“LUCIAN BLAGA” UNIVERSITY OF SIBIU

FACULTY OF MEDICINE

VASCULAR FACTOR IN GLAUCOMA

ABSTRACT OF Ph.D. THESIS

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CONTENTS

I. GENERAL PART

PhD Thesis comprises a number of 136 pages, has an iconography consists of a total of 70 figures (photographs and charts) and 34 tables.

The thesis is divided into 3 main parts: the general part, personal research and bibliography Bibliography account are 116 references from the specialized literature

ABBREVIATION LIST

AA - arteries
OA - ophthalmic artery
CRA - central retinal artery
CPA - posterior ciliary artery
PSV - peak systolic velocity
EDV - end diastolic velocity
RI - resistivity index
CDI - colour Doppler imaging
GON - glaucomatous optic neuropathies
NTG - normal tension glaucoma
IOHT -intraocular hypertension
ON - optic nerve
RE - right eye
LE - left eye
IOP - intraocular pressure
VF - visual field
POAG - primary open angle glaucoma
MD -mean defect
PD - pattern defect
PSD - pattern standard deviation
VFI - visual field index
HTA - arterial hypertension
TA - arterial tension
DZ - diabetes
PP - perfusion pressure
O_2 - oxygen
CO_2 - carbon dioxide

KEYWORDS

- ocular blood flow;
- color Doppler echography;
- retrobulbar ocular blood circulation;
- glaucomatous optic neuropathy

INTRODUCTION

Primary open-angle glaucoma (POAG) is a bilateral, chronic, multifactorial, and progressive optic neuropathy characterized by morphological changes at the optic nerve (ON) head level and the retinal nerve fiber layer in the absence of other eye diseases or congenital abnormalities. These changes are associated with progressive death of retinal ganglion cells and visual field loss [1-3].

Simultaneously with the loss of nerve fibers is produce activation of glial cells, tissue remodeling, with the consequence of the occurrence of characteristic NO excavation and a reduction of the blood flow [2,4]. The intraocular pressure (IOP) is the main and most known risk factor; as the IOP is higher, the greater is the likelihood of developing glaucomatous optic neuropathy (GON).

The proportion of patients with glaucomatous optic neuropathy (GON) despite a normal IOP (i.e.. Normal tension glaucoma -NTG) seems to be increasing and varies considerably from one part of the world to another. The relationship between IOP and GON, although extremely important, is surprisingly weak in the bottom of the IOP spectrum (i.e.. NTG) which indicates that other risk factors are involved [2-11]. Of these, it seems that vascular factors would play an important role.

An argument of this is 6th meeting of the "World Association of Glaucoma" (WGA) in 2009 which had the theme "Ocular blood flow in glaucoma", which was attended by over 200 ophthalmologists and researchers worldwide [8,12,13]. Also, at ESCRS 2014 London was launched by the company Optovue a new device: Angio-OCT's and at EGS Congress Nice 2014 was announced the Doppler- OCT device, aimed has just measuring the retinal blood flow.

In 1858 Jaeger argued the hypothesis that the GON can have other causes, intrinsic, independent of the IOP, and in 1885 Smith suggests two factors involving: mechanical (IOP) and the vascular.

As a clinician ophthalmologist, meet in the current practice cases of glaucoma patients whose disease progresses despite an IOP at lower limit.

Due to its size and location, retrobulbar circulation has been difficult to investigate. By the occurrence of color Doppler ultrasound this was able to achieve, opening new horizons in the investigation and diagnosis of ocular vascular disease.

In the present study I used color Doppler ultrasound for measuring hemodynamic parameters from the main retrobulbar vessels (ophthalmic artery, central retinal artery and posterior ciliary arteries) in patients diagnosed with GON normotensive or hypertensive but medication compensated and I propose to identify changes in blood flow in patients with glaucoma (normotensive and hypertensive), the particularities of these changes of the patients with progression and if this investigation method can be approved in the diagnosis and monitoring of patients with GON.

I GENERAL PART

The first part of the paper consists of 4 chapters that dealt with theoretical concepts relating to ocular vascular flow and glaucomatous optic neuropathy.

In **Chapter 1**, entitled **"Anatomy of optic nerve"** present some fundamental concepts related to anatomy and topography of the optic nerve.

Chapter 2, entitled **"Anatomy and physiology of ocular blood flow"**, contains description the arterial and venous optic nerve (ON) vasculature segment corresponding to each segment of it. Are defined and described the Zinn-Haller ring and "watershed" areas of posterior ciliary artery. In the same chapter refers to optic nerve angioarchitecture, vascular wall structure and physiology of ocular vascular flow. During the last chapter insists on adjusting ocular blood flow that varies depending on its different structures (retina, choroid, optic nerve) and are present endothelial derivatives vascular factors.

In **Chapter 3**, named "**Glaucomatous optic neuropathy (normotensive and hypertensive)"**, is defined glaucomatous optic neuropathy -GON, are presented concepts of epidemiology, are classified risk factors of GON, insisting on vascular risk factors. Is briefly overview of the concepts of: perfusion pressure at the head of ON, ON excavation dynamics, vascular dysregulation, apoptosis, ocular reperfusion. Also, are presented specific investigations in GON and devices for examining vasculature and blood flow of the ON.

