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CLINICAL STUDY

Performance of colour Doppler imaging discriminating normal tension glaucoma from healthy eyes

N Plange[1], M Kaup[1], A Weber[1], A Harris[2], KO Arend[3] and A Remky[1]

Abstract

Purpose **Previous studies have shown decreased retrobulbar blood flow in normal tension glaucoma (NTG) compared to healthy controls. This study evaluates the ability of colour Doppler imaging (CDI) to identify patients with NTG.**

Methods **Sixty-two patients with untreated NTG (mean age 57 ± 14 years) and 40 age-matched controls (mean age 58 ± 9 years) were included in a prospective cross-sectional institutional study. Peak systolic velocity (PSV), end-diastolic velocity (EDV), and resistive indices (RI = (PSV–EDV)/PSV) of the ophthalmic artery (OA), central retinal artery (CRA), and short posterior ciliary arteries (PCAs) were measured by means of CDI. Using receiver operating characteristic (ROC) curves, sensitivity was determined at 90% specificity.**

Results **Patients with NTG showed significantly decreased PSV ($P < 0.0001$) and EDV ($P < 0.0001$) of the CRA, significantly decreased EDV of the nasal ($P = 0.004$) and temporal ($P = 0.002$) PCA, and significantly increased RI of the temporal ($P = 0.003$) PCAs compared to healthy controls. Sensitivity values at 90% specificity were calculated: PSV of the CRA, 30.6%; EDV of the CRA, 48.4%; EDV of the nasal PCA, 43.9%; EDV of the temporal PCA, 45.9%; and RI of the temporal PCA, 39.3%.**

Conclusions **The power to identify NTG using CDI reaches 48% sensitivity at 90% specificity. Further longitudinal studies are needed to determine the prognostic value of CDI in glaucoma.**

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[1]Department of Ophthalmology, RWTH Aachen University, Aachen, Germany

[2]Department of Ophthalmology, Physiology and Biophysics, Indiana University School of Medicine, Indianapolis, IN, USA

[3]Eye Center Alsdorf, Alsdorf, Germany

Correspondence: N Plange, Department of Ophthalmology, RWTH Aachen University, Pauwelsstr. 30, 52057 Aachen, Germany
Tel: +49 241 8089277;
Fax: +49 241 8082408.
E-mail: nplange@ukaachen.de

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Introduction

Ocular haemodynamics have been shown to be a major factor in the pathogenesis of glaucomatous optic neuropathy.[1–3] In addition, systemic vascular risk factors and vascular dysregulation have been identified to contribute to glaucomatous aetiology and may result in impaired ocular blood flow.[4–10] Previous studies have reported decreased perfusion of the optic nerve head[11,12] retina,[13] and reduction in blood flow velocities of retrobulbar vessels in normal tension glaucoma (NTG) compared to healthy controls.[14] Flow velocities of the ophthalmic artery (OA), central retinal artery (CRA), and nasal and temporal short posterior ciliary arteries (PCAs) can be measured using colour Doppler imaging (CDI). A reduction in flow velocities and an increase in the calculated resistive indices (RI) of all these retrobulbar vessels have been reported in NTG compared to healthy controls in different studies.[13–19] The blood flow velocities of retrobulbar vessels have been correlated to functional defects in glaucoma[20,21] and are associated with interocular differences in asymmetric visual field defects.[22] In addition, retrobulbar blood flow velocities are linked to perfusion deficits of the optic nerve head[13] and retina[23] in glaucoma. However, a considerable overlap of the flow velocities is present in all studies that compared NTG patients with controls. These studies showed that reduced flow velocities of the retrobulbar vessels are present in NTG, but the precision to detect a patient with NTG has not

been evaluated. As a consequence, the ability of CDI to discriminate glaucomatous pathology from healthy eyes remains unknown.

The presented study prospectively investigated the sensitivity of retrobulbar haemodynamics as measured by CDI to detect patients with NTG using receiver operating characteristic (ROC) curves in a clinical setting.

Methods

All study procedures adhered to the Declaration of Helsinki for research involving human subjects and informed consent was obtained from all participants. Data accumulation was carried out with Institutional Review Board approval. All patients with NTG and healthy controls underwent a detailed ophthalmological examination (including assessment of refractive error, ie spherical equivalent), visual field testing, and CDI analysis of the retrobulbar blood vessels.

Visual field examinations were performed with the Humphrey Field Analyzer (Model 750, Humphrey-Zeiss, San Leandro, CA, USA) using the achromatic 24–2 full threshold or Swedish Interactive Threshold Algorithm (SITA) program. The visual field global indices mean deviation (MD) and pattern SD (PSD) were used for statistical analysis.

