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Vascular risk factors in normal-tension glaucoma and techniques for evaluating ocular blood flow

Naczyniowe czynniki ryzyka w jaskrze normalnego ciśnienia i metody pomiaru ocznego przepływu krwi

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S u m m a r y

The most common optic neuropathy is the glaucomatous neuropathy. It involves progressive loss of retinal ganglion cells including their axons and disc damage resulting in visual field loss. The disease, if not treated, can lead to irreversible vision loss. Apart from the age-related macular degeneration glaucoma is the main cause of blindness in civilized countries. Until recently the diagnosis and treatment of glaucoma mainly focused on the detection and reduction of the intraocular pressure, which is found the main risk factor for glaucoma. However, in spite of the normal intraocular pressure some glaucoma patients develop the neuropathy and experience progression of the disease. These patients mostly suffer from the normal-tension glaucoma. According to the current state of knowledge it is believed that one of the leading causes of the optic disk damage in glaucoma is the ischemia of the secondary to elevated intraocular pressure or a disturbance of ocular blood flow. It is considered that the intraocular pressure within statistically normal limits is relatively too high for disk resistance in eyes with normal-tension glaucoma. In these patients the failure of blood circulation in eye usually co-exists with systemic hemodynamic alternations. It is also possible that the disturbances of blood supply to the optic nerve head may cause increased susceptibility of the retinal nerve fibres to the intraocular pressure.

The review discusses the mechanisms that (may) affect the regulation of the ocular blood flow and the vascular risk factors that may compromise the systemic and ocular blood flow. The second part of the article summarizes some new visualization techniques for evaluating ocular blood flow.

Key words: normal-tension glaucoma, ocular blood flow, autoregulation, vascular dysregulation

S t r e s z c z e n i e

Neuropatia jaskrowa jest najczęstszą neuropatią nerwu wzrokowego. Charakteryzuje ją postępująca utrata komórek zwojowych siatkówki i ich aksonów oraz uszkodzenie struktury tarczy nerwu wzrokowego, co skutkuje wystąpieniem ubytków w polu widzenia. Nieleczona prowadzi do nieodwracalnej utraty widzenia. Choroba ta jest – obok zwyrodnienia plamki związanego z wiekiem – najczęstszą przyczyną ślepoty w krajach cywilizowanych. Do niedawna diagnostyka i leczenie jaskry koncentrowały się zasadniczo na wykrywaniu i obniżaniu podwyższonego ciśnienia wewnątrzgałkowego, które stanowi główny czynnik ryzyka rozwoju jaskry. Jednakże u części pacjentów pomimo prawidłowych wartości ciśnienia wewnątrzgałkowego dochodzi do rozwoju i dalszej progresji neuropatii jaskrowej. Do tej grupy należą pacjenci z jaskrą normalnego ciśnienia. Według obecnego stanu wiedzy uznaje się, że jedną z zasadniczych przyczyn uszkodzenia nerwu wzrokowego w jaskrze jest mechanizm niedokrwienia: wtórnego do podwyższonego ciśnienia śródgałkowego lub pierwotnego, spowodowanego zaburzeniami ocznego przepływu krwi. Uważa się, że w jaskrze normalnego ciśnienia ciśnienie śródgałkowe nawet w granicach statystycznej normy jest za wysokie w stosunku do indywidualnej oporności struktury tarczy nerwu II. W tej postaci jaskry upośledzenie krążenia krwi w gałce ocznej bardzo często współistnieje z zaburzeniami hemodynamiki krążenia systemowego. Możliwe, że zaburzenia ukrwienia tarczy nerwu wzrokowego powodują wzmożoną podatność jego włókien na działanie ciśnienia śródgałkowego.

W niniejszym artykule zostaną omówione mechanizmy regulacji ocznego przepływu krwi oraz naczyniowe czynniki ryzyka, które mogą upośledzać krążenie systemowe i w gałce ocznej. W drugiej części pracy zostaną przedstawione metody wizualizacji i pomiaru ocznego przepływu krwi.

