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# HIGHLIGHTS OF HYPERTENSIVE AND NORMOTENSIVE GLAUCOMA

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## SUMMARY

The paper presents the up-to-date overview of pathogenesis, functional and structural changes in normotensive glaucoma (NTG) and its differences from hypertensive glaucoma (HTG).
The autors point out new facts that distinguish both diagnostic groups. In the first place are the results of OCT angiography, which verify the pathology of NTG to the anterior part of optic nerve.
Our findings confirmed that vascular component (VD) is more involved in changes of visual field than in perfusion parameters, especially in arteria ophtalmica (AO). Perfusion in arteria centralis retinae (ACR) does not play a significant role in NTG changes in the visual field.
VD has very little effect on changes in visual field in HTG. Similarly, the retinal nerve fiber layer (RNFL) for changes in the visual field. However, VD is moderately influenced by changes in RNFL. It should be emphasized that we compared the sum of sensitivity in the central part of the visual field (0-22 degrees) with RNFL and VD. In NTG, the anterior part of the optic nerve is altered. Mainly VD contributes to visual field changes in NTG. It is also important to note that when the intraocular pressure (IOP) increased above 20 mm Hg, the macular and papillary VD was significantly reduced.
Antiglaucomatous treatment with prostaglandins and beta-blockers is essential for the reduction of IOP in HTG. This reduction shoud be bellow 20 mm Hg, in eyes with thinner cornea the decrease in IOP should be more pronounced. It does not matter which antiglaucoma treatment was used. However, it should be noted that prostaglandins have a greater effect on disease progression, but the greater protective effect on the visual field have beta-blockers. Neuroprotectives should be recommended systemically in patients with HTG.
When treating NTG, it is important to maintain blood flow of the posterior pole of the eye, but mainly of the anterior part of the optic nerve. Prostaglandins are not suitable in NTG patients, although their effect on IOL reduction is high. Beta-blockers (betaxolol and carteol) and brimonidine are most suitable. Corneal thickness has no effect on disease progression.
**Key words:** glaucomas, OCT angiography, antiglaucomatous treatment with prostaglandins and beta-blockers

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## INTRODUCTION

In the conclusion of the recent study by Zarei et al., who analysed 1162 reports (from 2011 to 2017) on the theme of normotensive glaucoma (NTG), the authors in first place recommend antiglaucomatous treatment of this disease. If this treatment is not sufficient, then a surgical reduction of intraocular pressure (IOP) is required. They also recommend neuroprotective agents, which should offer patients with NTG new hope of preventing the progression of the disease [1].

Symes and Mikelberg in their study present the results of an analysis of 419 addressed ophthalmologists who apply prostaglandins as the drug of first choice for NTG in 88 % of cases, and brimonidine in 10 % [2].

With regard to the fact that the results of our study do not correspond with the recommendations of the authors of the above-cited studies, we would like to take this opportunity to present the interesting results of our most recent investigations dealing with the issue of HTG and NTG. In this we follow on from a summary overview which was published in our journal last year, in which we stated that due to the influence of high IOP, damage to the retinal ganglion cells and subsequently to the entire visual pathway occurs in HTG. By contrast, in NTG the nerve fibres are altered, in which the main causes is most probably ischemia of the anterior part of the visual pathway [3].

Following on from this study, we now present a number of new observations in the study of both pathologies. In all the publications listed below, the inclusion criteria

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for the study were as follows: visual acuity 1.0 with applicable correction of less than ± 3 dioptres, approximately the same changes in the visual fields in all patients, in which this concerned an incipient pathology, with no other ocular or neurological pathology. Glaucoma was confirmed in all patients by means of a comprehensive ocular examination, including electrophysiological.

**1. OCT angiography and Doppler sonography in normotensive glaucoma**

Ischemic change of retrobulbar haemodynamics is one of the important manifestations in NTG. Haemodynamic parameters measured with the aid of Doppler sonography may be potential diagnostic tools for NTG [4,5].

As a result, the aim of our next study was to verify the existence of a correlation between vessel density and flow values in the arteria ophthalmica and arteria centralis retinae of the same eye in patients diagnosed with normotensive glaucoma (NTG).