Chapter 4, entitled **"Color Doppler ultrasound – Applications in evaluating ocular blood flow**" presents some fundamental concepts of color Doppler ultrasonography: sound waves, Doppler principle, ultrasound machine, color coded examination. Are presented: eco-Doppler examination of oculo-orbital vascularization (ophthalmic artery, central retinal artery, posterior ciliary arteries, upper and lower ophthalmic veins, central retinal vein), applications of color Doppler ultrasound of oculo-orbital pathology, advantages, and disadvantages of color Doppler ultrasound.

II PERSONAL PART

Due to gravity and its prevalence, identifying risk factors in glaucoma preoccupied ophthalmic world for decades. Glaucoma is the 2nd cause of blindness worldwide (WHO), in the Caucasian population having a prevalence of 2% in those over 40 years and 4% in those over 80 years. In 2010: 60 million glaucomatous patients, of which 8.4 million with bilateral blindness. In 2020 is expected glaucomatous 79.6 million glaucomatous patients, of which 11.2 million cases of bilateral blindness [58]. Between the patients diagnosed with glaucoma, in 20 years, 10% become bilaterally blind and 20% monolateral.

Glaucoma is an underdiagnosed disease, population studies suggesting that> / = 50% of cases have not yet been diagnosed many patients suffering severe amputations of the visual field before being diagnosed [58].

Glaucomatous optic neuropathy has a multifactorial etiology, most commonly and the first risk factor is increased IOP. The fact that this parameter has long been the most easily measured, delayed probably identify, measure and combating other possible risk factors. Currently, of all the risk factors involved in the glaucoma etiopathogenesis, only IOP and vascular factor can be quantified and influenced therapeutically. The intraocular pressure (IOP) is the main and best known risk factor; as the IOP is higher, the greater is the likelihood of developing glaucomatous optic neuropathy (GON).
In our country there are few studies regarding retrobulbar circulation. Due to its size and location, retrobulbar circulation has been difficult to investigate. By the occurrence of color Doppler ultrasound this was able to achieve, opening new horizons in the investigation and diagnosis of ocular vascular disease.
As a clinician ophthalmologist, meet in the current practice cases of glaucoma patients whose disease progresses despite an IOP at lower limit.

That is why it is necessary to develop modern methods to quantify better the emergence and evolution NOG, which constitute part of the **motivation** of the current study.

Like **purpose**, in this study, I proposed to identify and evaluate changes in blood flow of the retrobulbar circulation to patients with GON (normotensive and hypertensive drug compensated) using color Doppler sonography for the measuring hemodynamic parameters from the main retrobulbar vessels (ophthalmic artery, central retinal artery, and posterior ciliary arteries). Also, I will analyze the particularities of these changes in patients with progression glaucoma compared with those stable, in those with normotensive versus hypertensive GON and if this method of investigation could be approved in diagnosis, prognosis and monitoring of patients with GON.

Regarding the **material and method** of research, we opted to collect information recorded in the observation charts of patients with various forms of GON, whom I have in evidence in the cabinet of Ophthalmology (Medical Center Ghencea Bucharest Clinic), and I selected according to the criteria for inclusion, a number of 102 patients (202 eyes). The study was conducted over a period of 6 years (2010-2016). All patients signed an informed consent to participate, according to the Declaration of Helsinki on studies with human subjects. This study is retrospective, observational, and descriptive.

The study group consists of patients with a confirmed diagnosis of compensated GON (normotensive or hypertensive), with specific topic antiglaucoma drug therapy, in different stages of evolution of disease and different visual field changes. GON diagnosis was made in accordance with the European Glaucoma Society guide.

Associated systemic disease, received general specific medication.

Inclusion criteria: confirmed GON drug compensated drug; age> / = 40 years; refractive error: +/- 6D; compensated drug systemic disease; informed consent for the study participation and **exclusion criteria**: other forms of primary or secondary glaucoma; other ocular pathologies: diabetic retinopathy, retinal vascular disease; serious systemic diseases, uncompensated; other diseases of the optic nerve.

The **objectives** of the research: the detection of GON patients (normo- and hypertensive) drug compensated and their systematization; patient monitoring and the identification of visual field progression; if there are correlations between data obtained through color Doppler ultrasound in glaucoma patients with glaucoma apparently stationary and the progression or between those with GON normotensive and hypertensive patients.

I have made fact sheets for each patient participating in the study and I has been filled with **data** at each examination.

All patients in the study group was performed color Doppler sonography of retrobulbar vessels using Siemens Acuson X300 apparatus (Figure 4 and Figure 5).