Słowa kluczowe: jaskra normalnego ciśnienia, oczny przepływ krwi, autoregulacja naczyniowa, dysregulacja naczyniowa

INTRODUCTION

Normal tension glaucoma (NTG) is a chronic optic neuropathy distinguished by a progressive loss of retinal ganglion cells along with their axons, and an alteration of the optic disc including the cribrum. These processes result in a loss of the field of vision. The term "normal tension glaucoma" was first used by A. von Graefe in 1857. Due to numerous similarities between the normal tension glaucoma and the primary open-angle glaucoma (POAG), i.e. open filtration angle, glaucomatous damage to the optic disc and visual field defects, normal tension glaucoma was acknowledged by most researchers, as well as by the European Glaucoma Society, as a variation of the primary open-angle glaucoma. The essential difference between these two forms of glaucoma is the value of intraocular pressure. Measurements of the diurnal curve of intraocular pressure in patients with a diagnosed NTG do not exceed 21 mmHg. It is advisable to exclude other causes of optic atrophy in the diagnosis confirmation, although traits of glaucomatous damage to the optic nerve, with a formation of a characteristic cup in its disc, are considered pathognomonic for this disease (1-4).

PREVALENCE

There are discrepancies regarding the prevalence of NTG. Many researches show that this disease occurs much more often than medical practice would indicate. Numerous studies report that almost 25-50% of primary open-angle glaucoma patients had normal intraocular pressure values during the first examination. **In screening examinations of a group of glaucoma patients, 114 persons (58.8%) demonstrated an intraocular pressure value of less than 21 mmHg.** Other authors have estimated that 20-30% of open-angle glaucoma patients suffer from NTG. In Japan, NTG patients account for more than 50% of all glaucoma patients – this disease occurs more frequently in this population than among people of Caucasian origin. It also occurs twice as often in women than in men (5).

ETIOPATHOGENESIS

It has been proven, both clinically and experimentally, that elevated intraocular pressure causes damage to the optic disc. In 1858, Müller presented a so-called mechanical theory of glaucoma, which was then modified over time. It is based on an assumption that elevated pressure in the eyeball (or relatively high as in the case of NTG) deforms the cribrum, exerts pressure on the optic nerve and causes disturbances in the axoplasmic flow, which leads to ganglion cells' death. The second theory was proposed by von Jaeger, also in 1858 and is called the vascular theory. The premise of this theory is that the main cause of the development of glaucomatous neuropathy is generalized ischemia of the optic nerve (6, 7).

The fact that intraocular pressure in NTG persons remains within normal limits (statistically determined value of normal intraocular pressure) suggests that it can be harmful to the optic nerve. According to Yamamoto and Kitazawa, NTG can be defined as a glaucomatous neuropathy developing in eyes with normal intraocular pressure, for which eyes this pressure is relatively high and determines damage to the optic nerve (6). The Collaborative Normal Tension Glaucoma Study shows that a 30% reduction of intraocular pressure in patients with diagnosed NTG lowers the risk of progression from 35 to 12% (8). Cartwright, Anderson and Crichton indicate in their research that NTG patients with elevated intraocular pressure had larger visual field defects than patients of the same group but with lower values of the pressure in the eyeball (5).

It was postulated for many years that the main risk factor in the development and progression of glaucoma is high intraocular pressure. Numerous studies (Ocular Hypertension Study, Early Manifest Glaucoma Trial, Collaborative Initial Glaucoma Treatment Study and Advanced Glaucoma Intervention Study) document the principal role of intraocular pressure in the pathogenesis of glaucoma, however, whether it is the only damaging factor is still a matter of dispute (5, 9-12). In recent years, the role of vascular risk factors for glaucomatous neuropathy development has been highlighted, especially in the context of NTG. It seems that abnormalities in the ocular blood flow or in the vascular autoregulation can be a leading cause of glaucoma in many cases.

ANATOMY AND PHYSIOLOGY OF OCULAR BLOOD FLOW

The anatomy and physiology of the ocular circulation is quite complex. We can distinguish three basic ocular vascular systems: choroidal circulation, retinal circulation and optic disc circulation.

The choroidal circulation accounts for 85% of the total ocular flow (13). Posterior ciliary arteries, branches of the ophthalmic artery, are responsible for supplying the choroid. The choroid is extensively autonomically innervated. Its vessels are characterized by the presence of fenestration, which allows the hormones circulating in the blood, as well as mediators produced by the vascular endothelium, to penetrate the vascular wall. The choroid is distinguished by a high blood flow and low oxygen extraction. The choroidal flow plays an important role in the supply of nutrients for the external retinal layers and is responsible for maintaining constant temperature and volume of the eye.

Retinal vessels are supplied in blood by the central retinal artery which is a branch of the ophthalmic artery. The branches of the central retinal artery supply the inner retinal layers. Contrary to the choroid vessels, they are devoid from autonomic innervation and are not subject to influences of sympathetic and parasympathetic systems. Also, unlike the choroid vessels, tight junctions between retinal vascular endothelial cells create an inner "blood-retina" barrier. Likewise, unlike in the case of choroid circulation, the retinal circulation

is characterized by a low level of blood flow and high oxygen extraction.

