Does the Evaluation of Ocular Blood Supply Play a Role in Glaucoma Diagnostics and Prognosis of Progression?

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Abbreviations

ANS	Autonomic nervous system
ARI	Autonomic regulation index
BP	Blood pressure
CDI	Color Doppler imaging
CPT	Cold provocation test
CRA	Central retinal artery
CV	Coefficients of variation
EPS	Enhanced polarization-sensitive
FLV	Focal loss volume
FR	Functional reserves
FS	Functional status
GCC	Ganglion cell complex
GLV	Global loss volume
GON	Glaucomatous optic neuropathy
HF	High-frequency range
HRV	Heart rate variability
HTG	High tension glaucoma
ILM	Internal limiting membrane
IOP	Intraocular pressure
IPL	Inner plexiform layer

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LF	Low-frequency range
MD	Mean deviation
MOPP	Mean ocular perfusion pressure
MvD	Microvasculature dropout
NFI	Nerve fiber indicator
NTG	Normal tension glaucoma
OCTA	Optic coherence tomography angiography
ONH	Optic nerve head
OPP	Ocular perfusion pressure
PACG	Primary angle closure glaucoma
PERG	Pattern electroretinogram
pfVD	Perifoveal vessel density
POAG	Primary open-angle glaucoma
PPPM	Predictive preventive personalized medicine
PVD	Primary vascular dysregulation
PVEP	Pattern visual evoked potential
RGC	Retinal ganglion cells
RI	Resistivity index
RMSSD	Parameter of parasympathetic autonomic regulation activity
RNFL	Retinal nerve fiber layer
ROP	Rate of progression
SAP	Standard automated perimetry
SDNN	Standard deviation of NN-interval
SD-OCT	Spectral-domain optic coherence tomography
SNA	Sympathetic neural activity
SPCA	Short posterior ciliary artery
SSADA	Split-spectrum amplitude-decorrelation angiography
TP	Total spectral power
VD	Vessel density
VF	Visual fields
VFI	Visual field index
wiVD	Whole image vessel density

1 Introduction

Primary open-angle glaucoma (POAG) is a neurodegenerative disease characterized by a progressive course and an irreversible blindness worldwide.

Accurate prediction of optimal treatment beneficial and adverse effects could improve the results of therapy. The early detection of the specific features of the patient is a key point of the personalized approach in glaucoma treatment. Individualized patient profiling is an instrumental for implementing 3PM strategies in glaucoma management [1, 2].

It is believed that there are two groups of factors responsible for the development of glaucomatous optic neuropathy (GON): (1) vascular dysregulation associated with the decrease of ocular blood flow of the optic nerve disc [3] and (2) mechanical dysregulation associated with the scleral membrane damage and infringement of the optic nerve axons. According to well-known Flammer syndrome, patients with an instable ocular blood flow respond stronger to psychological stress as it has been described in patients with primary vascular dysregulation (PVD) [4, 5]. It has also been emphasized that any psychological stress leads to vascular dysfunction [6]. PVD is believed to be a main cause of local vasospasm and impaired autoregulation as well as a possible contributing factor in glaucoma pathogenesis [7, 8]. It has been shown that PVD patients have stronger reaction to psychological stress than non-PVD subjects. It is known that any psychological stress leads to vascular dysfunction and may become a risk factor of glaucoma development and progression.

The small branches of the central retinal artery provide the blood supply of the superficial ONH layer. The prelaminar region (a small area anterior to the lamina cribrosa), however, is mainly supplied by branches from the choroidal arteries and directly from the short posterior ciliary arteries [9]. As the choroidal microcirculation is regulated by the autonomic nervous system (ANS), the ANS dysfunction is involved in glaucoma pathogenesis.

Indeed, there is a growing body of evidence suggesting that glaucoma pathogenesis is related to vascular dysfunction [10–16]. The consensus on this issue, however, still has not been found due to the lack of adequate techniques for the study of ocular blood flow despite of different measurement tools [17–20]. Therefore, it highly recommended to search for new visualization methods of the vascular bed for early diagnosis and monitoring of glaucoma. Optical coherence tomography (OCT) is a common tool for diagnosis and treatment of glaucoma disease. Doppler OCT has been used to obtain precise measurements of total retinal blood flow [21]. Although Doppler OCT may be effectively used to detect blood flow in the large vessels around the optic disc, it is not sensitive enough for the accurate measurement of low velocities in the small vessels forming the disc microcirculation. The same refers to the most widely used method—color Doppler imaging (CDI). A new method—OCT angiography (OCT-A)—has been recently introduced. This method allows measuring vessel density in the retina and choroid in the peripapillary and macular areas using high-speed OCT to perform quantitative angiography.

This book chapter will primarily discuss a role of heart rate variability (HRV) assessment and OCTA in glaucoma diagnostics and monitoring.

2 Heart Rate Variability in Glaucoma Patients

According to the literature sources, patients with cardiovascular diseases have 2.33 times more rapid glaucoma progression despite significantly lower intraocular pressure (IOP) values [22]. Moreover, the concept that vascular changes in the eye may be an early indicator of heart diseases is also discussed in literature [23].

Recent studies have shown the role of vascular disturbances and vascular dysregulation in glaucoma [24–29]. This makes glaucoma common with such forms of pathology as arterial hypertension/hypotension, migraine, and vascular spasm [29].

According to the existing literature, POAG patients have significantly smaller diameter of the arterial and venous retinal vessels compared to the control subjects. Nevertheless, both venous and arterial dilatation was normal during the activation of neurons, despite their smaller diameter. The dilatation varied among patients and did not depend on the visual field deterioration. This fact was explained by chronic vasoconstriction leading to the limited energy flow to the retinal and brain neurons, followed by hypometabolism (so-called, silent neurons) and, finally, by the death of neurons [30].

Excessive activity of the sympathetic ANS is among the possible causes of ONH blood supply violation and decreased ocular perfusion pressure (OPP) in the optic nerve and choroidal vessels. Moreover, it has been demonstrated that excessive activity of the sympathetic link of the ANS is associated with glaucoma progression due to instability of the ocular blood flow [26].

