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Feasibility of MRI to assess differences in ophthalmic artery blood flow rate in normal tension glaucoma and healthy controls

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ABSTRACT.

Purpose: **To examine feasibility of phase-contrast magnetic resonance imaging (PCMRI) and to assess blood flow rate in the ophthalmic artery (OA) in patients with normal tension glaucoma (NTG) compared with healthy controls.**

Methods: **Sixteen patients with treated NTG and 16 age- and sex-matched healthy controls underwent PCMRI using a 3-Tesla scanner and ophthalmological examinations. OA blood flow rate was measured using a 2D PCMRI sequence with a spatial resolution of 0.35 mm^2.**

Results: **The blood flow rate in the NTG group was 9.6 ± 3.9 ml/min [mean ± SD] compared with 11.9 ± 4.8 ml/min in the control group. Resistance Index (RI) and Pulsatility Index (PI) were 0.73 ± 0.08 and 1.36 ± 0.29, respectively, in the NTG group and 0.68 ± 0.13 and 1.22 ± 0.40, respectively, in the healthy group. The mean visual field index (VFI) was 46% ± 25 for the worse NTG eyes. The measured differences observed between the NTG group and the control group in blood flow rate ($p = 0.12$), RI ($p = 0.18$) and PI ($p = 0.27$) were non-significant.**

Conclusions: **This case–control study, using PCMRI, showed a slight, but non-significant, reduction in OA blood flow rate in the NTG patients compared with the healthy controls. These results indicate that blood flow may be of importance in the pathogenesis of NTG. Considering that only a limited portion of the total OA blood flow supplies the ocular system and the large inter-individual differences, a larger study or more advanced PCMRI technique might give the answer.**

Key words: blood flow – glaucoma – magnetic resonance imaging – normal tension glaucoma – ophthalmic artery

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Introduction

Glaucoma is a progressive optic neuropathy and a leading cause of irreversible blindness worldwide. (Quigley 2011; Tham et al. 2014) The disease is characterized by retinal ganglion cell loss and visual field damage. Elevated intraocular pressure (IOP) was originally thought to be the pathogenesis of the disease, but it is now rather seen as a risk factor, since many individuals sustain increased IOP for years and never develop glaucomatous damage.

At the other end of the spectrum, normal tension glaucoma (NTG) refers to patients with normal IOP who still exhibit the traditional signs of glaucomatous damage in terms of structural and functional nerve fibre damage. The pathophysiology of NTG is not fully understood. It has been indicated that NTG pathophysiology differs from that of high tension glaucoma (Butt et al. 1997) and vascular factors have been proposed to be a major component (Fechtner and Robert, 1994). Studies have suggested a link between NTG and risk factors such as low systemic blood pressure (Leske et al. 2008; Nesher et al. 2012), vascular dysregulation and vasospasm (Harris et al. 1994; Broadway & Drance 1998; Galassi et al. 2011), migraines (Wang et al. 1997) and gender (Mozaffarieh & Flammer 2013). In several of these conditions, abnormal blood flow is

proposed as the pathogenesis, further enhancing the suspicion of a blood flow-related cause. In comparison with healthy subjects, increased vascular resistance (Harris et al. 1994) and decreased autoregulation (Harris et al. 2003) further support the role of vascular insufficience in the pathogenesis of NTG. Thus, it is of great interest to investigate the blood flow rate to the eye in NTG.

The main blood supply to the eye is provided by the ophthalmic artery (OA), which is the first branch of the internal carotid artery (Sobotta et al. 2001; Michalinos et al. 2015). However, individual anatomical variations exist (Hayreh 2006). The OA exhibits a pulsatile flow and that flow supplies the retinal artery and ciliary arteries (Sobotta et al. 2001). The OA flow affects the IOP (Silver et al. 1989). The current gold standard for assessing flow in retrobulbar vessels is colour Doppler imaging (CDI), though the method measures flow velocities and is unable to measure volumetric blood flow rate (Stalmans et al. 2011; Harris et al. 2020). Previous studies of glaucoma patients utilizing this technique have found lower flow velocities in the OA of NTG patients (Galassi et al. 1994; Kaiser et al. 1997; Harris et al. 2007; Galassi et al. 2011; Abegao Pinto et al. 2016) as well as higher vascular peripheral resistance, although contradictory studies exist (Samsudin et al. 2016). An important weakness of the traditional approach with CDI is the approximation of blood flow from velocity (Hansen et al. 1983; Meng et al. 2013). Methods that can adequately measure the blood flow rate are thus warranted to further investigate its role in NTG.

