OCT angiography, RNFL and the visual field at different values of intraocular pressure

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Abstract. The aim of the present study was to investigate the relationship between intraocular pressure (IOP), vessel density (VD), retinal nerve fiber layer (RNFL) parameters and overall defect (OD) of the visual field in eyes where antiglaucoma treatment had not yet been initiated. A total of 61 subjects (122 eyes) who had an IOP of >20 mmHg on several occasions, in at least one eye, in routine outpatient care were included. These were subjects who had never been treated for hypertension glaucoma. The cohort was divided into four subgroups. In the first group, there were 18 eyes with an IOP value of <20 mmHg. In the second group, there were 39 eyes with IOP values of 20-22 mmHg. The third group consisted of 32 eyes with IOP values of 22-24 mmHg and the final group consisted of 33 eyes with IOP values of >24 mmHg. The IOP results were compared with VD, RNFL and OD using Pearson's correlation coefficient to assess the relationship between the selected parameters. RNFL and OD were moderately correlated only in the group of eyes with an IOP value >24 (r=0.48); in the other groups the correlation was very weak. However, changes in visual field were already observed in eyes with IOP 20-22 mmHg (r=-0.27). There was a moderate correlation in eyes with an IOP value >24 mmHg (r=-0.53). The most significant result observed was the relationship between VD and RNFL. In eyes with an IOP value ≤20, a moderate to strong correlation between these parameters was observed. This relationship increased with increasing IOP values up to a very strong correlation in the group with an IOP value >24 mmHg. A moderate to strong dependence between VD and RNFL in eyes with an IOP value ≤20 mmHg was observed, and this dependence was very strongly correlated in the eyes with an IOP value >24 mmHg.

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Introduction

In hypertensive glaucoma (HTG), the ganglion cells of the retina and subsequently the entire visual pathway, including the cortical centers in the brain, are damaged, with high intraocular pressure (IOP) playing a major role (1). Early diagnosis and treatment are important for the preservation of visual function in this disease. Current detection of HTG is based on changes in the nerve fiber layer (RNFL), ganglion cell complex and visual field (VF), in addition to a high IOP. Optical Coherence Tomography (OCT) angiography has improved glaucoma diagnosis as well as research on the examination of vessel density (VD) (2).

With increased IOP, a number of biochemical and morphological processes occur in the visual pathway. Of the pathological changes, the most important change is the shrinkage of predominantly retinal ganglion cells (3-6).

Changes in RNFL are likely secondary; Naskar *et al* (5) found that ~40% of retinal ganglion cells were lost within 2.5 months of glaucoma induction. However, they did not observe the initial changes in the optic nerve target until 2 months later. In experimental glaucoma, retinal ganglion cell axons degenerate first in their retrolaminar and then in their intraocular regions (7). As not all ongoing abnormalities have been demonstrated in early glaucoma (*in vivo*), whether certain parameters would be of higher value for determining changes than others should be determined. In the present study, a focus was placed on the status of the blood vessels (based on VD), which play a major role in this disease. In the literature, a large body of research has shown the influence of the amount of IOP on VD in HTG. Conversely, work on the relationship between VD and RNFL in normal IOP is lacking in the ophthalmic literature.

The aim of this study was to investigate the relationship between IOP and VD, RNFL parameters and total visual field (VF) defects in eyes with values of IOP ranging from 17-34 mmHg.