Cold stimulation, or cold provocation test (CPT) is a well-established provocation test used for detecting abnormal vascular reactivity in patients with autonomic failures [31]. The testing procedure is rather simple: a patient's hand is dipped into cold water (+4 ° C) with small pieces of ice for 30 seconds and the cardiovascular response is registered (Fig. 1). It has been revealed that the cold provocation test (CPT) may increase the ET-1 level in plasma in glaucoma patients reflected their vascular dysregulation [22]. This phenomenon may also indicate the imbalance of ANS that is manifested mostly during provocation tests, including CPT [33].

Altered ocular blood flow or reduced visual field sensitivity during sympathetic provocation tests has been demonstrated in POAG patients [34–36].

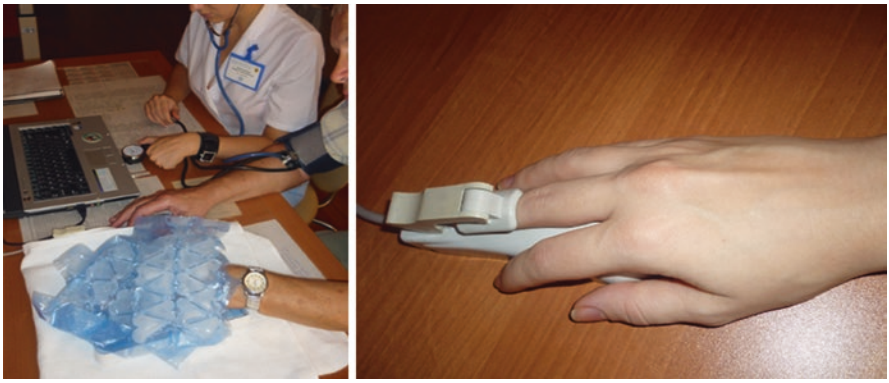

Fig. 1 Cold provocation test (CPT). Photoplethysmography with infrared sensor records from a phalanx with an infrared sensor, located in the microprocessor module of data on HRV and peripheral blood flow [32]

2.1 HRV Assessment

HRV assessment is a standard method to evaluate ANS function. The lower the HRV, the more severe the ANS dysfunction with sympathetic predominance [37].

Compared with other methods of assessing autonomic dysfunction, which include cardiovascular reflex tests, sudomotor tests, Valsalva maneuver, the tilting test, HRV assessment is simpler and non-invasive. Numerous studies have validated HRV as a reliable measure of ANS function in cardiac and non-cardiac diseases. The studies showed that POAG patients had autonomic dysfunction characterized by a HRV drop [32, 38].

We have introduced a special hardware–software complex Rhythm-MET that is based on a comprehensive analysis of HRV, systemic hemodynamics, and vegetative regulation [32].

Photoplethysmograms showing the blood flow measurements in a phalanx were recorded using an infrared detector, located in the microprocessor module of data input and processing, and served as the source of HRV and supplemental blood inflow data. Cardiointervals obtained from photoplethysmograms is processed in accordance with the recommendations for the assessment of HRV parameters and their subsequent generalization, including hemodynamics parameters, and for assessment of the functional status (FS) and functional reserves (FR) of the cardiovascular system according to the results of the examination at rest and after CPT in order to form groups homogeneous in both FS and FR.

The ensuing characteristics should be considered in agreement with the transnational standard:

- Standard divagation of NN-interval (SDNN) is the HRV parameter characterizing the total effect of autonomic blood circulation regulation. A reduction in SDNN reflects low HRV indicating a high tone of heart sympathetic exertion. The drop in SDNN reflects a drop in HRV, which indicates an increase in the heart sympathetic exertion tone.
- The parameter of parasympathetic autonomic regulation exertion (RMSSD).
- Total spectral power (TP) is the parameter of absolute exertion level of non-supervisory systems.
- Power in the high-frequency range (HF) is the parameter of the spectral power of heart rate respiratory undulations reflecting the exertion position of respiratory center. The high-frequency band reflects rapid changes in beat-to-beat variability due to parasympathetic exertion.
- Power in the low-frequency range (LF). The low-frequency band is considered to be a fair approximation of sympathetic exertion. The low-frequency band reflects substantially sympathetic stimulation.
- The low/high-frequency rate is a rate of low-frequency to high- frequency power (LF/HF). An advanced rate indicates increased sympathetic exertion or reduced parasympathetic exertion.
- The number of pairs of successive NN-intervals is the parameter of ascendance degree of parasympathetic regulation over sympathetic one (pNN50).

- Autonomic regulation indicator (ARI) is the parameter for assessment and exertion of ANS. The increased ARI shows the activation of sympathetic regulation, but the decreased ARI shows the activation of parasympathetic regulation.
- Variation range characterizing the degree of HRV (TINN).

SDNN is a representative parameter of HRV. The lower HRV is associated with enhanced SNS exertion, which may be characterized by ANS dysfunction [37].

2.2 The Results of HRV Assessment in High Tension Glaucoma (HTG) and Normal Tension (NTG) Glaucoma

The strict definition of POAG includes HTG and NTG. As far as HTG and NTG are concerned, they appear to be a continuum of glaucomatous process, in which the underlying mechanisms shifts from predominantly elevated IOP in HTG to hemodynamic change in NTG. In other words, both HTG and NTG are related to hemodynamics, but it was hypothesized that the evidence of vascular dysfunction would be more pronounced in NTG patients. One of the possible reasons for this is autonomic dysfunction that may contribute to unstable or fluctuating blood pressure and thereby may induce the dysfunction of autoregulation leading to glaucoma development and progression [3].

Some authors report on autonomic dysfunction in HTG with short term and daily analysis of heart rate variability [26, 34, 38–40]. However, the existing data on autonomic dysfunction in HTG and HTG are contradictory. According to Riccadonna M. et al., HRV and nocturnal diastolic BP variability were reduced in NTG compared to HTG [39]. Furthermore, these differences were more prominent in more severe clinical forms of NTG. The authors suggested a correlation between the extent of autonomic dis-order and severity of glaucoma.

