease, stroke, and renal dysfunction. The Ibaraki Population Health Study found that mild hypertensive retinopathy is a risk factor for cardiovascular mortality independent of other risk factors for cardiovascular disease. For patients with mild hypertensive retinopathy, multivariate hazard ratios for all-cause cardiovascular mortality were 1.23–1.24 for men and 1.12–1.44 for women, and multivariate hazard ratios for all-cause stroke mortality were 1.31–1. .38 for men and 1.30–1.70 for women.

Signs of mild hypertensive retinopathy, including retinal hemorrhages, cotton flakes, hard exudates, and microaneurysms, are even more strongly associated with an increased risk of death from cardiovascular causes. The ARIC study found that features of mild hypertensive retinopathy are associated with a two- to fourfold increased risk of stroke, independent of other risk factors, including long-term elevated blood pressure, smoking, and lipid levels. This study also found that, after controlling for existing risk factors, mild hypertensive retinopathy was associated with a twofold increased risk of heart failure. Habib et al. found that higher grades of hypertensive retinopathy were significantly associated with higher angiographic severity of coronary artery disease as assessed by the syntactic index.

Hypertensive chorioretinopathy is more common in younger patients with acute increases in blood pressure and is associated with a poor prognosis if untreated. It is seen in conditions such as malignant hypertension, preeclampsia, eclampsia, acute or chronic renal failure, renal artery stenosis and adrenal cancer. These conditions are medical emergencies that require immediate treatment.

Currently, there is an increase in the number of studies in the field of hypertensive retinopathy. Most of them are aimed at a deeper understanding of the pathogenesis of this disease. One study indicated that endothelins, a group of vasoconstrictive substances produced by endothelial cells, may cause damage to the blood-retinal barrier (BRB). It is mainly caused by the activation of endothelin receptors A and B (ETRA and ETRB) by endothelin 1 (ET-1). Stimulation of these receptors promotes vascular leakage and VEGF stimulation and is upregulated in animal models of hypertension and diabetes. In addition, antagonists of these receptors have been shown to reduce vascular damage and neovascularization, as well as exert protective effects on BRB. In addition, plasma ET-1 levels are increased in hypertensive retinopathy. It is important to further investigate the role of neovascularization in hypertensive retinopathy, as this may help achieve additional therapeutic benefits. Targeting agents that promote neovascularization such as platelet-derived growth factor (PDGF), pigment epithelium-derived factor (PEDF), hepatocyte growth factor (HGF), angiopoietins, and fibroblast growth factor (FGF) may be promising. Studies in a rat model of hypertensive complications of pregnancy, preeclampsia, have confirmed the connection between high blood pressure, RAAS and increased levels of pro-angiogenic factors such as VEGF and PEDF. In preeclampsia, there is massive endothelial dysfunction, which also causes minor retinal vasoconstriction. Proteomic analysis of the vitreous may help determine the involvement of these factors in the pathogenesis of hypertensive retinopathy due to its close location to the damaged retina. One difficulty with this method may be the small sample size.

Serum uric acid concentration (SUC) is an independent risk factor for hypertension. It is also associated with hypertensive retinopathy, as shown in a large study in the Chinese population.

Elevated SMC levels can lead to damage to endothelial cells. In addition, additional increases in blood pressure may have a negative cumulative effect on the microcirculation and may mediate vascular damage. It is possible that reducing SMC levels may reduce the risk of developing hypertensive retinopathy. Another substance, marinobufagenin, which is a biomarker of salt sensitivity and increases with salt intake, was found to be associated with decreased retinal microvascular dilatation in young normotensive adults. In addition, increased levels of marinobufagenin have been shown to promote endothelial damage and prevent the decrease in blood pressure at night, which is a physiological process.

Genetic testing can also provide new data. Attempts have been made to identify the genes responsible for the diameter of the reticular vessels. To date, 8 single nucleotide polymorphisms (SNPs) have been identified for CRVE diameter and 2 SNPs for CRAE diameter. Additional research into their role in microcirculatory diseases may explain the predisposition to microcirculatory disorders. Additionally, ALK-1 and endoglin polymorphisms have been shown to be risk factors for cardiovascular events. Both ALK-1 and endoglin are receptors for transforming growth factor beta1 (TGF-β1), which is important in the regulation of blood pressure and vascular homeostasis. In addition, TGF-β1 has been shown to be involved in the destruction of the capillary basement membrane, which serves as a support for epithelial cells.

Much attention is paid to the issues of inflammation and its connection with damage to the retinal microcirculation. Particular attention is paid to the role of LMP10, the catalytic subunit of the interferon-γ-induced proteasome, which has trepsin-like activity. Ang II can cause an increase in the level of this subunit, and studies in mouse models and humans have shown that its level and activity are increased in the retina during hypertension. Moreover, ablation of LMP10 reduces the increase in retinal vascular permeability, remodeling, and inflammation. Inhibition of this subunit may be a potential drug. Another proteasome subunit, b5i, plays an essential role in the development of hypertensive retinopathy in a mouse model of hypertension. The b5i subunit reduces the stability of its associated AT1R protein (ATRAP), which normally inhibits the development of AT1R-induced retinopathy. Ablation of b5i attenuated Ang II-induced retinal thickness increases, inflammation, oxidative stress, and remodeling. An excess of this subunit, on the contrary, enhances these effects. Another study in a mouse model of hypertension showed that G protein-coupling receptor 174 (GPR 174) plays an important role in regulating the immune and inflammatory response. Removing the gene encoding this protein caused a decrease in vascular permeability and had a protective effect on the retina. Recent research has proposed acetylsalicylic acid glycoproteins (GlycA) as a new marker of chronic and cumulative inflammation. High GlycA levels were associated with wider venule diameter and narrower arteriole diameter. The relationship between GlycA and hypertensive retinopathy remains to be investigated.

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