The cohort comprised 20 patients with NTG, of whom 17 were women (mean age 56.1 years) and 3 men (mean age 60 years). We determined the parameter of vessel density (VD) with the aid of Avanti RTVue XR (Optovue), perfusion parameters by Doppler sonography (Affinity 70G Philips, probe 5-12 MHz). We measured peak systolic velocity (PSV), end systolic volume (EDV) and the resistance index (RI) in the arteria ophthalmica (AO) and arteria centralis retinae (ACR). The visual field was evaluated according to a glaucoma test with a fast threshold strategy (Medmont M700). The sum of sensitivities in apostilbs (asb) was evaluated within the scope of 0-22 degrees of the visual field. The results of sensitivities in the visual field were compared with VD and the measured flow parameters. The correlation coefficient between the visual field and VD of all blood vessels peripapillary, VD of small vessels peripapillary and VD of all vessels of the entire recorded image demonstrated a medium correlation (r = 0.54, r = 0.55, and r = 0.52 respectively). The relationship between the visual field and the perfusion parameters showed a weak correlation. For the relationship between VD and flow parameters of the ACR and AO, a medium indirect correlation of PSV in AO was determined with peripapillary VD of all vessels (r = -0.49), small vessels (r = -0.46) and VD of the entire measured area (r = -0.45). A similar correlation was recorded in the case of EDV in AO with peripapillary VD of all vessels (r = -0.41), small vessels (r = -0.41) and the entire measured area (r = -042). The other correlations between VD and flow parameters were insignificant.

Our findings confirm that a larger role is played in changes in the visual field mainly by the vascular component of VD rather than perfusion parameters, especially in the AO. Perfusion in the ACR does not play a significant role in changes in the visual field in NTG [6].

**2. OCT angiography in HTG and NTG**

For a further examination of HTG and NTG, a key factor was the introduction of optical coherence angiography (OCTA) into clinical practice. We concentrated on a comparison of both pathologies by means of an examination of VD in the peripapillary region.

The cohort comprised 20 patients with HTG, of whom 13 were women (average age 64.7 years) and 7 men (average age 60.8 years). The thickness of the retinal nerve fibre layer (RNFL) and VD were measured with the aid of Avanti RTVue XR from the Optovue company. The visual field was examined by a fast threshold glaucoma program using the instrument Medmont M 700 (Medmont International Pty Ltd., Australia). The sum of sensitivities in apostilbs (asb) was evaluated within the range of 0-22 degrees, in both the upper and lower halves of the visual field. The results of sensitivities in the visual field were then compared with RNFL and VD of the opposite altitudinal half of the same eye. A Pearson correlation coefficient (p = 0.001) was used for assessment of the dependency between selected parameters. By comparing the RNFL and VD in the upper halves (r = 0.5) and lower halves (r = 0.51) we demonstrated a medium strength correlation. By comparing VD from the upper half with the sum of sensitivities in the visual field (r = 0.2) of the other eye, we demonstrated a weak correlation. No correlation was demonstrated between VD from the lower half and the sum of sensitivities in the upper half of the visual fields (r = 0.04). No dependency was demonstrated between the RNFL of the upper half and the visual field of the lower half (-0.04), and the RNFL of the lower half and the visual field of the upper half (-0.12).

We concluded the study with the finding that VD has very little influence on changes in the visual fields in HTG. The same applies to the RNFL on changes in the visual field. However, VD has a medium strength influence on changes in the RNFL. Here it is necessary to emphasise that we compared the sum of sensitivities in the central part of the visual field (0-22 degrees) with the RNFL and VD [7].

We proceeded in a similar manner also in the case of patients with NTG. The cohort comprised 20 patients with NTG, of whom 17 were women (mean age 56.1 years) and 3 men (mean age 60 years). By comparing the RNFL and VD in the upper halves (r = 0.62) and lower halves of the papilla (r = 0.6) we demonstrated a strong correlation. We recorded a similarly strong correlation also by a comparison of VD from the upper half of the papilla and the sum of sensitivities in the visual field (r = 0.7) from the lower half. VD from the lower half and the sum of sensitivities in the upper half of the visual fields demonstrated a medium dependency (r = 0.52). We recorded a weak dependency between the RNFL of the upper half and the sum of sensitivities of the lower half of the visual field (r = 0.37) and the RNFL of the lower half and the sum of sensitivities of the upper half of the visual field (r = 0.32).