Brown et al. assessed the baroreflective control of the blood and heart vessels using sinusoidal cervical aspiration and showed that the ANS response in healthy subjects was significantly higher than in glaucoma patients. However, they did not detect any difference between NTG and HTG. According to their data, the decreased sympathetic and parasympathetic modulation during baroreceptor stimulation in the patients with HTG and NTG suggested that autonomic dysfunction that may contribute to the pathogenesis of both diseases [40].

Mroczkowska et al. compared NTG and HTG patients with early glaucoma using 24-h outpatient blood pressure monitoring and measurement of peripheral pulse-wave analysis and thickness of the intima-media complex of the carotid arteries. The authors also evaluated reactivity of retinal vessels to flickering of light. Similar changes in systemic and ocular circulation were observed in glaucoma patients of both groups compared to healthy subjects, but no significant differences were revealed in nocturnal blood pressure, arterial or venous retinal atrial fibrillation, systemic arterial stiffness, and intima-media thickness between patients with NTG and HTG [41].

Bossuyt et al. reported on significantly reduced OPP in patients with HTG and NTG compared to the control healthy subjects. They suggested that perfusion-associated vascular changes play an important role in the pathogenesis of both conditions [42].

On the other hand, there are some important differences between HTG and NTG. The nature of VF progression in HTG differs from other types of glaucoma [43]. It is worth noting that NTG of the eye usually progressed in the central region of the VF, and this response was associated with unstable or strong fluctuations in the average 24-h ocular perfusion pressure and excessive nocturnal drops in systemic arterial blood pressure [26, 44]. Consequently, the division into NTG and HTG in clinical practice is still accepted [45].

A significant decrease in retrobulbar blood flow in HTG is described in the literature [46, 47]. Furthermore, Kaiser et al. revealed that ocular blood flow was decreased both in patients with NTG and HTG who progressed despite normal IOP values [46].

Vascular risk factors varied in HTG and NTG [7, 23, 25]. It was hypothesized in the literature that the vascular dysfunction would be more pronounced in NTG patients compared to HTG [7, 31, 48]. However, some authors reported on similar changes in systemic and ocular circulation in the early stages of the disease in patients with HTG and NTG [41].

The decrease in arterial ocular blood flow was more significant in HTG than in NTG, while lower venous blood flow was detected in patients with NTG [47]. It was emphasized in the literature that decreased blood flow rates in the central retinal artery and central retinal vein were significantly associated with the glaucoma progression both in patients with NTG and HTG with well-controlled IOP (21 mmHg or less) [46]. Circulatory disorders can occur in both NTG and HTG, regardless of the IOP level. One of the reasons is increased sympathetic nervous activity (SNA). This leads to increased vascular resistance and, especially in conditions of endothelial dysfunction, may have consequences for blood circulation related to the pathogenesis of glaucoma. The SNA activation causes an increase in stroke volume, heart rate, and vasoconstriction, as well as regulates circadian blood pressure fluctuations, and it is closely related to night dives.

Recently, we compared the shift in HRV indicators in patients with NTG and HTG after a cold provocation test (CPT). MOPP, 24-h blood pressure and HRV were studied in 30 NTG, 30 patients with HTG and 28 healthy individuals. The cardiovascular system condition was assessed before and after CPT. We applied a method of comparing regression lines to identify the differences between groups. Minimum daily diastolic blood pressure and MOPP were reduced in patients with HTG and NTG in comparison with healthy subjects. There were no differences in MOPP between HTG and NTG before CPT. However, all HRV parameters reflected the predominance of sympathetic innervation in glaucoma patients compared to healthy subjects ($p < 0.05$). Up to CPT standard deviation of NN intervals (SDNN) HRV was lower at HTG compared to NTG, 27.2 ± 4.1 ms and 35.33 ± 2.43 ms ($P = 0.02$), respectively. After CBT, SDNN decreased in NTG by 1.7 ms and increased in HTG and healthy individuals by 5.0 ms and 7.09 ms,

respectively ($P < 0.05$). Analysis of the relative shift of other HRV parameters after CPT also revealed a significant difference between NTG and HTG in relation to the predominance of sympathetic innervation in NTG compared to HTG. The conclusion was made that NTG patients had a more pronounced violation of ANS than HTG patients, which was manifested by sympathetic nervous system activation in response to CPT. This discovery relates to the pathogenesis of NTG and suggests the use of HRV assessment in the diagnosis and monitoring of glaucoma [32].

Besides, we observed a significant dipping of diastolic BP both in NTG and HTG patients compared to healthy subjects. Probably, this was a consequence of the sympathetic innervation activation. There is evidence of the presence of a choroidal nerve plexus, represented by numerous internal autonomic ganglia forming an autonomous perivascular network around choroidal vessels [49]. It is considered that it plays a vasodilating function aimed at increasing ocular blood flow. Apparently, vascular mechanisms of optic nerve and retinal trophic disorders and their autonomic regulation play an important role in the ocular pathophysiology and physiology in general and in glaucoma. Vasoconstriction occurs against the background of the predominance of sympathoadrenal effects on arterioles and capillaries, as well as due to a decrease in the activity of parasympathetic effects on retinal vessels.

The abovementioned study contained the evidence of altered MOPP both in HTG and NTG patients compared to healthy subjects. However, there were no difference in the MOPP between HTG and NTG that is consistent with the results of previous studies [35, 39, 41]. The obtained results demonstrate that there may be a significant overlap in the development of NTG and HTG, especially at early glaucoma stage [41, 50]. From this point of view, it has been assumed that provocation tests may be used to reveal alterations in cardiovascular function in NTG patients [42]. Prior to CPT, there was a significant difference in all HRV parameters at rest both between glaucoma patient's groups and between HTG patients and control subjects. CPT confirmed a significant difference between the control group and glaucoma patients. In the present study we described a significant increase in the activity of the sympathetic ANS in NTG patients in response to CPT. Changes in the main HRV parameters (SDNN, HF, LF, S, and ARI) after CPT emphasize a significant difference between HTG and NTG patients. It is a well-known fact that PVD people have an increase in sympathetic ANS as a response to provocation tests. The NTG development is associated with the presence of PVD [7, 23]. But currently, this fact is not absolutely reliable, and therefore NTG is considered to be a form of open-angle glaucoma. Although the role of PVD in the pathogenesis of GON has been discussed for many years, only recent studies due to the use of modern technologies could prove that patients with NTG, but not healthy individuals, suffer from the retinal blood flow autoregulation failure in the conditions of provocation tests [51]. From this point of view, the dysfunction of the autonomic blood flow regulation seems to be of high importance and its study attracts attention of the

researches. Wierzbowska et al. revealed that the sympathovagal balance of ANS in NTG patients shifted towards sympathetic exertion with no change of 24-h pattern of BP variability as compared to the control healthy group [34]. Na et al. demonstrated significantly reduced SDNN values in NTG [38].