Blood flow velocities of retrobulbar vessels were measured by means of CDI using a 7.5 MHz linear phased-array transducer (Siemens Sonoline Sienna, Germany) by experienced operators (NP, MK). The operators were masked for the diagnosis and clinical data of the subjects. The method has been described in detail previously.[24,25] The transducer was gently placed on the closed upper eyelid using a coupling gel to minimise pressure on the globe. All subjects were in the supine position during the examination. CDI permits blood velocity measurements of the OA, CRA, and nasal and temporal PCAs. The peak systolic velocity (PSV) and the end-diastolic velocity (EDV) were obtained from the velocity waves of each artery. The RI (Pourcelot's ratio) was calculated ((PSV−EDV)/PSV) to characterise peripheral vascular resistance of the blood vessels. Before measurement of retrobulbar haemodynamics, systolic and diastolic blood pressures as well as the heart rate were measured after a rest of 5 min (Dinamap, Criticare Systems Inc., Tampa, FL, USA) in the supine position. Intraocular pressure (IOP) was measured in a sitting position using Goldmann applanation tonometry before CDI.

Patients

Sixty-two patients with NTG (mean age: 57 ± 14 years) and 40 age- and sex-matched healthy controls (mean age: 58 ± 9 years) were included in the study.

Patients with NTG were consecutive patients who presented at the outpatient clinic of the Department of ophthalmology, RWTH Aachen University and met the inclusion criteria. All patients with NTG had glaucomatous optic nerve head cupping and glaucomatous visual field defects as defined by the European Glaucoma Society[26] in the absence of retinal or neurological disease affecting the visual field. Visual field loss was considered significant when the glaucoma hemifield test was abnormal, if 3 points, not contiguous with the blind spot were abnormal ($P<0.05$), or the corrected pattern SD (CPSD) was abnormal with $P<0.05$. All parameters were confirmed on two consecutive visual fields performed with Humphrey Visual Field Analyzer (full threshold or SITA program 24–2). Patients with NTG never had IOP values above 21 mmHg in their medical history. Untreated IOP was confirmed at least once in the medical history by a diurnal IOP profile without IOP-lowering medication (at 0800, 1200, 1600, 2000, 2400 hours). The IOP profile without IOP-lowering medication was measured when glaucoma was diagnosed for the first time. Visual acuity was 20/40 or better and no previous laser or surgical treatment had been performed. Patients with refractive aberrations of more than ±8 D (spherical equivalent) or with diabetic retinopathy or age-related macular degeneration were excluded from this study. NTG patients were untreated at the time of analysis. Patients were either newly diagnosed NTG patients or underwent a washout period (no IOP lowering medication) for 3 weeks. According to the medical history, 22 patients with NTG were found to have systemic arterial hypertension treated with systemic medication, eight patients had arteriosclerosis (eg coronary heart disease, carotid occlusive disease), 20 patients presented with vascular phenomena related to vascular dysregulation (migraine, cold hands and feet, Raynaud's disease, systemic arterial hypotension).

The control subjects were recruited by notification at the RWTH Aachen University. Relatives of the glaucoma patients were excluded from the study. The control subjects did not have any ophthalmologic disease, presented with IOP values below 22 mmHg and did not receive any topical treatment. Visual field examinations did not reveal any significant visual field loss. Visual field parameters (mean deviation (MD) and pattern SD (PSD), Humphrey Visual Field Analyzer) were within normal range (ie $P>0.05$) and the glaucoma hemifield test was within normal limits. Funduscopy was performed independently by two glaucoma specialists (AR, OA) and presented a normal optic nerve head appearance (no thinning or notching of neuroretinal rim, no bared circumlinear vessels, no disc hemorrhages) by clinical judgement of both observers.

The clinical and demographic data of all individuals included in the study are presented in Table 1.

Statistical analysis

For statistical analysis of this study, one study eye was randomly selected in bilateral NTG and controls subjects. In cases of unilateral NTG, the diseased eye was included in the analysis. Using ROC curve analysis, sensitivity values at a fixed specificity of 90% were evaluated. Additionally, to determine the power to discriminate between groups, the area under the ROC curve was calculated for each parameter. An unpaired non-parametric test (Mann–Whitney *U*-test) was applied for comparisons between patients with NTG and controls. After Bonferroni's multiple comparison correction, a *P*-value <0.0042 was regarded as statistically significant.

Results

The global indices MD and PSD of the patients with NTG were significantly different compared to healthy controls. No significant differences were found for IOP or blood pressure between groups (Table 1).