The superficial layers of the optic disc are supplied with blood by small branches ramifying directly from the central retinal artery. The prelaminar region of the optic disc is supplied by the choroidal arterioles and by short posterior ciliary arteries. Because the choroid adheres directly to the prelaminar segment of the optic disc, this region can be affected by vasomotor mediators from the choroid. The optic disc is a special region on the border of retina and central nervous system, where there is no proper "blood-retina" barrier or, in other words, a "blood-brain" barrier.

REGULATION MECHANISMS OF THE OCULAR BLOOD FLOW

Different systems are engaged in the regulation of ocular blood flow, namely the autonomous nervous system, vascular endothelial cells and hormones circulating in the serum.

Choroidal flow takes place mainly under the control of signals coming from the autonomous nervous system and from hormones circulating in the serum. Neurogenic control of the ocular blood flow involves affecting vessels of the substances released from the autonomous system nerve endings, including norepinehrine, acetylcholine, substance P, cholecystokinin, vasoactive intestinal peptide (VIP), nitric oxide (NO), neuropeptide Y and ATP. Hormonal control involves the influence of hormones in the serum such as angiotensin, epinephrine, vasopressin and natriuretic peptide. They indirectly influence the endothelial cells and affect the vascular smooth muscles and pericytes directly.

Due to the "blood-retinal" barrier and a lack of autonomic innervation, the retinal circulation is based on autoregulation mechanisms, associated mainly with the function of vascular endothelium. Moreover, the retinal circulation is also regulated by nerve and glial cells. Autoregulation means an inner ability of a tissue to maintain a relatively stable blood flow despite alternating perfusion pressure, or a capability of changing the flow according to metabolic demand (5). The process of autoregulation depends on myogenic response, metabolic mechanisms and functions of the vascular endothelium. The myogenic mechanism is activated when the vascular blood flow increases. The result is a change in the calcium concentration of the vascular smooth muscle cells and a contraction of the vessel, leading to lowering of the blood flow. This mechanism protects against hyperperfusion. Metabolic mechanism consists in a change of vascular wall tension, which is a result of the influence of metabolites and ions (such as oxygen, carbon dioxide, potassium ions, adenosine), which are contained in the extracellular fluid. The vascular endothelium is primarily an active regulator maintaining adequate vascular tension. This happens in the mechanism of stimuli (physical, chemical and biological) reception and responding, in the form of production and release of vasoactive factors. The substances released by the vascular endothelium are: NO, endothelin-1 (ET-1) and prostacyclines including the so-called PGI2. The NO affects the smooth muscles and pericytes, leading to vascular relaxation. ET-1 causes an opposite effect, mainly affecting its ETa receptors. In a lower concentration, also in ocular circulation, the ET-1 can stimulate the production of NO and PGI, by connecting with ETb receptor, consequently leading to vasodilatation.

An exceptional vascular system in the eyeball is the one which is connected with the optic disc. Although the flow on the level of these vessels is regulated by endothelial cells, the direct adherence of choroid to the prelaminar segment of the optic disc causes the neurotransmitters, systemic hormones and endothelial mediators from the peripapillary choroid (e.g. endothelin-1 or angiotensin 2) to affect the sinews of the optic nerve in a place strategic for their damage in glaucoma, what may cause certain clinical implications (13). *In vivo* studies have shown a drop in perfusion of the optic nerve as a result of angiotensin 2. The effect of these mediators on the vessels in the optic disc region remains to be explained (5, 14, 15). Their angiospastic influence is considered to lead to autoregulation disorders and a heightened susceptibility of the optic nerve's sinews to the damaging activity of intraocular pressure.

DISTURBANCES OF OCULAR BLOOD FLOW AND THE DEVELOPMENT OF GLAUCOMATOUS NEUROPATHY

Studies, in which it has been observed that the field of vision in some of the glaucoma patients has improved after the application of calcium channel blockers, have indicated the role of vascular factors in glaucomatous neuropathy development. Numerous studies confirm that the ocular blood flow in glaucoma patients is impaired (5, 16, 17). It concerns the flows in the choroid, retina and optic disc. According to Gasser and Flammer, the reduction of ocular blood flow can be of primary character, especially in normal tension glaucoma. This is confirmed by the fact that the blood flow in NTG patients is decreased not only in the eye but also peripherally in the whole body. There are studies that confirm the existence of lowered ocular blood flow in a number of people, long before they develop glaucomatous neuropathy (3, 5).