There are new highly relevant data indicating the influence of vascular factors on the NTG development. It can be concluded that the disorders of autonomic innervation underlying PVD lead to the development of NTG, but not its specific feature. The presence of ANS imbalance in POAG patients, including HTG, can also be considered as a risk factor for an unfavorable course of GON. In any case, the obtained results demonstrate the significant role of PVD in the pathogenesis of NTG. The results of our study demonstrating the ascendance of SNA in NTG can be useful for distinguishing HTG and NTG.

This conclusion has an important practical implication for detecting NTG (or if it is suspected), determining the prognosis and choosing more appropriate therapy, as well as making recommendations to patients concerning the proper lifestyle. Further studies are needed to verify our findings as well as studies on any therapies that favorably influence ANS activity in patients with glaucoma.

2.3 The Effect of Autonomic Nervous System Dysfunction on the Progression of Primary Open-Angle Glaucoma

Patients with systemic autonomic dysfunction might be at higher risk for glaucoma progression due to higher susceptibility of the optic nerve to fluctuations of IOP or MOPP.

Park et al. in their study described NTG patients with different types of HRV and reported on the fact that the VF progression in patients with sympathetic predominance occurs faster than in patients with higher HRV. The authors concluded that autonomic dysfunction, especially a decrease in SDNN, is a predictor of the progression of central VF in NTG [26]. This study concluded that IOP-independent risk factors, such as orthostatic hypotension, migraine, and autonomic dysfunction, are associated with the progression of central VF.

In another retrospective study of 40 cases of POAG patients who underwent regular reexamination with heart rate variability (HRV) assessment for more than 3 years Liu and co-authors revealed that patients with POAG in the lowest HRV group showed a faster thinning rate of RNFL than those in the highest HRV group. The progression was accompanied by greater fluctuation of intraocular pressure and a decrease of blood pressure and ocular perfusion pressure. Moreover, thinning rate of RNLF was negatively correlated with SDNN values: the more severe the ANS dysfunction is, characterized, the faster the glaucoma progression in POAG patients. The authors explained this by the enhanced activity of the sympathetic tone and concluded that the treatment of ANS may be useful in glaucoma [37].

3 Vascular, Structural, and Functional Deterioration in Glaucoma

3.1 The Association of Vascular, Structural, and Functional Parameters in Glaucoma

For many years, there has been a debate concerning the issue which parameters—structural or functional—have the greatest diagnostic value in glaucoma [52]. Perimetry was considered a golden standard for the diagnosis of primary open-angle glaucoma (POAG) for a long time. The peripapillary retinal nerve fiber layer (RNFL) and the layer of macular ganglion cells are described in the existing literature as the most significant structural markers for the glaucoma diagnosis [53]. Some authors also reported that the molecular parameters have a high discriminating ability and high reproducibility for the early detection of glaucoma compared to the parameters of the peripapillary RNFL [54].

According to our recent studies, the circulatory parameters serve as diagnostic glaucoma markers [55]. Reduction of retinal hemoperfusion in glaucoma has been repeatedly mentioned in the literature [10, 11]. Nowadays, there is much data on hemodynamic disorders in retina, ONH, and retrobulbar circulation in glaucoma [49, 56–58]. Moreover, several authors have concluded that color Doppler imaging is associated with a prognostic value for damage to visual function in glaucoma patients [59, 60].

However, it is not clear yet if reduced blood flow is the cause or the consequence of glaucoma damage secondary to retinal ganglion cell (RGC) death. This issue can be solved only due to long-term observation of patients by using available methods of clinical examination of retinal vessels, optic nerve, and choriocapillaris. One of the candidates for this method is optical coherence tomography angiography.

3.2 Optical Coherence Tomography Angiography in Glaucoma Diagnostics and Monitoring

Optical coherence tomographic angiography (OCTA) is a new non-invasive diagnostic technique to study the microcirculation in optic nerve, retina, and choroid. OCTA opens up new prospects for examining the blood supply to main structures usually affected by glaucoma (peripapillary retina, optic disc, and internal macular layers) [61]. The studies have consistently demonstrated reduced ONH [61, 62], peripapillary [63], and macular [63–67] perfusion in glaucoma patients using OCTA.

The cross coefficients of variation (CV) range from 3.2% to 9.0% for the global OCT-A parameters of the macular and peripapillary regions [62] and from 5.0% to 6.9% for the peripapillary region [68]. According to the results of some studies, OCTA measurements of vascular density may complement the existing structural parameters for glaucoma detection and its progression by detecting changes in the microcirculatory bed supplying ganglion cells and axons before changes in structural thickness measurements [12, 65–67, 69–71]. OCTA has opened the prospects

for novel imaging of retinal and ONH microcirculation [72]. OCTA is based on a new three-dimensional angiography algorithm called amplitude-decorrelation angiography with a split spectrum (SSADA), comparing successive B-scans at the same location to detect blood flow using motion contrast. The reproducibility of OCTA has been reported in several studies [61, 73, 74].

Reduced ONH and peripapillary perfusion parameters have been reported by different authors in subjects with glaucoma measured by OCTA [61, 64, 72–75]. The decreased vessel density (VD) was significantly associated with the severity of visual field damage independent of the structural loss [76, 77].