In NTG an alteration of the anterior part of the optic nerve takes place. VD makes a greater contribution to changes in the visual fields in NTG [7].

However, it is important to state that when intraocular pressure (IOP) increased above 20 mmHg, macular and papillary VD was significantly reduced [8].

We believe that in NTG a very important role is played by the loss of capillaries, mainly in the region of the optic nerve papilla and its anterior part. Changes of the flow parameters determined by Doppler ultrasonography are its

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consequence. So far we are unable to answer the question concerning the process by which this loss of capillaries occurs. An explanation may be provided by the study conducted by Cheng et al., who determined also higher blood viscosity in patients with NTG, which may be linked with impaired deformability of erythrocytes in connection with a change of their rigidity. Higher viscoelasticity and blood viscosity in patients with NTG upon low flow speed was caused by increased aggregability of erythrocytes. The impaired deformability of erythrocytes in NTG patients is also susceptible to the development of abnormalities of distal microcirculation. Increased blood viscosity and low effectiveness of blood oxygen transport may lead to hypoperfusion of the optic nerve in patients with NTG [9]. However, a genetic factor may also play a role here.

**3. Ischemic changes in the brain**

On the basis of our findings presented above in examination by OCT angiography in HTG and NTG, we were interested in whether a dysfunction of perfusion in the region of the optic nerve papilla in NTG was specific only for this region, or whether it was global for the entire brain, and also whether these findings differed from HTG. We returned once again to our summary study from 2019, or to the part which examined whether ischemic changes could occur in patients with NTG, which could be deeper than in patients with HTG [10].

However, we did not demonstrate our original idea concerning potential vascular damage to the brain in patients with NTG. We can only speculate as to whether damage to the blood vessels of the anterior part of the optic nerve in NTG is purely selective.

**4. Influence of prostaglandins and beta-blockers on the progression of HTG and NTG**

If we are dealing with the issue of the influence of treatment on the progression of HTG and NTG, it is necessary to note the different nature of changes in the visual fields in both of the evaluated groups. In our previous study, we compared changes in the visual fields with the aid of two basic indexes, which pertain to the technology Medmont, namely pattern defect (PD) and overall defect (OD). The HTG group numbered 25 patients (mean age 62.5 years). The NTG group contained the same number of patients (mean age 62.8 years). In all patients an examination was conducted on the instrument Medmont M700 using a fast threshold glaucoma program.

A statistical analysis with the aid of a paired t-test demonstrated that PD was statistically higher than OD in patients with NTG ($p = 0.0001$).

In patients with HTG, the same evaluation demonstrated statistically higher values of OD in comparison with PD ($p = 0.000$).

For the diagnosis and progression of changes in the visual fields, OD is more specific for HTG, and PD for NTG [11].

The aim of the next study was to evaluate the progression of changes in the visual fields in patients with HTG and NTG over time, following the application of prostaglandins and beta-blockers, and then in NTG also without antiglaucomatous therapy.

In the HTG group we observed 12 patients (mean age 66 years) with mean central corneal thickness (CCT) of 568 µm, who were treated with prostaglandins, and 12 patients (mean age 60 years, mean CCT 544 µm), who were treated with beta-blockers. Throughout the entire observation period, IOP was within the range of 12-18 mmHg.

The NTG group was further divided into three subgroups. The first subgroup was composed of 10 patients (mean age 57 years) who were treated with beta-blockers. The second subgroup comprised 14 patients (mean age 58 years) treated with prostaglandins. The third subgroup comprised 18 patients (mean age 57 years) who were without treatment. Throughout the entire observation period, IOP was within the range of 8-12 mmHg.

In all the patients we observed PD and OD over a period of five years. The treatment was not adjusted during the course of this period.

In HTG, over the course of time we did not record any statistically significant difference in PD ($p = 0.35$) or OD ($p = 0.09$) upon treatment with prostaglandins, or upon treatment with beta-blockers ($p = 0.37$ and 0.23 respectively). However, in the group treated with prostaglandin OD approached a statistically significant change.