Patients and methods

Patients. The cohort consisted of 61 subjects (122 eyes) who were measured to have an IOP >20 mmHg in at least one eye in routine outpatient practice. Data was collected between February and April 2021 at the Ophthalmology Clinic JL (Prague, Czech Republic). The IOP values obtained and used were based on the mean of three measurements using an Ocular

Response Analyzer (ORA, Reichert). The inclusion criteria were as follows: IOP >20 mmHg in at least one eye, visual acuity of 1.0 with possible correction of less than ±3 diopters, approximately equal changes in visual fields in all eyes, no other ocular or neurological diseases, and no previous treatment for hypertensive glaucoma. The cohort consisted of 27 women with a mean age of 45 (22-70) years and 34 men with a mean age of 53 (20-71) years, this cohort was divided into four subgroups. The first consisted of 18 eyes with IOP ≤20 mmHg, the second consisted of 39 eyes with IOP values of 20-22 mmHg, the third consisted of 32 eyes with IOP values of 22-24 mmHg, and the last consisted of 33 eyes with IOP values of >24 mmHg. The RNFL and VD thickness in the radial peripapillary capillaries region was measured using the Avanti RTVue XR (Optovue), and the VF was examined with a rapid threshold glaucoma program, using the Medmont M 700 instrument (Medmont International Pty, Ltd.), where the overall defect (OD) parameter was evaluated.

Statistical analysis. To assess the relationship between each range of intraocular pressure and the values of VD, RNFL, OD and patient age, Pearson's correlation coefficient r values were used (r, 0.00-0.19 very weak; 0.20-0.39, weak, 0.40-0.59, moderate; 0.60-0.79, strong; and 0.80-1.00 very strong). All analysis was performed using STATISTICA version 13 (StatSoft GmbH) $P<0.05$ was considered to indicate a statistically significant difference.

Results

The values of the correlation coefficients of the peripapillary vessel density of all vessels (PP-VDa), peripapillary vessel density of small vessels (PP-VDs), vessel density of all vessels of the whole image (WI-VDa), vessel density of small vessels of the whole image (WI-VDs), RNFL and OD of all 122 eyes, are shown in Table I, and for each category divided by the range of IOP in Tables II-V. For the entire set, a strong correlation was found between RNFL with PP-VDa and PP-VDs, and a moderate correlation between RNFL and WI-VDa. In the groups of eyes where the IOP was between 20-22 and 22-24 mmHg, a strong positive correlation was found between VD and RNFL, and for the group with the highest pressure value (>24 mmHg), a very strong positive correlation was found.

Discussion

Early diagnosis and treatment is very important for preserving visual function in patients with HTG. The question remains as to which investigations, other than IOP values, are most relevant for improving diagnosis.

However, more important for clinical ophthalmology are the results of the examinations, which can provide clues about the early diagnosis as well as the pathogenesis of glaucoma. These undoubtedly include OCTA and RNFL (8-19). Relatively recently, in the study of glaucoma, special interest has been paid to VD in glaucoma. In PubMed alone, at the time of writing, there were 512 papers on this subject. Feher *et al* (20), using electron microscopy, demonstrated that increased IOP induced ultrastructural modifications of the microvessels of the optic nerve head. The number of β-adrenergic receptors increased markedly in the eyes of patients with raised IOP values. Further studies are required to clarify the physiological and pathological roles of these receptors (20).

A high correlation between VD and RNFL was also observed by Yu *et al* (8). Lee *et al* (9) suggested that the decrease in VD in glaucoma is a secondary consequence of RNFL loss, and Triolo *et al* (10) took a similar view.

As glaucoma progresses, VD decreases (12), whilst RNFL decreases (10-13). However, Khayrallah *et al* (14) demonstrated a lower validity of OCTA than RNFL at different stages of HTG (15), with other studies having reached similar conclusions (15,16). Thus, as HTG progresses, VD and RNFL decrease (17). Rao *et al* (18) demonstrated a faster progression of RNFL loss with reduced VD (18). In addition to the direct effect of IOP on VD, glutamate may have a secondary effect; with higher levels of glutamate at all levels of the visual pathway in HTG (21), there is also an ischemic effect on the surrounding vascular system (22). This may be one of the reasons why vascular alteration may occur before the degeneration of RNFL, even with in a patient with a normal IOP. Conversely, with RNFL atrophy, there is a subsequent change in VD.