Phase-contrast magnetic resonance imaging (PCMRI) is a method for measuring blood flow rate (Moran 1982; Enzmann et al. 1994), which is well-established for cardiac applications (Hom et al. 2008) and measurements in larger intracranial blood vessels (Enzmann et al. 1994; Zarrinkoob et al. 2016) It has also been demonstrated that PCMRI can be used to quantify blood flow rate in small vessels such as the OA in healthy individuals (Ambarki et al. 2013), suggesting that it could be a useful method for investigating the potentially altered blood flow rate in NTG. Therefore, the main objective of this case–control study was to investigate the feasibility of using PCMRI to assess and characterize the blood flow rate of OA in NTG patients in comparison with healthy controls.

Materials and Methods

This prospective single-centre study measured the blood flow rate in the OA of patients with NTG and age- and sex-matched healthy subjects. The study was approved by the Regional Ethical Review Board at Umeå University, Umeå, Sweden, and was performed in accordance with the Declaration of Helsinki. All participants received oral and written information about the study before they gave their written consent to participate.

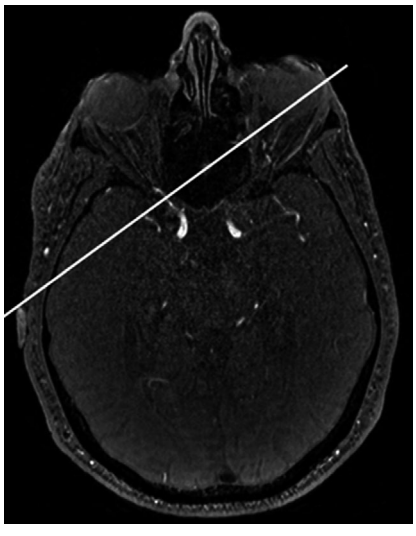

Fig 1. Cross-sectional segment visualizing the OA and the plane selected for measurements

Measurement protocol

Participants underwent MRI of the brain with a 3-Tesla scanner (GE Discovery MR750; General Electric Healthcare, Waukesha, WI, USA) with a 32-channel head coil. The MRI measurements followed the protocol as detailed in Ambarki et al. (2013) In summary, a 3D time-of-flight (3DTOF) MR angiography sequence was performed and used to locate the OA. Flow was measured using a 2D PCMRI sequence with a 3 mm imaging slice with in-plane resolution of 0.35×0.35 mm^2. The imaging plane was placed perpendicular to the vessel ~10 mm distal of its bifurcation from the internal carotid artery (Figure 1) as this segment is straight and far from the root of the OA branch, and thus likely to be free of turbulence. This specific location was chosen for the straightness of this segment and to avoid close proximity to air-filled sinuses. The MRI sequence parameters were as follows: velocity encoding 35 cm/s, TR/TE 9/5 ms, flip angle 15°, acquisition matrix 512×512, field of view 180×180 mm, six views per segment and two signal averages. Retrospective cardiac gating was applied using a peripheral pulse detector, and 32 magnitude and phase image pairs were reconstructed that represent a complete cardiac cycle. The images were quality checked at the scanner, and 10 out of 64 arteries were immediately rescanned at the same examination (motion artefacts, signal void due to susceptibility or misaligned image planes).

Ophthalmological examinations were performed on the same day as MRI. These included measurements of IOP with Goldmann's applanation tonometer and corneal biomechanical properties with Ocular Response Analyzer (Reichert Ophthalmic Instruments, Inc., Buffalo, NY, USA). Best corrected visual acuity was also assessed. Furthermore, blood pressure of each subject was measured in sitting position on the day of MRI examination. These data were used to calculate ocular perfusion pressure (OPP) using the supine formula (Liu et al. 2003; Harris et al. 2020) for comparison with blood flow measurements during the MRI sequence as 115/130*MAP – IOP, where MAP was defined as diastolic blood pressure + 1/3*(systolic blood pressure – diastolic blood pressure).

Participants

Charts of all patients diagnosed with NTG at the Department of Ophthalmology, Umeå University Hospital, Umeå, Sweden, were reviewed. To be included the patients were required to have uni- or bilateral NTG with optic nerve head damage and corresponding visual field defects measured with Humphrey Field Analyzer HT 24-2 (Carl Zeiss Meditec AG, Jena, Germany). Exclusion criteria were neurological disease, previous intracranial surgery, coronary heart disease and

previous ocular surgery in the examined eye except for cataract extraction. Patients thought to fulfil these criteria were consecutively contacted by phone and invited to participate. Twenty-five patients accepted the invitation. All examined eyes were treated with IOP-lowering topical substances (median n = 3, range 1–4). After examination, nine patients were excluded due to the following reasons: circulatory disease disorders (n = 3), misclassification (n = 4), previous stroke (n = 1) and claustrophobia preventing MRI examination (n = 1). Thus, a total of 16 patients (ten women and six men) with NTG were analysed.