The blood flow depends on the perfusion pressure, which is a difference between the arterial and venous pressure (in the eye, the latter levels out with the intraocular pressure), and on vascular resistance. The ocular blood flow can be disturbed in two situations: in case of intraocular or arterial pressure fluctuations exceeding the possibility of compensation through autoregulation, and in case of disorders of vascular wall tension. If the increase of intraocular pressure is too high or the systemic pressure drop is too severe, the efficiency of autoregulation (which depends on

maximum possible dilation of the arterial vessel, so-called depletion of "autoregulation reserve") may be exhausted and the blood flow may drop. The impairment of the autoregulation ability, which can lead to tissue ischemia, is connected with an increased rigidity (functional or anatomic) of the arterial wall. As a consequence, the vessel cannot relax properly – adequately to the oxygen requirement.

In recent years, the theory of glaucomatous neuropathy development resulting from lowered ocular blood flow has been changed. It has been observed that in persons with carotid artery closure the NTG occurs with similar frequency as in a control group of healthy people. In many patients with multiple sclerosis and reduced ocular blood flow resulting from a high level of ET-1 in the serum the glaucomatous neuropathy does not develop. In older NTG patients with a history of circulatory system diseases, especially atherosclerosis, with stably reduced blood flow in the optic nerve, a typical glaucomatous excavation of the optic nerve also does not develop, but an atrophic image of the optic disc does. The above mentioned examples led to creation of a new hypothesis in the vascular theory in glaucomatous neuropathy development. It seems that the development of glaucoma is connected with instability of ocular blood flow rather than with permanent ischemia of the optic nerve (2). Numerous studies seem to confirm this hypothesis: Baltimore Eye Survey, Barbados Eye Study, Barbados Incidence Study of Eye Diseases and Enga-Neumarkt Study (5, 18, 19).

VASCULAR RISK FACTORS FOR GLAUCOMA

Changes in the systemic pressure, especially episodes of arterial hypotonia, are the most important systemic cause of the destabilization of ocular blood flow. As early as 1963, Sachsenweger noticed a correlation between the low arterial pressure, intensifying visual field defects and progression of the optic disc excavation, basing on studies performed on 240 POAG patients (3). In another study, it was observed that in NTG patients, a change of body position from horizontal to vertical and vice versa causes severe fluctuations of arterial pressure, compared with the control group. It was then acknowledged that the hypotension connected with the body position change plays an important role in the NTG development. Numerous studies confirm the fact that nocturnal arterial blood pressure drops stimulate the progress of glaucomatous neuropathy, including the development of NTG. Nonphysiological deep nocturnal hypotension can induce a lowering of perfusion pressure and ischemia of the optic nerve head. This state can cause the progression of glaucomatous excavation and progressive changes in the field of vision in NTG patients. Studies carried out by Tokunaga and Kashiwagi confirm this thesis (5, 20). Some authors presume that arterial hypertension might be a risk factor for the development of NTG (3, 5). While examining a group of 276 persons, Kashiwagi et al. have shown that the arterial blood pressure in NTG patients was significantly higher than in the control group (21). On the basis of the work by Wong et al., it can be assumed that chronic arterial hypertension can lead to glaucomatous neuropathy, as a result of atherosclerotic lesions and impairment of vessel autoregulation. However, Graham et al. indicate that it is the hypotensive treatment, leading to profound drops in arterial blood pressure that is responsible for the development of glaucoma in arterial hypertension patients (5). Considering the above mentioned studies it can be stated that the development of glaucoma is connected with unstable blood flow in the eyeball which is a derivative of episodes of hypotonia or abnormal fluctuations of arterial blood pressure. A hypothesis by Tielsch et al. seems very interesting. According to them, the arterial hypertension in its initial phase can act protectively on retinal ganglion cells by increasing the blood flow. Only as the disease progresses the minute vessels are damaged and the blood flow resistance increases, what results in ischemia and damage of the optic nerve (3).