Mansoori *et al* (19) demonstrated that peripapillary VD is responsible for RNFL nutrition. A high IOP induced a significant decrease in vessels per unit area in the laminar and retrolaminar regions of the optic nerve (23). There was also a decrease in the capillary length per unit volume. After the application of timolol and latanoprost, the diameter of the vessels of the studied area improved, but the density of the capillaries did not change (23). This is important information for understanding the development of HTG. In clinical ophthalmology, one cannot wait for other significant irreversible changes to appear, and it is hypothesized that these irreversible changes have likely already occurred after an increase in IOP on the optic nerve vessels.

The present study showed a strong correlation between VD and RNFL. At normal IOP values, there was a strong correlation between PP-VDs and RNFL, and between PP-VDa and RNFL. In eyes where IOP >24 mmHg, there was a strong correlation between RNFL and all VD values. This is an important observation, and it should be noted again that the recruited cohort consisted of patients a higher prevalence of higher IOP values. Perimetric examination of magnocellular ganglion cells, which are likely to be damaged (4,5,24) has not been performed, to the best of our knowledge.

Magnocellular ganglion cells are localized in the periphery of the retina (24), and thus does not have the same validity as RNFL examination. Existing VF examination programs in glaucoma mainly focus on the central region of the VF. Regarding the choice of the test, Heijl and Patella recommend the use of a central 30˚ examination in glaucoma with 54 examination points (Humphrey field analyzer from Carl Zeiss Meditec SRN) (25). This view is shared by the authors of the fourth edition of Essential Perimeters (26). The Medmont device examines the VF in glaucoma from 0-22˚ temporally, and 0-50˚ nasally, for a total of 104 points.

As ganglion cell fibers converge on the optic nerve target, their examination is also much more accessible and has a higher sensitivity than VF examination. Therefore, even changes in ganglion cells that are not detectable by VF examination will

Table I. Correlation analysis between the measured parameters in the entire cohort.

Parameter	PP-VDa	PP-VDs	WI-VDa	WI-VDs	RNFL	IOP	OD	Age
PP-VDa	1.00	0.93[a]	0.81[a]	0.82[a]	0.72[a]	-0.41[a]	0.13	-0.08
PP-VDs	0.93[a]	1.00	0.68[a]	0.87[a]	0.70[a]	-0.42[a]	0.09	-0.08
WI-VDa	0.82[a]	0.68[a]	1.00	0.70[a]	0.58[a]	-0.36[a]	0.13	-0.57
WI-VDs	0.82[a]	0.87[a]	0.70[a]	1.00	0.63[a]	-0.46[a]	0.06	-0.07
RNFL	0.72[a]	0.70[a]	0.60[a]	0.63[a]	1.00	-0.39[a]	0.14	-0.06
IOP	-0.41[a]	-0.42[a]	-0.36[a]	-0.46[a]	-0.39[a]	1.00	-0.19[a]	0.21[a]
OD	0.14	0.09	0.13	0.06	0.14	-0.19[a]	1.00	0.23[a]
Age	-0.08	-0.08	-0.06	-0.07	-0.06	0.21[a]	0.23[a]	1.00

[a]P<0.05. PP-VDa, peripapillary vessel density of all vessels; PP-VDs, peripapillary vessel density of small vessels; WI-VDa, vessel density of all vessels of the whole image; WI-VDs, vessel density of small vessels of the whole image; RNFL, retinal nerve fiber layer; OD, overall defect; IOP, intraocular pressure.

Table II. Correlation between the measured parameters in the 18 eyes with an IOP ≤20 mmHg.