Different authors have found a significant decrease in IOP in patients with glaucoma compared with healthy people. Wang et al. reported reduced blood flow index in the entire optic disc and inferotemporal segment of the optic disc [73]. The study by Chichara et al. demonstrated the priority of detecting superficial peripapillary retinal VD to differentiate between glaucoma and ophthalmic hypertension and healthy eyes [78]. Liu et al. in their study revealed that there was a significant decrease in peripapillary VD in glaucoma patients compared to healthy subjects of the same age [74]. According to the authors, this indicator had a high diagnostic value for the early detection of glaucoma. Some other studies reported that quantitative OCT-A analysis made it possible to distinguish eyes with glaucoma from healthy eyes by evaluating the entire peripapillary vascular network, from the ILM to the Bruch membrane [76]. According to Yarmohammadi et al., the decreased VD was significantly associated with the severity of visual field damage independent of the structural loss, and whole image vessel density (wiVD) of the disc scan showed the best AUC in their study (AUC: 0.94) [77].

Previously, we have reported better diagnostic accuracy by using capillary density in the macular area over the peripapillary area and the optic disc in the early glaucoma detection [64]. These data are consistent with the literature data on early macular lesions with a high concentration of RGC in glaucoma and explain the localization of the vulnerable area of the retina affected at the very beginning of glaucoma [79, 80].

The functional activity of retinal ganglion cells can be measured using a pattern electroretinogram (PERG). The other objective method of checking visual function is the pattern of visual evoked potentials (PVEP). Glaucomatous changes in PVEP and PERG were reported before the appearance of anomalies in the peripapillary retina and ONH [80–86]. Moreover, PVEPs were used to assess reversible ganglion cell damage in the studies of neuroprotective agents for glaucoma treatment [87, 88].

Having compared the diagnostic ability of the vascular, structural, and functional parameters in differentiation between the normal eyes, early glaucoma, and moderate to severe glaucoma, we have revealed that the results of the electrophysiological testing along with the retinal microcirculation measured by OCTA demonstrated superiority over the structural variables in early glaucoma detection (Fig. 2) [89].

According to our study, a strong correlation between the amplitude of the P100 PVVP and the density of vessels in the ZEN and peripapillary retina, on the one hand, and a correlation between the density of vessels in the superficial macular plexus and the GCC thickness in inferior hemisphere, on the other hand, were

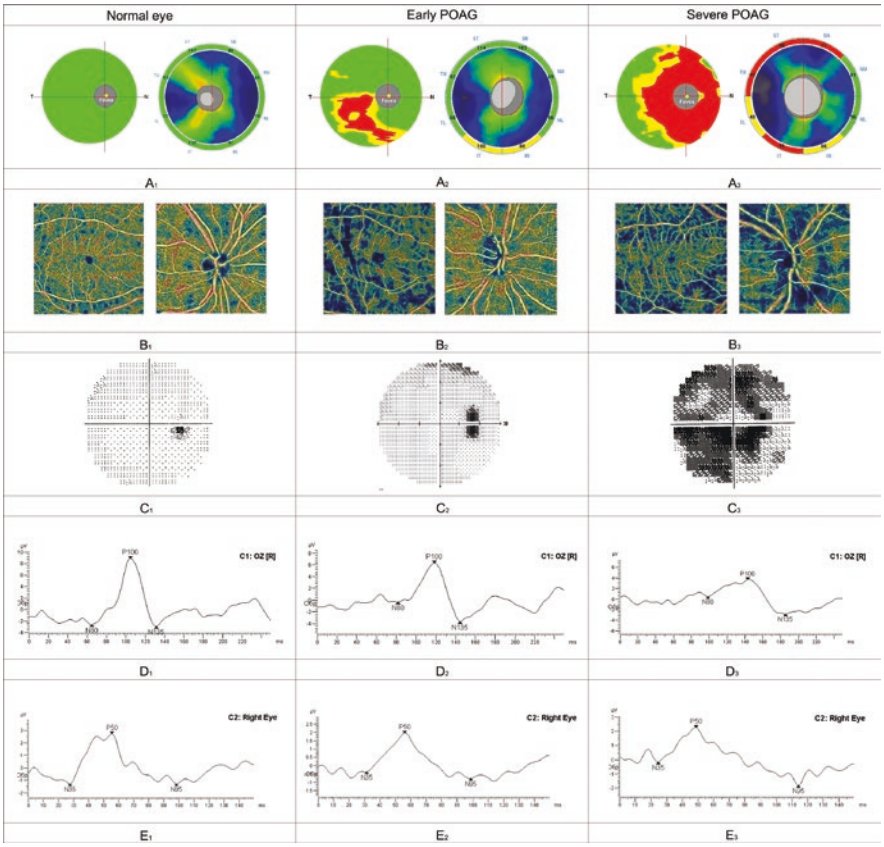

Fig. 2 Clinical examples of the normal controls, early glaucoma, and severe glaucoma. GCC map and RNFL thickness map (**a**), SAP visual field results showing corresponding visual field defects (**c**), PVEP-protocols (**d**), PERG-protocols (**e**). Figure **b** show a stepwise decrease of vessel density both in the circumpapillary VD map and Fovea and circum parafovea VD map (wiVD Disc is reduced from 54.25% (normal eye) to 52.26% (early glaucoma) to 42.17% (severe glaucoma); wiVD Macula Superficial is reduced from 52.56% (normal eye) to 41.95% (early glaucoma) to 41.29% (severe glaucoma). Figure **d** show a stepwise decrease of the amplitude and prolonged latency of P100 component of PVEP and **e** show a decrease of the amplitude and prolonged latency of N95 component of PERG in glaucoma eyes compared to normal eye. (*Modified from the National Journal of Glaucoma (RUS), 2019 with permission)*

revealed. It can be concluded that the damage of ganglion cells may be associated with decreased blood supply to the retina. It was shown that the macular capillary vessel area density strongly correlated with inferior hemimacula or structural damage [65]. Inferior hemimacular retinal structure is subject to a decrease in the area of the capillary vessels of the retina in eyes with glaucoma. Moreover, the blood flow parameters in ophthalmic artery, central retinal artery, and short posterior ciliary arteries in early glaucoma significantly correlate with the retinal thickness in the inferior hemisphere [90].

The existing results of studies demonstrate the importance of microcirculation parameters of the peripapillary retinal and macular region, PERGs and PVEPs, for early detection and monitoring of glaucoma.

3.3 The Detection of Glaucoma Progression Using OCTA

Successful monitoring of POAG depends on early detection of the disease progression. An individual treatment plan should be based on the risk factors and specific clinical markers that allow predicting the rate of disease progression and avoiding unreasonable prescriptions.