Lists with age- and sex-matched inhabitants in Umeå were obtained from Statistics Sweden. Subjects from the list were contacted by phone, invited to a screening visit and included for further examination if the inclusion and exclusion criteria were met. At the screening visit, the subjects underwent a comprehensive ophthalmological examination including best corrected visual acuity, tonometry, fundoscopy and ocular coherence tomography (OCT) of the optic nerve head using Topcon 3D OCT 2000 (Topcon Corporation, Tokyo, Japan). The exclusion criteria for control subjects were the same as for the glaucoma patients.

PCMRI analysis

PCMRI data were exported and analysed using the freely available software Segment version 1.8 (http://medviso.com/segment/) (Heiberg et al. 2010). The OsiriX Lite 9 software was used to confirm if the sequence corresponded to the left or right OA and to locate the OA in cases of unclear position in the phase-contrast image. To measure the flow using Segment, a region of interest (ROI) was manually drawn around the vessel in the magnitude images and corrected if necessary with the aid of the phase images. The ROI was kept constant during the entire cardiac cycle. The data contained in the phase images correspond to velocity. For each time frame of the cardiac cycle, the flow rate was obtained by integrating the velocity values across the area defined by the ROI. The ROI area was also stored. Before integration, the flow velocities were adjusted for eddy currents using the automated tool provided in the software for this purpose.

Three measurements (one NTG and two healthy subjects) were excluded, one due to low image quality and two because of non-perpendicular image planes. In these subjects the other eye was used for analysis. The OA was compared with the middle cerebral artery in terms of flow direction to exclude reversed blood flow as seen in certain patient groups (Schneider et al. 1991). However, the flow was congruent in all cases indicating no reversed flow in any of the subjects.

Each scan was de-identified and analysed by the same researcher twice, two weeks apart, and the results were averaged.

Blood flow parameters

OA blood flow rate was defined as the mean flow rate during the cardiac cycle (i.e. mean of the 32 time frames). The highest measured blood flow rate during the cardiac cycle was denoted as peak systolic flow (PSF) and lowest as minimum diastolic flow (MDF). Three additional parameters were calculated for each OA:

1 Pulsatility index (PI) = (PSF – MDF)/ mean blood flow rate.
2 Resistance index (RI) = (PSF – MDF)/ MDF.
3 Peak Systolic Velocity (PSV) as defined by the pixel in the ROI with the highest velocity measured during systole.

Inter-observer correlations

In order to validate and explore inter-observer differences in the measuring technique, nine additional subjects that had been previously scanned with an identical MRI protocol were examined and analysed by three different blinded researchers independently prior to the analysis of the included subjects in the current study.

Statistical analyses

All statistical calculations were performed in IBM SPSS version 25. Statistical significance was defined as $p < 0.05$. A power calculation assuming a blood flow difference in NTG to be 4.5 ml/min with a standard deviation of 5 ml/min and an attrition rate of 20% estimated the sample size to 25 per group. Tests of normality were performed using the Kolmogorov–Smirnov test. Parameters with normal distribution were examined using two-sided Student's t-test for independent samples, and other parameters were tested using non-parametric Mann–Whitney *U*-tests. Correlations were calculated using Pearson's correlation. Inter-observer correlations were calculated using a one-way random model for intra-class correlation coefficients and evaluated according to existing methods (Cicchetti 1994).

The eye with the highest degree of glaucomatous damage, as defined by visual field index (VFI), was used for the analysis in the NTG group. In one case, no measurement of the most damaged eye was available, and therefore the other eye, which also had glaucomatous damage, was then chosen for comparison. For the control group, the average blood flow rate of both eyes was used. In two cases in the control group, PCMRI measurements were only available in one eye (one left eye and one right eye) due to low image quality; thus, only the available high-quality measurements were included for analyses.

Results

Sixteen patients with NTG and 16 healthy age- and sex-matched control subjects were analysed. The characteristics of the two groups are shown in Table 1. The mean VFI of the NTG patients was 46% (SD ± 25%) in the analysed eye.