Parameter	PP-VDa	PP-VDs	WI-VDa	WI-VDs	RNFL	IOP	OD	Age
PP-VDa	1.00	0.95[a]	0.94[a]	0.88[a]	0.73[a]	0.04	0.01	0.04
PP-VDs	0.95[a]	1.00	0.89[a]	0.92[a]	0.62[a]	-0.02	-0.02	0.12
WI-VDa	0.94[a]	0.89[a]	1.00	0.95[a]	0.56[a]	-0.04	0.12	-0.01
WI-VDs	0.88[a]	0.92[a]	0.95[a]	1.00	0.43	-0.06	0.12	0.08
RNFL	0.73[a]	0.62[a]	0.56[a]	0.43	1.00	-0.06	-0.05	0.23
IOP	0.04	-0.02	-0.04	-0.06	-0.06	1.00	0.29	-0.08
OD	0.01	-0.02	0.12	0.12	-0.05	0.29	1.00	0.47
Age	0.00	0.12	-0.01	0.8	0.23	-0.08	0.47	1.00

[a]P<0.05. PP-VDa, peripapillary vessel density of all vessels; PP-VDs, peripapillary vessel density of small vessels; WI-VDa, vessel density of all vessels of the whole image; WI-VDs, vessel density of small vessels of the whole image; RNFL, retinal nerve fiber layer; OD, overall defect; IOP, intraocular pressure.

Table III. Correlation between the measured parameters in the 39 eyes with an IOP of 20-22 mmHg.

Parameter	PP-VDa	PP-VDs	WI-VDa	WI-VDs	RNFL	IOP	OD	Age
PP-VDa	1.00	0.93[a]	0.80[a]	0.81[a]	0.72[a]	-0.43[a]	0.15	-0.08
PP-VDs	0.93[a]	1.00	0.67[a]	0.86[a]	0.71[a]	-0.45[a]	0.10	-0.10
WI-VDa	0.80[a]	0.67[a]	1.00	0.68[a]	0.59[a]	-0.34[a]	0.12	-0.05
WI-VDs	0.81[a]	0.86[a]	0.69[a]	1.00	0.66[a]	-0.48[a]	0.54	-0.08
RNFL	0.72[a]	0.71[a]	0.59[a]	0.66[a]	1.00	-0.42[a]	0.18	-0.10
IOP	-0.43[a]	-0.45[a]	-0.34[a]	-0.48[a]	-0.42[a]	1.00	-0.27[a]	0.21[a]
OD	0.15	0.11	0.13	0.05	0.18	-0.27[a]	1.00	0.18
Age	-0.08	-0.10	-0.05	-0.08	-0.10	0.21[a]	0.18	1.00

[a]P<0.05. PP-VDa, peripapillary vessel density of all vessels; PP-VDs, peripapillary vessel density of small vessels; WI-VDa, vessel density of all vessels of the whole image; WI-VDs, vessel density of small vessels of the whole image; RNFL, retinal nerve fiber layer; OD, overall defect; IOP, intraocular pressure.

show up in the RNFL on the optic nerve target (27). When using the Medmont device to examine the VF, the overall defect and pattern defect indices are used (28). In our previous study, the specificity of OD VF for HTG was confirmed (27). Therefore, this parameter was selected for analysis in the present study. In the present study, RNFL and OD were moderately correlated only in the group of eyes with IOP ≥24 mmHg. In the other groups, there was a very weak correlation. However, changes

Table IV. Correlation between the measured parameters in the 32 eyes with an IOP of 22-24 mmHg.

Parameter	PP-VDa	PP-VDs	WI-VDa	WI-VDs	RNFL	IOP	OD	Age
PP-VDa	1.00	0.93[a]	0.80[a]	0.83[a]	0.79[a]	-0.48[a]	0.24	-0.17
PP-VDs	0.93[a]	1.00	0.67[a]	0.89[a]	0.80[a]	-0.53[a]	0.18	-0.20
WI-VDa	0.80[a]	0.67[a]	1.00	0.67[a]	0.64[a]	-0.37[a]	0.22	-0.07
WI-VDs	0.83[a]	0.89[a]	0.69[a]	1.00	0.78[a]	-0.54[a]	0.16	-0.18
RNFL	0.79[a]	0.80[a]	0.64[a]	0.78[a]	1.00	-0.54[a]	0.19	-0.24
IOP	-0.48[a]	-0.53[a]	-0.37[a]	-0.54[a]	-0.54[a]	1.00	-0.33[a]	0.32[a]
OD	0.24	0.16	0.22	0.16	0.19	-0.33[a]	1.00	0.13
Age	-0.17	-0.20	-0.70	-0.18	-0.24	0.32[a]	0.13	1.00