Increased intraocular pressure (IOP) [91–95] and its fluctuations [96] are commonly considered to be the main recognized factors for POAG progression. However, there is an increasing interest in the influence of other factors as it is known that the disease can progress at normal IOP [27, 97, 98]. These factors include a thin cornea [93, 99], low corneal hysteresis [100], optic disc hemorrhages [95, 101], peripapillary atrophy of the choroid [91, 100], age of patients [91, 95, 102], female sex [95, 103], presence of pseudoexfoliation [92], late detection of glaucoma [93], and arterial hypotension [104, 105] or/and hypertension [103, 106]. Nevertheless, researchers disagree on many issues regarding progression risk factors and recommend to take into account only highly reliable results concerning significant parameters [95, 107].

A number of studies demonstrate the importance of using OCT angiography for the detection of glaucoma progression. Moghimi S et al. showed that a higher rate of RNFL thinning was associated with an initially reduced density of macular and peripapillary vessels in glaucoma patients [70]. An increase in the area of depletion of vascular macular blood flow, according to the literature, significantly correlates with the presence of structural and functional markers of glaucoma progression, such as the appearance of visual field defects and thinning of the RNFL [69]. According to literature, there is a direct relationship between the vascular, structural, and functional changes in patients with advanced glaucoma [108]. Figure 3 demonstrates a clinical example of the structural and vascular loss that is accompanied by the functional deterioration.

Retinal microvascular loss may be detected more often than structural ones due to the presence of the so-called floor effect in the late stages of the disease, which certainly puts the use of OCT angiography in the forefront in assessing progression of glaucomatous optic neuropathy [109]. Thus, in advanced glaucoma, the measurement of parameters of the microvascular superficial parafoveal vessel density is more prognostic due to the lack of “floor effect” [110].

According to Kwon and co-authors, the visual field progression rate was significantly faster in eyes with parapapillary deep layer microvasculature dropout detected by OCT-A than in those without dropout, and the location of dropout and VF progression was spatially correlated. These findings implicate dropout as a structural parameter suggestive of past glaucomatous VF progression [111].

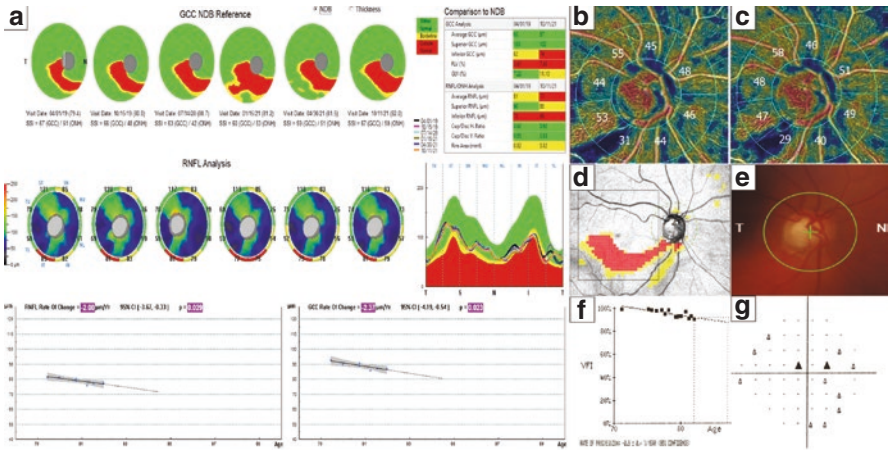

Fig. 3 Association of structural, functional progression with the decrease of microvascularity in the patient with early glaucoma. (**a**) Progressive RNFL and GCC loss; (**b**, **c**) A decrease of vessel density in the circumpapillary VD map; (**d**) A decrease of thickness of GCC and ONH corresponding to the loss of vessel density; (**e**) Fundus visualization of ONH; (**f**, **g**) SAP visual field results

An analysis of FAZ in glaucoma monitoring revealed that, as it manifested, there was a significant thinning of the RNFL and GC-IPL, while no changes in perimetric data were observed [112].

3.4 Role of the Peripapillary Choriocapillaris Loss in Glaucoma Development and Progression

Choroid is another important structure for OCTA assessment. It has the highest blood flow compared to any other tissue in the body [113]. The choriocapillary layer is formed from small arteries and veins, which then break up into many capillaries, passing several red blood cells in one row, which allows more oxygen to enter the retina. The choriocapillary layer of the choroid plays a crucial role in supplying oxygen and nutrition to the outer cells of the retina, especially the retinal pigment epithelium [114]. It should be emphasized that a lesion of blood flow in the choriocapillary layer in the area of the peripapillary retina leads to damage to the lamina cribrosa of sclerae, resulting in a weakening of the structures of the latter.

Optical coherence tomography and angiography mode have opened up new prospects in the study of choriocapillaris blood flow, or rather, the loss of choriocapillaris of the peripapillary retina in glaucoma (Fig. 4).

According to literature, more than the half of patients with primary open-angle glaucoma have a choriocapillary dropout in the beta zone of the ONH [115].

Also, during the examination of 118 patients, scientists revealed that with primary open-angle glaucoma and the presence of defects in the lamina cribrosa

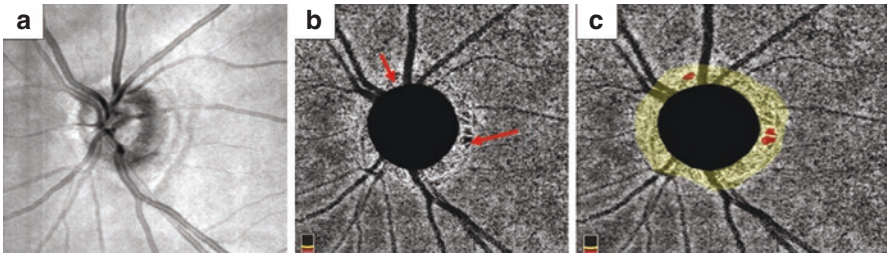

Fig. 4 (**a**, **b**, **c**). Determination of the area and localization of choriocapillary dropout within the beta zone on the density map using RTVue XR Avanti («Optovue», USA). On scans of 4.5 × 4.5 mm of ONH (**a**) at the level of the choroid inside the beta zone, the total dropout of choriocapillaris is determined (**b**: red arrows), with the help of ImageJ program, the area of choriocapillaris dropout in mm^2 inside the beta zone is calculated by pixels (**c**: red areas)