All patients in the study group was performed color Doppler sonography of retrobulbar vessels using Siemens Acuson X300 apparatus (Figure 4 and Figure 5). Were measured systolic blood velocities (PSV) and enddiastolice (EDV) in the ophthalmic artery (OA), central retinal artery (RCA) and posterior ciliary arteries (ACP) in both eyes, using a linear transducer (VF10- 5) (Fig. 6), with frequency of 10Mh. Pourcelot resistivity index (IR): IR = PSV-EDV / PSV, was calculated automatically by the device

Completed the data were obtained from each patient, in the tables.

Fig. 4. Ecograf Acuson Siemens X300

Fig. 5. Ecograf Acuson Siemens X300

Fig.6. Transductor linear (VF105)

Values in normal subjects: over the time, have conducted several studies have reported different values for normal subjects. In this study, we used (for the measuring hemodynamic parameters) in order to achieve statistical analysis, average the values of mean values reported in the literature. (Table 2)

OA			CRA			CPA		
PSV	EDV	IR	PSV	EDV	IR	PSV	EDV	IR
39,12	11,83	0,72	14,10	5,31	0,65	15,70	5,85	0,61

Table nr.2: Normal values of hemodynamic parameters using in the statistical analysis OA-ophthalmic artery; CRA- central retinal artery; CPA-Posterior ciliary arteries; PSV- maximum systolic velocity; EDV- end diastolic velocity; RI- resistivity index

Statistical analysis: Data were collected and processed by statistical program SPSS version 21. Descriptive statistics (mean, standard deviation, minimum / maximum) was used for the presentation / analysis of demographic and basic characteristics: age, intraocular pressure, blood velocities (systolic and end diastolic), resistivity index in the studied vessels. Was used the non-parametric Mann-Whitney U test (independent t-test test equivalent) for the statistical analysis of the two conditions with non-parametric distribution. The ROC curve was used to assess the sensitivity and specificity of the variables to predict the development and progression of glaucomatous optic neuropathy.

In **Chapter results** are presented statistical analyzes performed.

The composition of the study group: mean age: 66,41ani (9,57sd) (Figure 11); gender distribution: 84 (82.35%) women and 18 (17.65%) men (Figure 12); type of GON: 16 patients (15.69%) of GON normotensive and 86 patients (84.31%) with hypertensive GON (Figure 13); the mean IOP: 15,52mmHg (sd: 1.72) OD şi15,45mmHg (sd: 1.81) to OS.

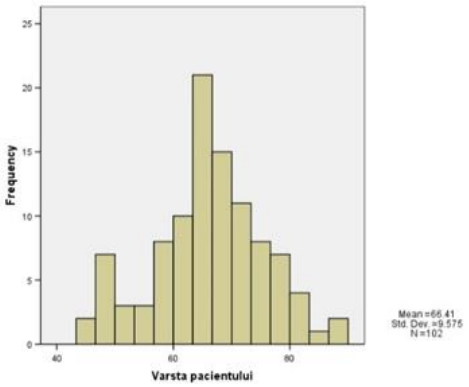
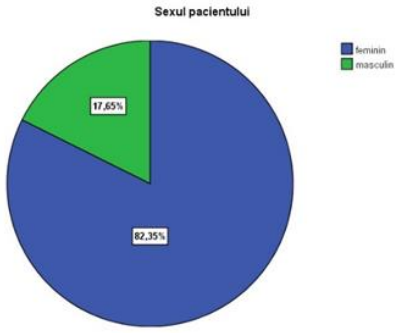


Fig.11: The distribution by age ranges of the studied group



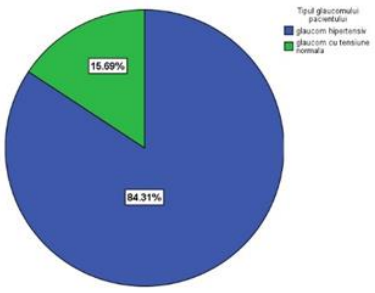


Fig.12: The gender distribution of the study group

Fig.13: Type of glaucoma in the study group

The mean values obtained for hemodynamic parameters measured with CDI are in Table 3:

Table 3: The mean values obtained for hemodynamic parameters measured with CDI

	OA	CRA	CPA
PSV	34.01 (sd: 11,12)	18,73 (sd: 2,35)	19,37 (sd: 2,33)
EDV	10,07 (sd: 3,37)	6.75 (sd: 1,78)	6,74 (1,47)
RI	0,726 (sd: 0,052)	0,694 (sd: 0,060)	0,688 (sd: 0,060)

OA-ophthalmic artery; CRA- central retinal artery; CPA-Posterior ciliary arteries; PSV- maximum systolic velocity; EDV- end diastolic velocity; RI- resistivity index

Statistical analysis of association parameters CDI with variable preached age

Statistical analysis was performed separately for the two types of glaucoma (normotensive and hypertensive) which form the study sample. For statistical analysis, Pearson correlation test was used.

1.The subgroup of patients with hypertensive glaucoma: there were statistically significant results for the resistivity index to all vessels studied ($p < 0.001$), end diastolic velocity in the ophthalmic artery ($p < 0.001$) and less for the maximum systolic velocity in central retinal artery ($p < 0, 05$).