The blood flow results are presented in Table 2, and the average blood flow rate waveform over the cardiac cycle for the two groups are shown in Figure 2. There was a tendency towards lower blood flow rate in the NTG group, but the difference was not statistically significant ($p = 0.12$). There was also a tendency towards reduction in blood flow rate of the worse eye compared with the better eye in the NTG patients ($p = 0.14$). The blood flow rate was correlated between the right and left eye in the same person (Pearson correlation 0.71) in NTG subjects. The inter-observer analysis between the three masked researchers showed high intra-class correlation of 0.92 (95% CI 0.84–0.96, p-value < 0.01).

Table 1. Descriptive statistics of normal tension glaucoma (NTG) patients and healthy control subjects

Descriptives	NTG (n = 16)	Healthy (n = 16)	p-value
Female/male	6/10	6/10	1.0
Age [years]	69 ± 9	71 ± 9	0.72
Visual acuity [logMAR]	0.08	0.01	0.06
Systolic blood pressure [mmHg]	156 ± 22	161 ± 28	0.56
Diastolic blood pressure [mmHg]	85 ± 10	90 ± 10	0.11
Ocular perfusion pressure [mmHg]	82 ± 10	87 ± 14	0.30
Hypertensive substances	0.8 ± 1.1	0.4 ± 0.7	0.34
Corneal hysteresis [mmHg]	8.6 ± 1.4	10.2 ± 1.1	0.01
Corneal resistance factor	8.2 ± 1.3	10.0 ± 1.2	0.01
Goldmann intraocular pressure [mmHg]	13.8 ± 2.4	13.8 ± 2.1	0.97

Table 2. Ophthalmic artery blood flow measurements in normal tension glaucoma (NTG) patients and healthy control subjects

	NTG (n = 16)		Healthy (n = 16)		
Blood flow parameters	Mean	Range	Mean	Range	p-value
Blood flow [ml/min]	9.6 ± 3.9	5.6–16.8	11.9 ± 4.8	6.0–24.0	0.12
Resistance index (RI)	0.73 ± 0.08	0.52–0.88	0.68 ± 0.13	0.42–0.86	0.18
Pulsatility index (PI)	1.36 ± 0.28	0.77–2.04	1.22 ± 0.40	0.52–1.82	0.27
Peak Systolic Velocity [cm/s]	29.2 ± 10.2	17.8–54.5	28.0 ± 7.4	16.3–43.4	0.96
Vessel area [mm^2]	1.68 ± 0.35	1.24–2.23	1.94 ± 0.51	1.40–3.37	0.22

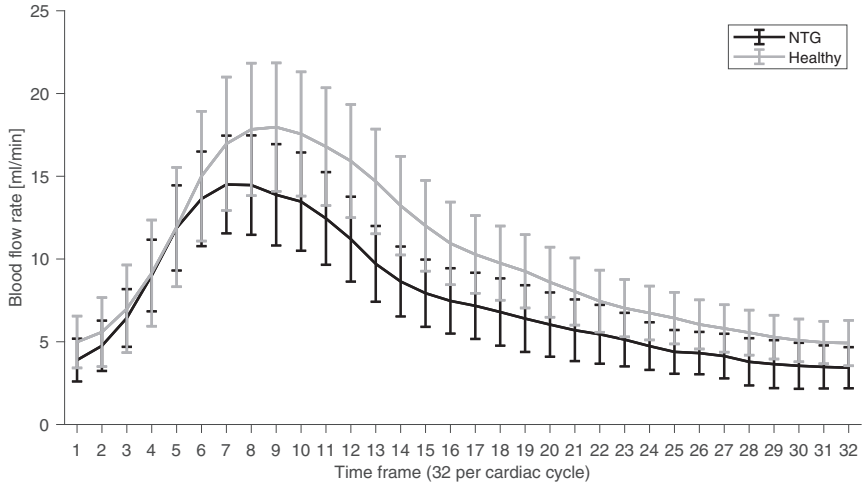

Fig 2. The figure shows the average waveform curves of the flow rate in the OA during 32 phases of the cardiac cycle in subjects with normal tension glaucoma (NTG) (n = 16) and healthy control subjects (n = 16). The error bars describe 95% CI for the mean, calculated as $2SD/\sqrt{n}$