Patients with NTG showed significantly decreased PSV and EDV of the CRA and significantly decreased EDV of the nasal and temporal PCAs. The RI of the temporal PCAs were significantly increased in NTG compared to healthy controls. The RI of the CRA and nasal PCAs were not statistically and significantly different after Bonferroni's correction for multiple comparisons. Blood flow velocities and RI of the OA did not reveal statistically significant differences between groups. The blood flow velocities and RI are presented in Table 2.

The calculated sensitivity values at fixed specificity of 90% for all parameters and the corresponding cutoff criteria using ROC curve analysis are presented in Table 3. The calculated area under the ROC curve to evaluate diagnostic precision for each flow parameter is shown in Table 4.

Discussion

Various studies have been published revealing significantly reduced retrobulbar blood flow velocities in NTG compared to healthy controls.[13–19] A reduction of

Table 1 Clinical data of patients with NTG and controls (mean ± SD)

	NTG (n = *62*)	*Controls* (n = *40*)	P-*value*
Age (years)	57 ± 14	58 ± 9	0.88
Sex (males/females)	23/39	16/24	0.84
Mean defect (dB)	−5.3 ± 4.5	−0.8 ± 1.5	<0.0001
PSD dB	6.5 ± 4.3	1.9 ± 0.6	<0.0001
IOP (mmHg)	16.2 ± 2.6	15.7 ± 2.9	0.33
Systolic blood pressure (mmHg)	127 ± 17	134 ± 22	0.12
Diastolic blood pressure (mmHg)	76 ± 10	78 ± 12	0.56
Heart rate (beats/min)	73 ± 12	70 ± 12	0.36
Spherical equivalent (D)	0.2 ± 2.0	−0.1 ± 1.9	0.54

Abbreviations: NTG, normal tension glaucoma; IOP, intraocular pressure; PSD, pattern SD.

Table 2 Flow velocities and resistive indices of the OA, CRA, and nasal and temporal PCAs (mean ± SD) with corresponding *P*-values

	NTG (n = *62*)	*Controls* (n = *40*)	P-*value*
OA PSV (cm/s)	30.8 ± 8.8	32.8 ± 9.1	0.27
OA EDV (cm/s)	7.8 ± 3.2	7.4 ± 3.5	0.40
OA RI	0.75 ± 0.07	0.78 ± 0.07	0.03
CRA PSV (cm/s)	7.6 ± 1.8	9.3 ± 1.9	<0.0001
CRA EDV (cm/s)	2.0 ± 0.9	2.9 ± 0.9	<0.0001
CRA RI	0.74 ± 0.09	0.69 ± 0.06	0.007
TPCA PSV (cm/s)	7.3 ± 2.3	7.5 ± 1.7	0.26
TPCA EDV (cm/s)	2.3 ± 1.0	2.8 ± 0.7	0.002
TPCA RI	0.69 ± 0.1	0.62 ± 0.07	0.003
NPCA PSV (cm/s)	6.9 ± 1.5	7.6 ± 1.8	0.07
NPCA EDV (cm/s)	2.2 ± 0.9	2.7 ± 0.7	0.004
NPCA RI	0.69 ± 0.09	0.63 ± 0.07	0.01

Abbreviations: CRA, central retinal artery; EDV, end-diastolic velocity; NTG, normal tension glaucoma; OA, ophthalmic artery; PSV, peak systolic velocity; RI, resistive indices; TPCA and NPCA; temporal and nasal posterior ciliary arteries.

Table 3 Sensitivity values at fixed 90% specificity of the different retrobulbar flow velocities

	Sensitivity (%) (95% confidence interval)	*Criterion*	*Controls (n = 40)*
OA PSV	11.3; (4.7–21.9)	$\leqslant$19.6 cm/s	32.8 $\pm$ 9.1
OA EDV	6.5; (1.8–15.7)	$>$13.2 cm/s	7.4 $\pm$ 3.5
OA RI	11.3; (4.7–21.9)	$\leqslant$0.67	0.78 $\pm$ 0.07
CRA PSV	30.6; (19.6–43.7)	$\leqslant$6.6 cm/s	9.3 $\pm$ 1.9
CRA EDV	48.4; (35.5–61.4)	$\leqslant$1.8 cm/s	2.9 $\pm$ 0.9
CRA RI	37.1; (25.2–50.3)	$>$0.78	0.69 $\pm$ 0.06
TPCA PSV	14.8; (7.0–26.2)	$\leqslant$5.2 cm/s	7.5 $\pm$ 1.7
TPCA EDV	45.9; (33.1–59.1)	$\leqslant$2.1	2.8 $\pm$ 0.7
TPCA RI	39.3; (27.1–52.7)	$>$0.71	0.62 $\pm$ 0.07
NPCA PSV	28.1; (17.0–41.5)	$\leqslant$5.8 cm/s	7.6 $\pm$ 1.8
NPCA EDV	43.9; (30.7–57.6)	$\leqslant$1.8 cm/s	2.7 $\pm$ 0.7
NPCA RI	43.9; (30.7–57.6)	$>$0.72	0.63 $\pm$ 0.07