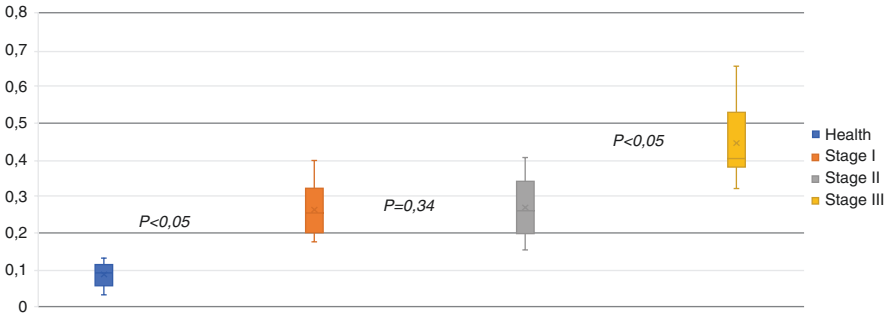

Fig. 5 Peripapillary microvasculature dropout area as a reflection of glaucoma severity

sclerae (59 patients), the frequency of detection of choriocapillary dropout was more frequent than in patients with glaucoma without defects in the lamina cribrosa sclerae (59 patients) [116].

The study by Eun Ji Lee et al. found out that larger lamina cribrosa curvature index (LCCI), disc hemorrhage, and the presence of cMvD were associated with faster global RNFL thinning in multivariate regression analysis. The regression tree analysis revealed three stratified groups based on the RNFL thinning rate divided into LCCI and the presence of cMvD. Eyes with LCCI ≥11.87 had the fastest RNFL thinning (−2.4 ± 0.8 microns/year). Among the eyes with LCCI <11.87, the presence of cMvD was the strongest factor influencing the faster thinning of RNFL (−1.5 ± 0.8 microns/year). Eyes with LCCI <11.87 and without cMvD showed the lowest RNFL thinning (−0.8 ± 0.9 μm/year) [117].

In a recent study, we also showed that the higher the stage of glaucoma, the larger the area of loss of choriocapillaris measured in mm^2 (Fig. 5).

Youn Hye Jo in their study showed that the initial parameters of choroidal microvasculature dropout (CMvD) can be predictors of the rapid development of visual field defects [118].

We have been obtaining glaucoma patients with the fast thinning of choroid that was associated with the rapid visual field deterioration despite the normal IOP (Fig. 6).

A thin peripapillary choroid is also considered a predictor of glaucoma progression [119]. The study by Kim et al. reported that the eyes with the loss of capillaries in the lower temporal quadrant of the peripapillary vasculature have more pronounced visual field damage compared to the eyes with preserved peripapillary choroidal microcirculation. Kim et al. noted an inverse relation between the VD in the peripapillary vasculature and the SNVS thickness [120]. The data of the present study on the prognostic role of the thickness of the peripapillary vasculature are consistent with these results.

Two-year observational study by Park H. et al. revealed the prolapse of peripapillary choroidal microvessels (MvD) in glaucomatous eyes with or without disc hemorrhage (DH). The authors demonstrated that MvD was significantly higher in patients with progressive glaucoma than in stable patients in both the DH and no-DH groups. Park H. et al. concluded that MvD is associated with progressive RNFL thinning. They suggested that OCTA was a new biological marker for glaucoma progression, and this biomarker is a peripapillary choroidal microvascular system [69]. The authors explained this phenomenon is caused by choroidal vascular insufficiency, which may play a significant role in the lack of prelaminar nutrition of the optic nerve during the progression of glaucoma.

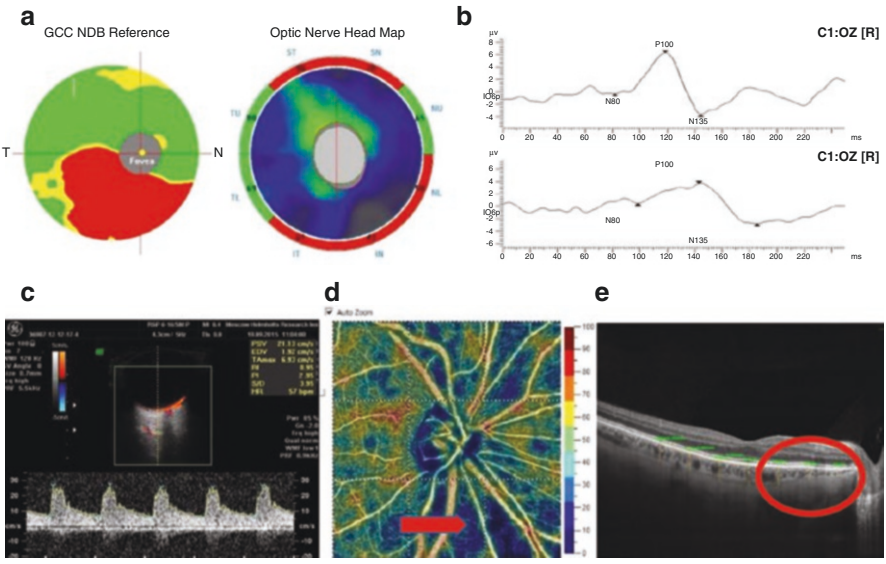

Fig. 6 Clinical example of the choroidal thinning in correspondence with structural, functional and vascular deterioration. (**a**) A decrease of thickness of RNFL and GCC; (**b**) A decrease of amplitude of PVEP; (**c**) A decrease of end-diastolic velocity in the short posterior artery; (**d**) A deep layer microvasculature dropout; (**e**) Decrease of the peripapillary choroidal thickness

3.5 The Prognosis of Glaucoma Progression on the Basis of Functional, Structural, and Circulatory Data

It is rather complicated to define glaucoma progression, since many various factors influence the course of glaucoma [92, 103]. The study by De Moraes reported on the fact that combining data can be useful when discussing risks and treatment options with individual patients, as well as when standardizing the quantitative assessment of the risk of progression in treated patients with glaucoma [100]. From this point of view, the application of new biomarkers as the vessel density, measured by OCTA, may improve the prediction of glaucoma progression.