In NTG the largest changes were in PD ($p = 0.0001$) in the untreated patients. OD did not manifest any statistically significant changes ($p = 0.25$). Similarly, the patients treated with prostaglandins had a statistically significant difference in PD ($p = 0.04$), while OD did not demonstrate any statistically significant changes ($p = 0.4$). We did not record statistically significant differences in progression in NTG treated by beta-blockers, either in PD ($p = 0.7$) or OD ($p = 0.4$).

Antiglaucomatous treatment with prostaglandins and beta-blockers is of fundamental significance in HTG. However, beta-blockers have a greater protective effect on the visual field. The same cannot be said of NTG, in which we demonstrated this effect only after the application of beta-blockers [12].

Because in HTG an alteration of the entire visual pathway takes place, from the photoreceptors to the ganglion cells of the visual cortex of the brain, it is appropriate to recommend systemic neuroprotective agents [13].

**5. Influence of CCT on progression of patients with HTG and NTG**

Why did we state the values of CCT in the previous study on patients with HTG and NTG?

In the case of HTG, in 132 eyes we observed the dependency between CCT and the progression of changes in the visual fields over a period of 5 years. We determined a weak correlation between changes in the visual field and CCT. Eyes with a thinner cornea had a greater progression than eyes with a thicker cornea. Patients who had larger changes in the visual fields at the time of inclusion in the study had greater progression within the observation period [14].

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The situation is different in the case of eyes with NTG. In a group of 50 eyes observed over the course of five years we did not determine any dependency between CCT and the progression of changes in the visual field [15].

### 6. Betaxolol, brimonidine and carteolol in the treatment of normotensive glaucomas

Following on from the study "The Influence of Prostaglandins and Beta-blockers on the Progression of Hypertensive and Normotensive Glaucomas", we were interested in whether any ophthalmological drugs from the range of beta-blockers had a different influence than brimonidine on the progression of NTG [12]. We included 30 patients with NTG in the cohort. The first group was composed of twenty eyes of ten patients (mean age 58.5 years) treated with betaxolol, the second group also of twenty eyes of ten patients (mean age 62.6 years) treated with brimonidine, and the third group of the same number (mean age 61.1 age) treated with carteolol. We examined the visual field with a fast threshold glaucoma program on the instrument Medmont M700. We compared PD of the visual field within the range of three years.

In PD we did not record a statistically significant difference in any of the groups. We also did not determine any difference upon assessment of the other measured parameters.

Local treatment with betaxolol, brimonidine or carteolol has fundamental significance in NTG. All the above pharmaceuticals have a protective influence on the visual field. We did not record any differences between the pharmaceuticals [16].

### 7. Conclusions ensuing from the above overview of new observations in HTG and NTG

1. Our findings confirmed that the vascular component of VD contributes to changes in the visual fields in NTG to a greater degree than perfusion parameters, especially in the AO. Perfusion in the ACR does not play a significant role in changes in the visual field in NTG.
2. VD has very little influence on changes in the visual fields in HTG. The same applies to the retinal nerve fibre layer (RNFL) on changes in the visual field. However, VD has a medium strength influence on changes in the RNFL. Here it is necessary to emphasise that we compared the sum of sensitivities in the central part of the visual field (0-22 degrees) with the RNFL and VD. In NTG an alteration of the anterior part of the optic nerve takes place. VD has a greater share in changes in the visual fields in NTG. However, it is important to state that when intraocular pressure (IOP) increased above 20 mmHg, macular and papillary VD was significantly reduced.
3. Antiglaucomatous treatment by prostaglandins and beta-blockers is of fundamental significance for reducing IOP in HTG. This reduction should be below 20 mmHg, in eyes with a thinner cornea the reduction of IOP should be more pronounced. It is not of fundamental significance as to which antiglaucomatous agents are used. It is nevertheless necessary to point to the fact that prostaglandins have a greater influence on the progression of the pathology. Beta-blockers have a greater protective effect on the visual field. In patients with HTG it is appropriate to recommend neuroprotective agents systemically.
4. In the treatment of NTG it is important to preserve blood perfusion of the posterior pole of the eye, but above all of the anterior part of the optic nerve. Prostaglandins are not suitable for patients with NTG, even if they have a large influence on reducing IOP. The most appropriate drugs are beta-blockers (betaxolol and carteol) and brimonidine. Corneal thickness has no influence on the progression of the pathology.

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