One of the vascular causes of ocular blood flow destabilization is a disorder named by Meier 1978 "the primary vasospastic syndrome". However, as Flammer later noticed, this syndrome can be associated with both inadequate spasm and insufficient relaxation of vessels. For this reason, a substitute term was created in 1999: vascular dysregulation (13). Two vascular dysregulation syndromes are distinguished: primary and secondary. The primary vascular dysregulation (PVD) is a congenital predisposition to abnormal vasospastic response to different stimuli, including cold, emotions and trauma. Secondary vascular dysregulation (SVD) is formed as a result of other, mainly autoimmune, diseases, characterized by elevated concentration of ET-1 in the serum e.g. multiple sclerosis (MS) or rheumatoid arthritis (RA). In SVD, a reduction in the ocular blood flow is observed but the vascular autoregulation remains unimpaired, consequently lowering the risk of developing glaucomatous neuropathy. By contrast, the PVD disrupts autoregulation, causing fluctuations in ocular flow in case of perfusion pressure variations. This way, the PVD remains closely related to the development of glaucoma, especially NTG. PVD symptoms occur more often in women. These signs can appear as early as childhood, although generally they intensify during puberty and yield after menopause. **Certainly, an important role in this syndrome is played by hormones, especially oestrogens.** This points to the fact that PVD mainly affects women, and that the substitutive hormonal therapy can provoke occurrence of symptoms. Considering PVD as one of the main risk factors of the development of glaucomatous neuropathy, it seems logical that PVD and NTG risk factors (including vascular risk factors) are very similar (2, 15). Both PVD and NTG are more often diagnosed in Japanese and Korean people (22, 23). Other risk factors include migraine, low arterial blood pressure, peripheral vasospastic symptoms (cold limbs – mainly hands and feet) and haemorrhages on the border of the optic disc (24, 25).

Phelps and Corbett where the first to put forward a hypothesis, on the basis of special, standardised surveys, that headaches, especially those of migrainous nature, occur much more often in NTG patients (32%) than in POAG (23%) and healthy persons (5). A similar questionnaire was presented to patients from Japan, with analogous relations observed. The incidence of migraine in NTG patients was 17 and 11% in POAG patients (3). Researchers from The Collaborative Normal Tension Glaucoma Study group drew a conclusion from analyses performed that the incidence of migraine, a vasospastic disease, may significantly support the progression of changes in the field of view in NTG patients (26).

The occurrence of haemorrhages on the optic disc is characteristic especially for NTG. In their study, Healey et al. observed that haemorrhages on the optic disc were present in 25% of NTG patients and only in 8% of POAG patients. According to Drance et al., haemorrhages are a symptom of ischemia of the optic nerve in glaucoma patients. Numerous studies show that in patients with NTG and haemorrhages on the optic disc the probability of glaucoma progression increases considerably (5). The Normal Tension Glaucoma Study Group suggests even that it is the main risk factor for the deterioration of parameters in glaucoma (26).

From the theoretical point of view, blood viscosity disorders, apart from the lowered perfusion pressure and the increased vascular resistance, should also lead to the reduction of ocular blood flow. Consequently, Klaver et al. proved that the blood viscosity in NTG patients is significantly higher than in POAG patients with high intraocular pressure and in group of healthy persons (5). Some studies suggest the existence of an increased aggregation of erythrocytes and impairment of their deformability in glaucoma, including NTG (3, 5). Researches performed in the Netherlands, Croatia and Japan on a small group of glaucoma patients also show an increased aggregation of platelets in this group. Hemorheology changed in such way can lead to impairment of circulation, ischemia of ocular tissues and to damaging of the optic nerve (3, 27, 28).

Recently, the correlation between NTG and immunological disorders is being researched into. Considering the vascular aspect of the development of glaucoma, deliberations about antiphospholipid antigens (from which anticardiolipin, antiphosphatidylserine and anti-beta2-glycoprotein antibodies can be distinguished) seem noteworthy. Numerous reports show that clinically these antibodies play an important role in thrombus episodes, pulmonary hypertension, thrombocytopenia, migraine and in occlusion of retinal vessels, which can cause ocular blood flow disturbances (3). Kremmer's prospective study, in which the concentration of antiphosphatidylserine antibodies in glaucoma patients and healthy volunteers was determined, showed that an elevated titre of these antibodies occurred much more often in NTG patients (29). Similarly, the Canadian Glaucoma Study and the project of Chauhan et al. showed that high levels of anticardiolipin antibodies occur more often in the serum of glaucoma patients and that these persons have a higher risk of the progression of glaucomatous neuropathy. However, a study by Tsakiris et al. did not confirm such dependence; therefore additional studies into this matter seem to be required (5).

Diabetes has been a controversial vascular risk factor for glaucoma for many years. Many studies, including Beaver Dam Eye Study, Wisconsin Epidemiologic Study of Diabetic Retinopathy, Blue Mountains Eye Study, have shown that glaucoma occurs much more often in diabetes patients and that the duration of diabetes is associated with the progression of glaucomatous changes (3, 5). On the other hand, such dependency was not found in the Framingham Study, Barbados Eye Study, Diabetes Audit and Research In Tayside Study (3, 5, 30). Moreover, some researchers claim that carbonate disorders can act neuroprotectively. Vascular endothelial risk factor (VEGF), secreted as a reaction to retinal hypoxia in diabetes, is thought to have a protective influence on the retinal ganglion cells. Furthermore, vascular regulation disorders, flow impairment and hypoxia in diabetes can immunize the retinal against the development of glaucoma (31, 32).