2. The subgroup of patients with normotensive glaucoma: there were statistically significant results for resistivity index to all vessels studied ($p < 0.001$) and enddiastolic velocity in the ophthalmic artery ($p < 0.001$).

Statistical analysis of CDI parameters obtained report to normal values, of the reference

The mean values of the measured parameters with CDI in the present study were centralized (Table 3) and were used to perform statistical analysis of the comparison with the reference values (Table 2).

For statistical analysis was used: T-test for all measured parameters.

1. For the ophthalmic artery, we obtained a significant decrease of the systolic (PSV) ($p < 0.001$) and the end diastolic velocity (EDV) ($p < 0.001$).

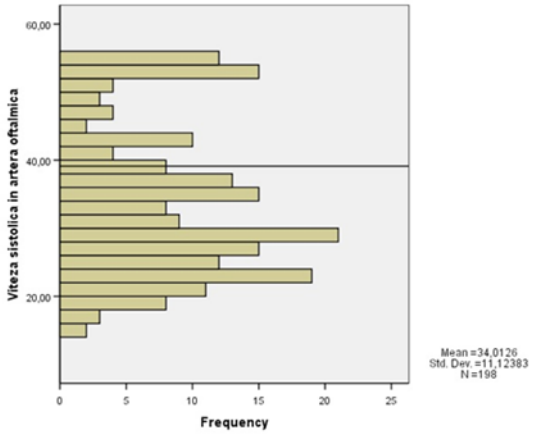


Fig.23: Graphic distribution of ophthalmic artery systolic peak velocity reported to the reference value

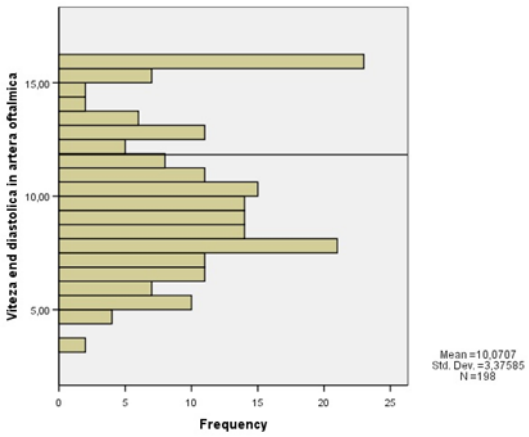


Fig.24: Graphic distribution of enddiastolic velocities in the ophthalmic artery reported to the reference value

2. For central retinal artery, we obtained a statistically significant increase of resistivity index ($p < 0.001$)

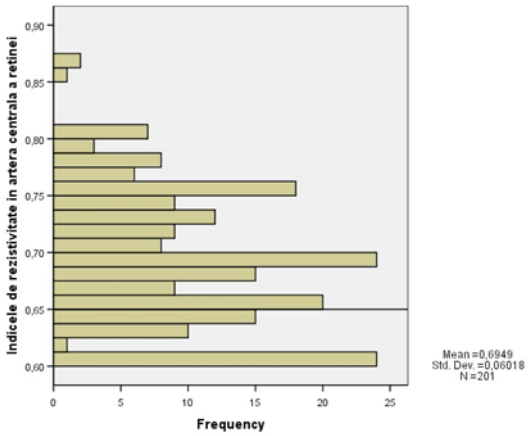


Fig.25: Graphic distribution of resistivity index values in central retinal artery reported to the reference value

3.For posterior ciliary arteries, obtained a statistically significant increase of resistivity index ($p < 0.001$)

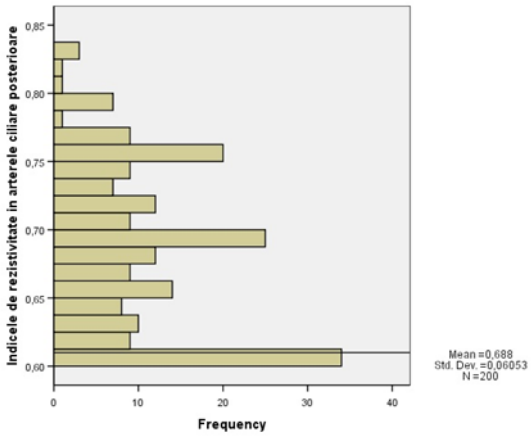


Fig.26: Graphic distribution of resistivity index values in posterior ciliary artery reported to the reference value

Statistical analysis of the CDI parameters compared between RE and LE

The average values obtained for the CDI hemodynamic parameters measured in the right eye and left eye were summarized in Table no. 10:

Table no. 10: The average values of hemodynamic parameters measured with color Doppler ultrasound in both eyes

	RE			LE		
	OA	CRA	CPA	OA	CRA	CPA
PSV	33.92 (sd:11.39)	19.10 (sd: 2.36)	19.20 (sd: 2.034)	34.10 (sd:10.91)	18.34 (sd: 2.29)	19.54 (sd:2.59)
EDV	10.24 (sd: 3.43)	6.96 (sd:1.89)	6.80 (sd: 1.38)	9.90 (sd: 3.33)	6.54 (sd: 1.64)	6.68 (sd: 1.55)
IR	0.72 (0.047)	0.69 (sd:0 .058)	0.68 (sd: 0.058)	0.73 (sd: 0.056)	0,.69 (sd:0.062)	0.68 (sd:0.063)

OA-ophthalmic artery; CRA- central retinal artery; CPA-Posterior ciliary arteries; PSV- maximum systolic velocity; EDV- end diastolic velocity; RI- resistivity index

Following statistical analysis (Mann-Whitney U test) were obtained statistically significant differences of the values of the PSV in the central retinal artery (low in LE) and in the posterior ciliary arteries (low in RE) ($p < 0.001$).