We conducted a comparative study of microcirculation parameters, predictors of glaucoma progression, and other clinical data [121]. The following results were obtained: decreased blood circulation, including regional microcirculation and retrobulbar blood flow, is associated with the progression of glaucoma. According to the multilevel analysis of models of mixed effects, four predictors were revealed: parafoveal superficial plexus vessel density, the end-diastolic velocity of the central retinal artery, the volume of focal loss of the ganglion cell complex and the peak follow-up IOP. The rate of disease progression expressed as a change of perimetric index MD of visual field and RNFL thinning correlated with the peak follow-up IOP and the end-diastolic velocity in posterior ciliary arteries. A positive correlation was also observed between the thickness of the retinal inner layers in parafovea and the parafovea vessel density in superficial layer. Mean ocular perfusion pressure (MOPP) correlated with the average ganglion cells complex thickness and its focal loss volume [121].

The present study concluded that only a decrease in parafoveal VD in the superficial layer was associated with the glaucoma progression, which was confirmed by both functional and structural disorders in all statistical models. Several existing studies have shown that OCTA makes it possible to detect the disease at the preperimetric stage, and OCTA parameters correlate better with functional parameters, including electrophysiological parameters, than with structural ones [61, 77, 89].

Some authors have reviled that the disease progression is mainly associated with low end-diastolic velocity in short posterior ciliary arteries [59] and the high resistive index in central retinal artery [122].

A decrease in OCTA VD may actually precede both structural and functional losses and, therefore, may be useful in the diagnosis and monitoring of glaucoma at the earliest stages [123, 124]. This decrease detected at early glaucoma stages may be used as a glaucoma progression predictor.

Generally speaking, the role of OCTA in identifying glaucoma progression predictors and the dynamic range of vascular density is insignificant. Moreover, the study conducted by Moghimi and co-authors also has underlined that the correlation between the rate of RNFL loss and VD measurements was not strong. However, Moghimi et al. concluded that the OCTA parameters can predict RNFL loss during the long-term follow-up. The authors reported that OCTA may provide the data concerning early RGCs dysfunction with lower metabolic needs.

According to our study, a decrease in parafoveal vessel density can serve as a predictor of death of cells and subsequent tissue thinning with functional loss. The inferior sector of the macula as a vulnerable region for glaucoma damage makes sense, since most of the nerve fibers of the lower macula are projected into the lower quadrant of the optic disc, an area that is particularly susceptible to glaucomatous damage. Hood et al. described that thinning of RGC and the nerve fiber layer is already present in preperimetric glaucoma patients and progresses with increasing loss of mean deviation (MD) [79]. Lommatzsch et al. confirmed first that the VD of the inferior perimacular sector is lower than in all other sectors, and that this value decreases in early forms of glaucoma with progressive losses with worsening of progressive losses with deteriorating MD [125]. The recent study showed that a decrease in VF MD for every 1 dB was associated with a decrease in macular wiVD by 0.43% and pfVD by 0.46%. According to their study, the correlation between macular vessel density and MD of the visual field in the whole image was stronger than ONH whole image capillary density and GCC and RNFL thicknesses [108]. However, the authors did not sufficiently study the reasons for early macula damage in glaucoma. This fact is probably due to retinal ischemia with increased metabolic needs of the area with the highest concentration of RGC. According to the results of our study, the thickness of the RGC and its characteristics (GLV and FLV) correlated with the average ocular perfusion pressure.

The assessment of macular VD in glaucoma monitoring also makes it possible to determine the disease progression in such cases when structural parameters are unacceptable due to the presence of floor effect. According to Moghimi, even a pronounced loss of visual function (MD reached −19 dB) did not result in the "floor effect" of VD [126]. Similar results were obtained by Rao [127] who demonstrated that the floor effect for the specified parameter did not occur at MD -15 dB. Other authors reported that the floor effect in the peripapillary retinal VD occurs somewhat earlier, which is observed at MP < −14.0 dB, but at the same time later than for such morphometric parameters as RGC thickness and RNFL [79, 128]. According to Hood et al., this effect for RNFL is already visible at MD of −10 dB [79]. Other authors have also noted the advantages of studying GCC thickness compared to RNFL [129]. Furthermore, the importance of assessing peripapillary VD in the late glaucoma stages has been described in the recent studies [130]. It has been revealed that the detection of glaucoma progression at early stages is more reliable with the use of SD-OCT, while functional deterioration is more visible in the middle and late stages. In our previous studies we reported that the structural parameters (in particular, retinal GCC) have priority over functional ones in early glaucoma compared to advanced stage of the disease [89]. However, peripapillary VD had the highest diagnostic accuracy to distinguish between early, middle and late stages, while parafoveal VD in the surface layer had the highest diagnostic accuracy to distinguish between early glaucoma and healthy eyes. In general, the diagnostic ability of the OCTA parameters in early glaucoma was higher compared to GCC and RNFL thickness.

According to some studies, a decrease in macula VD, OHN, and the peripapillary retina is associated with a higher rate of progression of RNFL loss in mild and

moderate glaucoma, suggesting that a VD decrease may be a predictor of progression risk [126]. Their results have shown that vessel density measures tend to be more strongly associated with severity of visual field damage than thickness measures and may be an additional tool to monitor progression in advanced disease. These data are consistent with our results, according to which OCTA parameters serve as predictors of glaucoma progression [121].

There is a lack of information on the influence of lowering IOP on retinal microcirculation. The experimental studies have reported that microcirculation in the retina, choriocapillaris, sclera, and lattice plate remains unchanged even with significant IOP fluctuations [91]. On the other hand, according to some clinical studies, OCTA vessel density strongly correlates with IOP [131–133].

In conclusion, OCTA may significantly improve the early detection of glaucoma progression, as formerly OCT has provided more precise diagnostics in regard to this detection.

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