Abbreviations: CRA, central retinal artery; EDV, end-diastolic velocity; NTG, normal tension glaucoma; OA, ophthalmic artery; PSV, peak systolic velocity; RI, resistive indices; TPCA and NPCA, temporal and nasal posterior ciliary arteries.
The cutoff criterion for each parameter is given. The reference data of the control subjects are presented (mean $\pm$ SD).
Retrobulbar flow parameters of the controls subjects are presented to relate the criterion level to the normative data.

Table 4 The area under the ROC curve and 95% confidence interval for retrobulbar hemodynamics in NTG and controls

	Area under ROC	*95% confidence interval*
OA PSV	0.56	0.46–0.66
OA EDV	0.55	0.45–0.65
OA RI	0.63	0.53–0.72
CRA PSV	0.74	0.64–0.82
CRA EDV	0.75	0.66–0.83
CRA RI	0.66	0.56–0.75
TPCA PSV	0.57	0.46–0.67
TPCA EDV	0.68	0.58–0.77
TPCA RI	0.68	0.58–0.77
NPCA PSV	0.61	0.51–0.71
NPCA EDV	0.68	0.57–0.77
NPCA RI	0.66	0.55–0.75

Abbreviations: CRA, central retinal artery; EDV, end-diastolic velocity; NTG, normal tension glaucoma; OA, ophthalmic artery; PSV, peak systolic velocity; RI, resistive indices; ROC, receiver operating characteristics; TPCA and NPCA, temporal and nasal posterior ciliary arteries.

blood flow velocities in NTG might represent a significant pathogenic factor in the disease pathophysiology.

The presented study confirms reduced peak systolic and end-diastolic blood flow velocities of the CRA and reduced EDVs of the nasal and temporal PCAs in NTG patients compared to healthy controls. Further, the RI of the temporal PCAs were significantly increased in NTG suggesting increased vascular resistance. Simultaneous reductions of PSV and EDV of the CRA may be interpreted as reduced volumetric flow in this vessel.[27] Blood flow in the CRA is relevant for retinal haemodynamics enclosing the ganglion cell layer that is the site of damage in glaucomatous optic neuropathy. A previous study emphasizes the correlation between neuroretinal rim loss and CRA flow velocities in glaucoma.[28] The peripheral vascular resistance related to decreased flow velocities was higher in NTG patients in the presented study, but did not reach significance. In addition, the EDVs are thought to be more sensitive for changes in haemodynamics than the PSVs.[29] This could explain the results we found for the PCAs. In the present study, no significant differences for the flow parameters of the OA could be detected. Conflicting results were also reported in previous studies suggesting decreased flow velocities, as well as unaltered or even higher flow values in glaucoma.[13–19,30,31] The OA represents the major orbital vessel and only a minor part of its blood flow reaches the optic nerve and the retina, which could explain the lack of specificity of this vessel for NTG patients in the present study.

Although differences were found for various colour Doppler imaging parameters, a considerable overlap of reduced blood flow velocities of retrobulbar vessels between patients with NTG and healthy controls is apparent even for the parameters that were significantly different. Therefore, this study investigated the diagnostic power of CDI analysis to reveal NTG patients. In the present study, the sensitivity at 90% specificity to detect NTG patients with CDI did not exceed the level of 48% sensitivity. At 90% specificity, PSV, EDV of the CRA, EDV of the nasal and temporal PCAs and RI of the temporal PCAs are significantly different between groups exhibiting sensitivities between 30.6 and 48.4% (Table 3). The ROC curves describing the diagnostic performance of the parameters are presented in Figure 1.