Statistical analysis of the CDI parameters at patients with hypertensive compared with normotensive GON

From the lot of 102 patients (202 eyes) were identified 16 patients (15.7%) = 31 eyes with normotensive GON, with a mean age: 66.87 years (sd = 9.78), 13 women (81.25%) and 3 men (18.75%) and 86 patients (84.3%) = 171 eye with hypertensive GON , with a mean age: 66.33 years (sd = 9.59); 72 women (83.72%) and 14 men (16.28%).

Values obtained by measurements of CDI hemodynamic parameters at the 2 lots were summarized in two tables (Table 12 and 13) and then statistically analyzed

Hypertensive glaucoma:

OA			CRA			CPA		
PSV	EVD	IR	PSV	EVD	IR	PSV	EVD	IR
33,96 (11,37)	10,03 (3,51)	0,72 (0,052)	18,60 (2,41)	6,70 (1,84)	0,69 (0,062)	19,39 (2,39)	6,78 (1,50)	0,69 (0,061)

Table 12: OA-ophthalmic artery; CRA- central retinal artery; CPA-Posterior ciliary arteries; PSV- maximum systolic velocity; EDV- end diastolic velocity; RI- resistivity index

Normotensive glaucoma:

OA			CRA			CPA		
VS	VD	IR	VS	VD	IR	VS	VD	IR
34,29 (9,78)	10,27 (2,50)	0,72 (0,073)	19,40 (1,88)	7,019 (1,421)	0,68 (0,057)	19,30 (1,98)	6,480 (1,206)	0,68 (0,055)

Table 13: OA-ophthalmic artery; CRA- central retinal artery; CPA-Posterior ciliary arteries; PSV- maximum systolic velocity; EDV- end diastolic velocity; RI- resistivity index

The only statistically significant differences between patients with hypertensive glaucoma and patients with normal-tension glaucoma was registered at the EDV of PCA level, respectively decrease EDV in subjects with NTG: Mann-Whitney U index has been 2076 ($p < 0.05$).

ROC curve

As mentioned earlier, the Mann Whitney test revealed there was a difference between patients with hypertensive glaucoma and normal tension glaucoma registered in the end diastolic velocity (EDV) of the PCA.

As a consequence, the ROC curve was employed to test whether EDV in the PCA was a predictable parameter for patients with normal tension glaucoma. Additionally, to determine the power of the test, the area under the ROC curve was calculated. Figure1 illustrates all the ROC Curves, but only the end diastolic velocity had significant area under the curve ($p<0.05$). (Figure 2). The area under the curve is 0.70 which makes it a fair but acceptable test of prediction, meaning that EDV of PCA is a good predictor. The power to identify the predictive value of patients with NTG using EDV of PCA reaches 72% sensitivity at 33% specificity (cut-off>5,95)

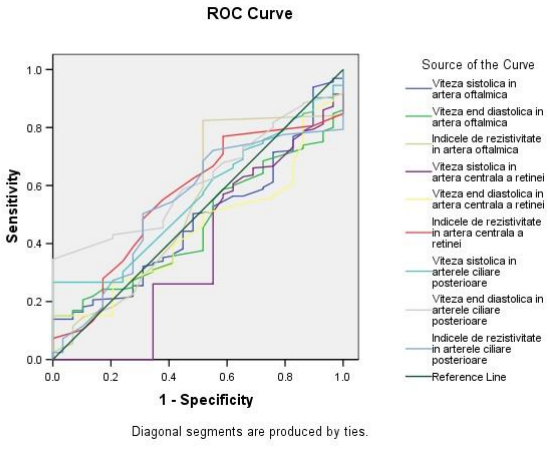


Fig. 28.: ROC curve for all the parameters

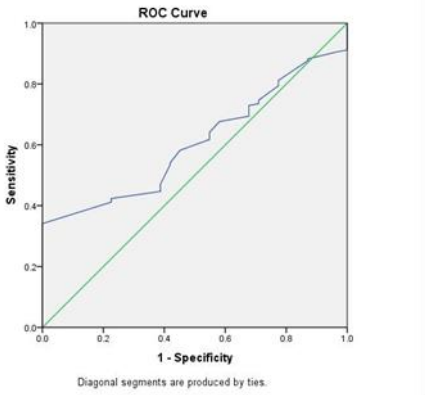


Fig.29: EDV in PCA

Statistical analysis of the CDI parameters of the eyes with progressive glaucoma compared to the eyes with stable glaucoma

To evaluate the hemodynamic parameters of retrobulbar circulation using color Doppler ultrasound at the patients with progressive GON in one eye, medication compensated, and compared with those obtained for the stable eye.