One of the most recent, currently discussed vascular risk factor for the development of glaucoma is the obstructive sleep apnoea syndrome (OSA) which is characterized by a recurring impairment of the respiratory tract patency during sleep. A hypothesis has been formed on the basis of numerous studies that glaucomatous damage in this syndrome can be caused by endothelium dysfunction and vessel autoregulation disorders (2). A so-called "steal phenomenon" can also occur. The OSA causes an increase of carbon dioxide in the serum and stimulates the dilation of cerebral vessels. The blood from optic disc circulation outflows (is being "stolen") to the dilated cerebral vessels what, in connection with vascular dysregulation which occurs in these patients, can lead to glaucomatous neuropathy (33). Additionally, a high level of ET-1 detected in the serum of OSA persons can affect the disorders of vascular blood flow (34).

REPERFUSION INJURY AND OXIDATIVE STRESS

According to the most recent hypotheses, the phenomenon of reperfusion injury and the related oxidative stress play a key role in the development and progression of glaucomatous changes. This phenomenon refers to a situation in which the blood returns to tissues after a prior period of their ischemia, as a result of autoregulation disorders and consequent unstable ocular blood flow. Both the unstable ocular blood flow and high concentration of ET-1 lead to an activation of endothelial nitric oxide synthase (NOS-1) and to an activation of astrocytes in the optic nerve, what is associated with a stimulation of the nitric oxide-2 synthase (NOS-2) present in them. This leads to a release of significant amounts of NO which penetrates

to surrounding tissues, including the optic nerve axons, extremely easily. The reperfusion is a period when the oxidative stress forms, associated with the production of reactive oxygen species like superoxide anion radical and with an activation of metalloproteinases, mainly MMP-9. A combination of a superoxide anion radical and nitric oxide (in a form of a radical) results in a creation of cytotoxic peroxynitrite (2, 13, 35). The latter, along with reactive oxygen species, can move in the optic nerve axons towards the retina, leading to apoptosis of ganglion cells or towards the lateral geniculate body, inducing the death of nerve cells in the central nervous system. Apart from the apoptosis of nerve cells, the MMP-9 causes a structural remodelling of the optic disc head (36). This way, the instability of the ocular blood flow determines the development of glaucomatous neuropathy through ischemia and reperfusion (2, 13).

VISUALIZATION TECHNIQUES FOR EVALUATING OCULAR BLOOD FLOW

The techniques for evaluating ocular blood flow are essential due to the role of disturbances of the blood flow in the pathogenesis of glaucomatous neuropathy Although in the past several decades a tremendous breakthrough have been made in this field, it is difficult to find a single method which would provide all the information in one readout (5, 13). In the following section several devices will be discussed, along with their use in the assessment of ocular blood flow in glaucoma.

A Colour Doppler ultrasound scanner has replaced the previously used Transcranial Doppler. The Colour Doppler Imaging (CDI) is an examination which uses ultrasounds to evaluate the parameters of blood flow in retrobulbar vessels e.g. in the ophthalmic artery, central retinal artery or short posterior ciliary arteries. Apart from the imaging of vessel structure in 2D, the peak systolic velocity (PSV) and the end-diastolic velocity (EDV) are also measured based on the Doppler effect (first described by Austrian physicist Christian Doppler in 1842) (5, 13). The above-mentioned data allow for a calculation of the mean flow velocity (MFV), pulsatility index and Pourcelot index, also known as the resistive index (RI). The CDI examination seems to be more preferable due to its noninvasiveness, satisfactory repeatability, possibility of use regardless of the width of pupils or optical media clarity (5). Many studies show that in glaucoma, the parameters of blood flow in retrobulbar vessels (PSV and EDV) are noticeably lowered, while the resistive index is significantly elevated. This especially concerns retrobulbar vessels supplying the optic nerve and short posterior ciliary arteries (37, 38). Moreover, it seems that the greater the glaucomatous damage, the more reduced the ocular flows are (5). Some claim that the decrease of blood flow in retrobulbar vessels precedes the progression of neuropathy and that on the basis of RI in the ophthalmic artery and in short posterior ciliary arteries the disease's progress can be predicted with great probability (39). The limitations of CDI are: inability to measure the diameter of vessels and consequently no possibility of quantitative evaluation of the blood flow in retrobulbar vessels. This examination only allows for a measurement of the blood flow velocity in these vessels.