Sensitivity of CDI in glaucomatous optic neuropathy is influenced by inter-individual variability of ocular haemodynamics in healthy and diseased eyes, as well as by the reproducibility of the analysis method. The between- and within-subject variability of CDI measurements has been reported to be higher in the short

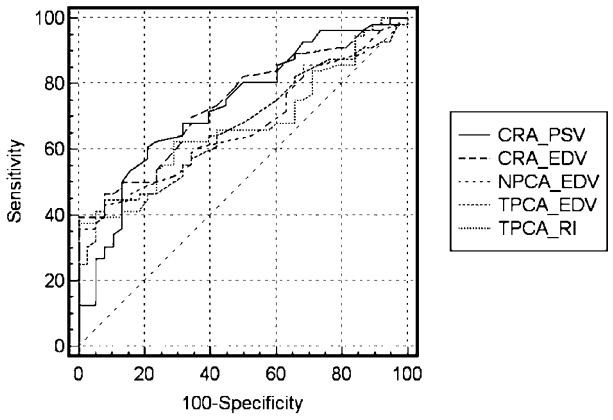

Figure 1 Receiver operating characteristic (ROC) curves of, PSV, and EDV of the CRA, EDV of the NPCA, and EDV and RI of the TPCA in NTG and controls.

PCAs compared to the OA and the CRA, while the variability of the RI is lower compared to the PSV and EDV in all retrobulbar vessels.[24,32] The EDV of all vessels shows high variability, likely due to the low blood flow velocities at the end of the diastolic phase in the small retrobulbar vessels.[24,33] Furthermore, individual variability of ocular haemodynamics may be influenced by individual habits, systemic vascular disease, autoregulatory capacity of retrobulbar vessels, and many other factors limiting standardization. Systemic vascular risk factors, eg arterial hypotension or systemic vascular dysregulation,[6,10] may contribute to the vascular aetiology of glaucoma and have a certain impact on ocular blood flow. In our study, we did not perform an analysis to detect the diagnostic performance in subgroups of patients with different vascular risk factors. Owing the heterogenity of systemic vascular disease and other confounding factors, such an analysis should be preserved for large-scaled multicentre studies.

The presented data suggest that retrobulbar flow velocities should probably not be considered as a diagnostic criterion for glaucomatous optic neuropathy in a clinical setting. For comparison, the detection of glaucoma using optic disc analysis aims to reveal changes of the optic disc as being key criteria for glaucoma diagnosis. Harizman *et al*[34] recently published a study that evaluates the sensitivity of the Heidelberg Retina Tomograph III to detect glaucomatous optic disc damage in perimetric glaucoma. Sensitivity of the Moorfields regression analysis was 71.4 at 91.9% specificity. However, in early glaucoma (ie MD <5 dB), sensitivity decreased to 59.6%. The patients included in our study also showed only early to moderate visual field loss with an average visual field MD of -5.3 ± 4.5 dB (Table 1). We recently investigated the diagnostic power of fluorescein angiography to detect fluorescein-filling defects of the optic nerve head in glaucoma. The presence of fluorescein-filling defects of the optic disc exhibits a sensitivity of 65 at 90% specificity. An arbitrary threshold of 5% fluorescein-filling defects in relation to the optic disc area reached a specificity of 100% to detect patients with NTG at 52.5% sensitivity. The average visual field MD was -7.8 ± 7.1 dB in that study.[11] Therefore, the sensitivity reaching 48% to detect NTG seems too low to consider CDI as a diagnostic tool to distinguish glaucoma from normal.

However, the Doppler measurements could be relevant for risk factor evaluation in patients with NTG. In 1997, Yamazaki and Drance performed a retrospective study showing patients with progressive NTG exhibit lower blood flow velocities of the CRA and PCA compared to patients with stable visual fields. The CDI measurements were performed at the final visual field examination after a follow-up of 5 years.[35] Galassi *et al*[31] published similar results in 2003 in a prospective study. Patients with progressive primary open-angle glaucoma (POAG) exhibited significantly lower EDV and increased RI of the OA compared to patients with stable visual fields. Satilmis *et al*[36] found patients with progressive POAG to have EDV of the CRA inversely correlated to the rate of progression of the visual field MD. Martinez and Sanchez prospectively investigated the prognostic value of CDI of the OA and PCA in a 3-year follow-up study in POAG patients. The risk of future progression increased with higher RI in the OA and short PCAs. In this analysis, a cutoff value of 0.72 for the RI of the OA and 0.65 for the RI of the PCAs was applied.[37] These studies suggest a potential role of CDI as a prognostic marker in glaucoma. In addition, patients with glaucoma undergoing trabeculectomy showed a significant increase in retrobulbar blood flow velocities.[38] Despite such promising studies, data on long-term fluctuations of CDI measurements in glaucoma are still missing. These long-term studies on CDI in glaucoma are crucial to identify the potential relevance for CDI measurements in the evaluation of an individually increased risk for future glaucoma progression.

In summary, assessing retrobulbar haemodynamics may discriminate patients with NTG from healthy controls with sensitivity up to 48% at 90% specificity. The validity of retrobulbar haemodynamics to identify patients at higher risk for progression in glaucoma needs further evaluation in prospective longitudinal studies.

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