From the study group, consists in 102 patients (202 eyes), were selected patients with progression glaucoma in one eye and stable glaucoma in congener eye. Progression was assessed by repeated perimetry.

Were selected 48 patients (96 eyes) who fulfilled the inclusion criteria , with a mean age of 68,67 years (sd = 8,54), 37 women, 11 men; mean IOP=15,22 mmHg (sd=1,67) in the progressive eyes and 15,20

mmHg (sd=1,57) in the stable eyes; " slope per year" mean for MD: -0,75 dB(sd = 0,37) in the progressive eyes and 0,07dB (sd=0,55) in the stable eyes; " slope per year" mean for PD : -2,9 dB (sd= 18) in the progressive eyes and 0,04 dB (sd=0,35) in the stable eyes.

The values obtained from measurements of hemodynamic parameters by color Doppler echography of those 2 groups of eyes (with progression and stabile) were summarized in two tables and were statistically analyzed.

Progressive glaucoma:

Ophthalmic artery			Central retinal artery			Posterior ciliary arteries		
PSV	EVD	IR	PSV	EVD	IR	PSV	EVD	IR
30.61 (sd-9.84)	8.69 (sd-2.76)	0.74 (sd-0.04)	17.28 (sd-2.81)	6.33 (sd-1.71)	0 .70 (sd-0.06)	18.07 (sd-2.90)	6,01 (sd-1.34)	0.70 (sd-0.06)

Table 20: PSV- peak systolic velocity; EVD= end diastolic velocity; IR= Resistivity index

Stable glaucoma:

Ophthalmic artery			Central retinal artery			Posterior ciliary arteries		
PSV	EVD	IR	PSV	EVD	IR	PSV	EVD	IR
33,61 (sd-10.04)	9,83 (sd-2.88)	0.72 (sd-0.05)	19.43 (sd-2.14)	7.25 (sd-1.61)	0.69 (sd-0,06)	19.25 (sd-2.27)	6.83 (sd-1.43)	0.68 (sd-0.06)

Table 21: PSV- peak systolic velocity; EVD= end diastolic velocity; IR= Resistivity index

By comparing the values from the two tables, it can be observed a decrease in the mean values of velocities flow and increased means values for IR at the progressive glaucoma eyes as compared with stable glaucoma eyes.

According Mann-Whitney U test, the statistically significant differences between eyes with progressive glaucoma and eyes with stable glaucoma was registered for the velocities flow values of the PSV (at central retinal artery $p<0,001$ and posterior ciliary arteries $p<0,04$ level), EDV (at ophthalmic artery $p<0,03$ and central retinal artery $p<0,006$ level) and IR of ophthalmic artery $p<0,05$.

ROC curve was performed for the parameters which were registered differences with statistical significance.

The present study found that relevant in glaucoma progression decrease of PSV values in CRA (statistically significant $p<0.001$ and has the area under the curve 0.73 with 72% sensitivity at 59% specificity - cut-off point >17,90).(Figure 57)

According to the Pearson values there were no registered correlations between perimetry indices (MD and PD) and hemodynamic parameters because the "p" value was higher than 0.05.

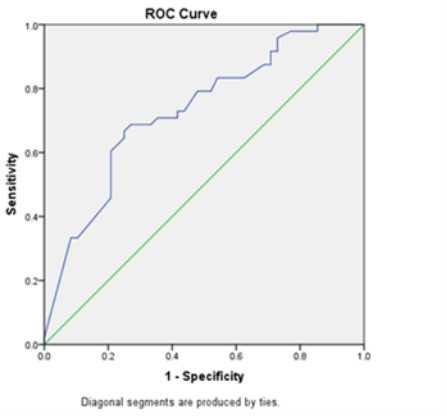


Fig.57. ROC curve for PSV in CRA

In **chapter discussions**, our results were compared with results of other studies on the same issue, found in the specialized literature.

In this paper, we studied the modification of hemodynamic parameters measured with color Doppler ultrasound in relation to age at patients with glaucoma. We evaluated separately patients with compensated hypertensive glaucoma and patients with normotensive glaucoma. All patients was increased resistivity index values in all the vessels, with age. The growth was weak-moderate at patients with hypertensive glaucoma and moderate to strong at normotensive glaucoma patients. Were also registered statistically significant falls of velocities blood flow both, in hypertensive and normotensive glaucoma patients.

Data in the literature is superimposed on these results: Transquart et al. (2002), Rojanapongpun and Drance (1993), Popa (2012).

Be noticed that with age, vascular resistivity increases, which overlaps with the physiological. This resistivity is growing important at normotensive glaucoma patients comparative with hypertensive glaucoma patients.