Laser Doppler flowmeter is yet another device which utilises the Doppler effect. The Heidelberg Retinal Flowmeter (HRF) is the system currently available on the market. It is based on laser Doppler flowmetry and laser scanning tomography and allows obtaining information about the blood flow in the optic nerve and about retinal capillaries. This noninvasive technique allows an earlier detection of changes in the blood flow, mainly in the superficial parts of the optic nerve head, omitting the choroidal component. Despite its numerous advantages, this device requires clear optical media, good fixation and is extremely sensitive to eye movements (5). Similarly to the CDI, the blood flow in the optic disc area and in the retina measured with HRF is lowered in glaucoma patients, however, not all studies confirm this (5, 40). Chung et al. noticed that the greatest drop of the blood flow took place in the peripapillary region (41). Lam et al. found that the flow velocity was significantly lower in these sectors of the disc which corresponded with the regions of the field of view with larger defects (42). Sato et al., with the help of Doppler flowmetry, proved a correlation between the circadian perfusion pressure fluctuations and deteriorating parameters in the field of view in NTG patients (43).

Many parameters of retinal and choroidal circulation can be determined with the use of scanning laser ophthalmoscope angiography (SLOA) of the fundus of the eye. By means of fluorescein angiography a detailed visualisation of retinal flow and blood circulation image in the area of the optic nerve head can be obtained. Indocyanine angiography allows the imaging of choroidal circulation because the luminescence of indocyanine penetrates the barrier of retinal pigment epithelium much more easily. However, it facilitates collection of data regarding vascular groups of the choroid only, and not the individual vessels, what is related with the structure of choroid vessels texture. The usage of angiography in the diagnostics of glaucoma may be hindered by its invasiveness, probability of allergic reactions and the need to install appropriate software which allows to measure the velocity of blood flowing through large retinal vessels and their branches, and not only, as in standard devices, qualitative evaluation of retinal or choroidal circulation (5). Many researchers have proven, with the use of angiography, the reduction of blood flow in the retina, choroid and optic disc head in glaucoma (5, 44). Furthermore, Nasemann et al. and Duijm et al. noted that in glaucoma patients, especially NTG patients, the retinal and the choroidal vascular bed fills with blood with a delay and its emptying of blood is significantly elongated (45, 46). According to the studies by Geijssen et al. it seems that

the impairment of choroidal flow is the most prominent in NTG patients while lowering of retinal flow characterizes POAG patients (5). Nanba, Schwarz et al., Plange et al. and other researchers have shown that in the optic disc region a local impairment of filling capillaries with blood and an increased shunt takes place (5, 47).

The retinal vessel analyser enables, on the basis of numerous algorithms, an estimation of the retinal vessel's diameter and even an analysis of many segments of a single vessel or several vessels simultaneously. The examination can be performed only in case of good fixation, clear media, with minimal eye movements and after pupil dilation (the latter can affect the ocular blood flow) (5). Sugiyama et al. detected an arterial vessels stenosis and phlebectasia in glaucoma patients, with the use of this technique (44). Rader et al. described a local artery stenosis on the border of the optic nerve head (5). However, there are too few studies that compare the size of retinal vessels between glaucoma patients and healthy volunteers.

Blue field entoptic stimulation is used to evaluate blood flows in macular capillaries. This technique utilises the patient's observation of leucocytes flowing through the retinal vessels. During the examination, the patient has to look at a blue light and, referring to the previously seen pattern of particle flow, determines the number and velocity of leucocytes seen before the examined eye. Data concerning the flow through retinal vessels can be obtained after the analysis. This measurement method has drawbacks, namely a frequent lack of patient's cooperation and that other retinal diseases may hinder the precision of this technique. According to Sponsel et al., the velocity of leucocytes can correlate with the vision function. It seems that in glaucomatous neuropathy this parameter is lowered. Riva et al. have found use for this technique in the evaluation of autoregulation mechanisms (5).

Laser interferometric measurement of fundus pulsation (FPA) is an examination which utilises the phenomenon of interference of two light waves, in this case a laser light reflected by the fundus and the cornea. This method allows the evaluation of fundus pulsation amplitude, which is a difference of the distance between the cornea and the retina depending on the cardiac cycle. It is believed that myocardial contraction causes filling of the choroid vascular bed, what makes the fundus move forward. In diastole, the outflow of blood from the choroid vessels causes the fundus to retract. The examination has a high repeatability and low invasiveness (5). Using this technique in glaucoma patients, Schmetterer et al. proved that due to a decrease in the elasticity of ocular vessels in glaucoma, the FPA values in these patients are reduced (48). Studies by Kerra et al., Findla et al. and also Fuchsjäger-Mayrl et al. confirm this (49-51). Arend et al. observed that in NTG patients a decrease in optic disc vessels blood flow accompanied a progression of changes in the field of view (52).