[a]P<0.05. PP-VDa, peripapillary vessel density of all vessels; PP-VDs, peripapillary vessel density of small vessels; WI-VDa, vessel density of all vessels of the whole image; WI-VDs, vessel density of small vessels of the whole image; RNFL, retinal nerve fiber layer; OD, overall defect; IOP, intraocular pressure.

Table V. Correlation between the measured parameters in the 33 eyes with an IOP of ≥24 mmHg.

Parameter	PP-VDa	PP-VDs	WI-VDa	WI-VDs	RNFL	IOP	OD	Age
PP-VDa	1.00	0.99[a]	0.96[a]	0.96[a]	0.87[a]	-0.56[a]	0.35	-0.17
PP-VDs	0.99[a]	1.00	0.95[a]	0.97[a]	0.85[a]	-0.56[a]	0.36[a]	-0.17
WI-VDa	0.96[a]	0.95[a]	1.00	0.99[a]	0.87[a]	-0.53[a]	0.32	-0.16
WI-VDs	0.96[a]	0.97[a]	0.99[a]	1.00	0.87[a]	-0.57[a]	0.35[a]	-0.17
RNFL	0.87[a]	0.85[a]	0.87[a]	0.87[a]	1.00	-0.59[a]	0.48[a]	-0.17
IOP	-0.56[a]	-0.56[a]	-0.53[a]	-0.57[a]	-0.59[a]	1.00	-0.53[a]	0.35[a]
OD	0.35	0.36[a]	0.32	0.35[a]	0.48[a]	-0.53[a]	1.00	0.19
Age	-0.17	-0.17	-0.17	-0.17	-0.17	0.35[a]	0.19	1.00

[a]P<0.05. PP-VDa, peripapillary vessel density of all vessels; PP-VDs, peripapillary vessel density of small vessels; WI-VDa, vessel density of all vessels of the whole image; WI-VDs, vessel density of small vessels of the whole image; RNFL, retinal nerve fiber layer; OD, overall defect; IOP, intraocular pressure.

in OD of VF were already observed in eyes where the IOP was 20-22 mmHg. There was a moderate correlation between IOP and OD in eyes with IOP >24 mmHg. With an increase in IOP, RNFL changes and damage of the posterior pole vessels was observed in this study. The most important factor of this study was the identification of the relationship between VD and RNFL; in the eyes with an IOP value ≤20, a moderate to strong correlation was observed between these parameters. This relationship increased as the IOP value increased, with a very strong correlation in the eyes with an IOP value >24 mmHg).

The clear and most important conclusion of this paper is the relationship between VD and RNFL. In the eyes with an IOP value ≤20, a moderate to strong correlation between these parameters was observed, and this relationship increased with increasing IOP, up to a very strong correlation in eyes with an IOP value >24 mmHg. Optic nerve angiography should be a useful and integral part of the diagnosis of hypertensive glaucoma.

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Availability of data and materials

All datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JK and JL are the authors of the main idea and designed and created the main theoretical parts of this review. EN contributed to the design and implementation of research, examination image results analysis and to writing of the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent participate

All patient results and images included in this review were retrospectively used with prior patient consent. The consent

was in accordance with the principles stated in the Helsinki Declaration and as approved by the Internal Ethics Committee of the Eye Clinic JL Faculty of Biomedical Engineering CTU in Prague.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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