Up to now, studies have been conducted which have comparison of CDI hemodynamic parameters at patients with various forms of glaucoma with those of a control group, of healthy patients. Some reported significant changes, some not: Pillunat et al, Mokbel at all., Cellini et al., Galassi et al., Samsudin et al., Trible et al., Hong-Jen Chiou et al., Plange et al. (2007), Popa (2012).

There are other studies that have reported decreases in retrobulbar blood flow velocities at patients with normotensive glaucoma compared to a healthy group: Plange et al. (2003), Butt et al. (1997), Harris et al. (1994), Huber et al. (2006), Kaiser et al. (1997), Rankin et al. (1995), Vecsei et al. (1998).

Sharma et al. (2006) has compared patients with POAG with a control group and found a significantly low value of the PSV in the OA ($p < 0.001$) and EDV in all three vessels and a significant increase in RI in all three vessels ($p < 0.001$).

Other studies: Sergott et al. (1994), KöÈnigsreuther and Michelson (1994), Durcan et al. (1993).

In the present study, we used to compare the mean values reported in the literature as normal. We obtained statistically significant differences for PSV ($p < 0.001$) and EDV ($p < 0.05$) in the OA and RI at CRA and CPA (increased IR $p < 0.001$), resulting in a decrease of the velocities in the ophthalmic artery and an increase of the resistivity of the central retinal artery and posterior ciliary arteries. The results obtained aligns with those obtained by Galassi et al. (1996), Trimble et al. (1993), Sharma et al. (2006), Sergott et al. (1994) and Durcan et al. (1993).

We compared hemodynamic parameters measured with CDI obtained at the right eye with those obtained of the left eye. We obtained statistically significant values for PSV in CRA with higher values in RE and PSV in the CPA with higher values in the LE. Differences between the two eyes can guide us to the quality of investigative technique, the operator may have preference (convenience in examination) for one eye. It is known that improper technique can create pressure on the eyeball and may influence the amount of data obtained. Taking into consideration that changed values have not found significant stastistic mainly on one eye, we conclude that the strategy was correct.

We compared the values obtained from Doppler between normotensive and hypertensive glaucoma patients.

Kaiser et al. (1997) conducted an extensive study that analyzed three categories of patients: with stable glaucoma, progressive glaucoma and normal tension glaucoma; they found significant hemodynamic changes in patients with progressive glaucoma and in patients with normotensive glaucoma.

In a study published in 1999, Simon J.A.Rankin found no significant differences between retrobulbar hemodynamic parameters in patients with normotensive glaucoma compared to hypertensive medication compensated glaucoma. The same point was stressed by Kuerten al. and Plange in a study from 2015 which mentioned an article published in 1997 by Butt et al.

In the present study, we obtained a statistically significant decrease ($p < 0.05$) of end diastolic velocity in posterior ciliary arteries, area under the curve by 0.70 with predictive power of normotensive glaucoma by 72% sensitivity at 33% specificity (cut off point> 5.95).

These results can be sustained by the study of Zeitz et al. (2006) which supports the importance of hemodynamic changes at the CPA level in progression of glaucoma, as the study published by Park et al. (2012) who affirm that perimetry changes in glaucoma normotensive due to alterations in the peripheral microcirculation. This shows that argument the Sung et al. (2011) study, which support the retrobulbar hemodynamic changes in normotensive patients with glaucoma, in particular in the CPA are similar to those of patients with ischemic anterior optic non-arteritic neuropathy. .

The results of the literature on this subject are few and inconclusive to be able to draw a conclusion. I studied hemodynamic parameters measured with CDI compared between eyes with glaucoma progression and eyes with stable glaucoma.

Only a few studies, spread limited, were conducted to investigate the relationship between hemodynamic parameters measured with color Doppler ultrasound and progression of glaucoma and studies with different numbers of participants have found correlations between the different hemodynamic parameters measured with CDI and changes progression in perimetry of both glaucoma normotensive and hypertensive. However, at present, the results are inconclusive.

In 2015, Kuerten et al. have centralized studies about correlations between CDI parameters and progression in glaucoma: Schumann et al. (2000); Gherghel et al. (2000); Martínez și Sánchez (2005); Satilmis et al. (2003); Galassi et al. (2003); Zeitz et al. (2006); Calvo et al. (2012); Jimenez-Aragon et al. (2013); Kuerten et al. (2014).

Other studies that have the same theme: Mokbel et al. (2010); Yamazaki and Drance (1997); Plânge et al.(2006); Sharma and Bangiya (2006); Cellini et al. (1996-97); Renklin et al. (1996); Suprasanna et al.(2014); Alconchel et al. (2012); Popa (2012).

Most of the studies published so far include healthy control group patients without risk of glaucoma. In our study, the control group is represented by the congener eye, in which glaucomatous disease is apparently stable.

Considering the values obtained from the ROC curve (PSV values decrease in central retinal artery p <0.001, area under the curve 0.73 with 72% sensitivity at 42% specificity - the cut-off point> 17.90), we conclude that this study is more in line with studies conducted by Zeitz et al. (2006), Plange et al. (2006) or Alconchel et al. (2012), which identified PSV decrease in CRA.