Calculating the optic pulse amplitude (*OPA*) during constant measuring of intraocular pressure with dynamic contour tonometry (DCT) method provides an image of choroidal flow which changes along with the cardiac cycle. The OPA is a difference between the extreme values of intraocular pressure registered by dynamic contour tonometer, dependent on myocardial contraction, diastole and the level of blood filling of choroid. Schenn et al. and Schmidt et al. noted a decrease of OPA in NTG patients in their tests (53). On the basis of research by Vulsteke et al. it seems that the decrease of OPA can affect the development of changes in the field of view (54).

Pulsatile ocular blood flow analyser (POBF) is used, similarly to the interferometric device, for evaluating the pulsatile component of ocular blood flow. This method is based on the change of the eye ball's volume and intraocular pressure which take place during cardiac phase. The device which is necessary for the measurements is a pneumotonometer. Despite its relatively simple construction, it is important that the device measures intraocular pressure and then, secondarily to this measurement, the pulsatile ocular blood flow. Numerous studies show that the pulsatile ocular blood flow in NTG patients is reduced when measured with this technique (49, 55-57). Although a visible lowering of POBF is definitely more frequent in patients with large glaucomatous defects in the field of view, Fontana et al. discovered that POBF disturbances can significantly precede, and harbinger at the same time, an impairment of visual functions (56).

Laser light and phenomenon of interference is also used in the so-called laser speckle method. In this examination, the vascular blood flow is evaluated by measuring the velocity of erythrocytes in retinal vessels. This method does not provide information regarding vessel diameter. There are few detailed *in vivo* studies in literature that utilise this method to measure the retinal flow and the optic disc region in glaucoma patients. For the time being, this technique remains in the realm of research (58).

In modern diagnostics of ocular blood flow, Doppler optical coherence tomography is also utilised. This technique combines high resolution cross-section images of retina and precise data regarding vascular blood flow in real time. The examination enables a detailed analysis of the haemodynamics of retinal circulation, i.e. allows to determine the peak and mean velocity of the flow and to evaluate the volumetric flow indicator (59). Moreover, vessel diameter can be determined with great precision. The method has its limitations related to the lack of data from clinical trials. The measurements made thus far concern mainly large retinal vessels and as of now, this method is of no use in the evaluation of blood flow in small capillaries (5). As of now, there are few clinical trials utilising this technique to determine the variability of ocular blood flow in glaucoma persons.

An entirely new method of ocular blood flow evaluation has been described in recent years. It is the retinal oximetry which allows measuring the saturation in the retinal blood vessels in a non invasive way. Maybe in the future, thanks to the analysis of metabolic changes on specific regions of the retina, it will be possible to identify the local impairments of blood flow which occurs in the eyes with glaucomatous neuropathy (60).

It is worth mentioning once again that currently it is quite difficult to point to a single examination method which would allow for an evaluation of all parameters in imaging and measuring of the ocular blood flow. Moreover, the vast number of measurement techniques and of parameters calculated limits the possibility of comparing different studies and creates a need for standardised data. A recent report by the International Glaucoma Association indicates to a need for improvement of the new techniques of ocular blood flow examining. Many have high hopes for methods based on metabolic changes in the eye structures and evaluation of such parameters like saturation, glucose uptake or carbon dioxide concentration (5).

CONCLUSIONS

Elevated intraocular pressure is a sufficient factor leading to the development of glaucomatous neuropathy in cases of congenital glaucoma, closed angle glaucoma or secondary glaucoma. However, in the pathogenesis of normal tension glaucoma the mechanical theory is not a satisfying explanation. Numerous studies evaluating blood circulation in ocular tissues lead to a discovery of correlation between the reduction of ocular blood flow and the development of glaucomatous neuropathy. What turned out was that local impairments of blood flow accompany systemic changes in the circulation and the reduction of ocular blood flow often precedes the development of glaucoma. Many studies highlight the significance of vascular dysregulation connected with perfusion pressure fluctuations and impaired autoregulation of circulation. Consequently, an unstable ocular blood flow can be observed, as well as optic nerve damage resulting from ischemia, reperfusion and oxidative stress.

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