These findings might be restricted by the small sample size and heterogeneity in the manifestation of the disease in the study population. In addition, the variability of the follow-up period, as well as of the number of visual field tests, might confound the results, although the visual field progression index (in dB per year) aims to be comparable between patients [22]. Also, the vessels with statistically significant correlations to visual field defect progression vary amongst the studies, possibly because of the variability in the measurement technique in the different studies and is no general consensus about the best diagnostic tool to identify progression in glaucoma (most authors prefer visual field changes; others prefer optic disc changes via morphometric techniques) [69].

Besides those aspects, numerous others factors may have affected the clinical course of the patients: various therapeutic interventions (topic or systemic medications, laser, and surgical procedures) that patients during the follow up, individual factors (genetics, life habits, and treatment compliance) might affect the results of these study [95].

Same authors of these studies give a greater importance of RI for involved in the progression of glaucoma: Kuerten et al.; Sharma et al.; Galasi and Calvo

Regarding the role of CDI in the progression of glaucoma can draw some general conclusions:

- retrobulbar hemodynamics and ocular perfusion appear to play a major role among other factors (some of them not yet clearly defined) [69];
- CDI can be an important criterion in identifying patients at increased risk of glaucoma progression (biomarker in glaucoma) [75,87,102];
- CDI measurement accuracy and reproducibility of these are variable [69.114], which is why it is still not possible to determine the best parameter that is correlated with the progression of glaucoma [69];
- CDI can help to establish a more aggressive clinical management in cases of atypical or extreme, with very high risk of progression (prognostic role) [69,75,95,116].

Interpretation of results from research through correlation with data obtained in the specialty literature that also discussed the role of vascular factor in glaucoma, have led to some important **conclusions.**

In recent years, increasingly attention is given to vascular factor in etiophatogeny of glaucoma. A proof of this are the works presented at the latest national and international glaucoma congresses and improvement or identification of the new investigative and measurement techniques of the retrobulbar circulation and vascular flow at this level.

Age is one of the risk factors of glaucoma occurs. In the present study, we found that with age, vascular resistivity increases, which overlaps with the physiological. This resistivity is growing more important at normotensive comparative with hypertensive glaucoma patients. Another parameter that seems to be important, with older, is the end diastolic velocity of OA which drops significantly in both groups of glaucoma patients (normotensive and hypertensive).

By comparing the study group with normal values of reference we obtained statistically significant changes: decreased velocities in the ophthalmic artery (PSV: $p < 0.001$ and EDV $p < 0.05$) and increased resistivity in the CRA and CPA (IR: $p < 0.001$).

We also found differences in hemodynamic parameters measured, with statistical significance, between patients with GON normotensive compared with patients with GON hypertensive drug compensated. These differences were just to the end diastolic velocity values of posterior ciliary artery ($p < 0.05$). End diastolic velocity of CPA has predictive power to identify patients with normotensive GON with a sensitivity of 72% for specificity 33%. These values are considered to be satisfactory in statistical terms, but not enough to have predictive value in identifying patients with normotensive GON.

this study we found a decrease in mean blood velocities and an increase in the average values of resistivity indices in eyes with glaucomatous progression compared to those stable in all the hemodynamic parameters investigated. There were significant changes at the resistivity index ($p < 0.05$) and the end diastolic velocity ($p < 0.03$) in the ophthalmic artery, the maximum systolic velocity ($p < 0.001$) and end-diastolic ($p < 0.006$) from the central retinal artery and systolic maximum velocity ($p < 0.001$) in the posterior ciliary arteries at progressive glaucoma eyes. The most important parameter as a

result of ROC curve is the PSV of central retinal artery with an area under the curve of 0.73, having predictive value for glaucoma progression with a sensitivity of 72% to 59% specificity (cut off point > 17.90).

In summary, the present study shows the following results:

- with increasing age, increases the resistivity and decreases velocity of the retrobulbar circulation (more pronounced in patients with normotensive GON), overlapping the physiological;
- compared with reference values, in glaucoma decrease velocities of ophthalmic artery and increase the resistivity of the central retinal artery and posterior ciliary;
- in normotensive glaucoma decrease end diastolic velocity values in posterior ciliary arteries, compared with hypertensive glaucoma;
- in the case of progression of glaucomatous decreases the PSV of the central retinal artery.

Colour Doppler ultrasonography is useful for visualizing vascularization and assessment of the retrobulbar hemodynamic and help discerning glaucomatous disease pathogenesis which could lead to the identification of innovative, vasoprotective therapies, which prevent optic nerve damage.

The fact that perfusion of the optic nerve head is directly related to the retrobulbar circulation, accessible to direct evaluation with Doppler ultrasound, can make it of this an evaluation technique for early vascular changes in glaucoma.

In conclusion, we align the recommendations of the World Glaucoma Association, regarding the ocular blood flow, according to which the investigation should include longitudinal studies with larger numbers of patients and to use standardized methods to confirm whether the changes of vascular flow precede the visual field defects and correlate with disease severity.

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