Discussion

This is the first study to present PCMRI-derived volumetric blood flow rate measurements in the ophthalmic artery in NTG patients. The ophthalmic artery is the main supplier of blood to the eye, but it is important to keep in mind that the eye is not the sole receiver of blood from the artery. More specifically, only a small portion of the blood volume in the ophthalmic artery goes to the ocular system through the central retinal artery and the ciliary arteries (Michalinos et al. 2015). A considerable portion of the blood flow is passed on to extraocular tissue surrounding the eye, tissues that are expected to have similar perfusion in both NTG subjects and healthy. While we found a tendency towards lower blood flow rate, approx. 2.3 ml/min lower, in NTG patients than in age- and sex-matched healthy control subjects, this difference did not reach statistical significance ($p = 0.12$; [$p = 0.06$ in a one-sided test]). However, any reduction in blood flow rate of NTG patients should be related to compromised blood flow to the choroidal and retinal structures. According to Williamson and Harris (1994), the ocular blood flow rate may be as low as 1 ml/min. We performed calculations using previously reported data on flow (Kaiser et al. 1997), vessel area and number of OA branches (Michalinos et al. 2015) supplying the eye, which indicate that approximately 15–20% of the OA blood flow goes to the ciliary and retinal arteries. This would lead to an estimated ocular blood flow rate in the range of 1.5–2 ml/min. Thus, in the same range as the reduction indicated in NTG patients in this study. In light of this, one could argue that the assumption behind this study of 4.5 ml/min difference could be considered too high implicating that the study was underpowered. Despite that, with a one-sided test, the difference of 2.3 ml/min was borderline significant, and thus, if a difference is confirmed in an adequately powered study, it would be of major relevance since it would support ocular hypoperfusion in the NTG pathophysiology.

The results show a large inter-individual variation in blood flow rate in both groups, which may be partly explained by the anastomotic connection between the ophthalmic artery and the external carotid circulation (Kaufman et al. 2003). An important aspect to note is that while the blood flow rate varied greatly between different subjects, the results correlated strongly between the right and left eye in the same subject (Pearson correlation coefficient 0.71, $p < 0.01$). This would indicate that the main source of variability of the blood flow rate was inter-individual and may be explained by differences in body size, general vascular status, personal anatomy of the vessels or cardiac output, rather than an effect from carotid or other stenoses which are known to recruit asymmetric collateral blood flow in the ophthalmic artery (Zarrinkoob et al. 2019).

Comparison to previously published studies on OA measurements in NTG subjects is challenging as most of these

(Harris et al. 1994; Butt et al. 1997; Kaiser et al. 1997; Stalmans et al. 2011; Nesher et al. 2012; Abegao Pinto et al. 2016; Samsudin et al. 2016) are based on CDI, which measures blood flow velocity in contrast to volumetric blood flow rate. However, some of the measured parameters with PCMRI can be compared with the CDI technique. Peripheral vascular resistance measured as RI and PI were analysed since they are well-documented parameters in ocular blood flow assessment (Harris et al. 2020) and have been shown to be altered with CDI in glaucoma (Harris et al. 1994; Martinez & Sanchez 2005; Plange et al. 2009; Abegao Pinto et al. 2016) as well as in other diseases with suspected vascular dysregulation such as migraine (Chernyshev et al. 2001). We did not find a significant difference in RI or PI between NTG patients and healthy subjects. This is in line with results reported by Butt et al. (1997) and Samsudin et al. (2016) but in contrast to findings reported by others (Harris et al. 1994; Butt et al. 1997; Plange et al. 2009; Galassi et al. 2011; Abegao Pinto et al. 2016). The ambiguity may reflect study size but also the problem of large inter-individual variability, again stemming from the ophthalmic artery being an anastomosis and thus not an end artery with a well-defined vascular resistance.

The same phenomenon is also reflected in the peak flow velocity analysis. In our material, there was no difference in PSV between the groups. This is in line with results reported by Samsudin et al. (2016) and Butt et al. (1997) but in contrast to several studies on NTG patients with CDI, which have demonstrated lower peak flow velocities in the OA of NTG patients (Harris et al. 1994; Galassi et al. 2011; Abegao Pinto et al. 2016). Although Plange et al. (2009) did not find lower flow velocities in OA, this was found in other ocular vessels in NTG subjects. Despite the methodological differences between CDI and PCMRI, the observed values appear similar. Earlier studies have proposed the involvement of OPP (ocular perfusion pressure) as a possible cause for glaucomatous damage in NTG (Leske 2009; Costa et al. 2014), but we found no significant differences between the groups possibly due to sample size. Both groups had a similar profile in terms of hypertensive treatment.

PCMRI is a well-established method for measurements of blood flow rate in larger vessels (Enzmann et al. 1993; Enzmann et al. 1994), and we have previously shown that the PCMRI methodology can also be used to measure blood flow rate in smaller vessels such as the ophthalmic artery (Ambarki et al. 2013). The blood flow results from the healthy group in the current study show similar values and blood flow profiles as those reported for an elderly healthy group by Ambarki et al. (2013), thus validating the stability of the methodology. Furthermore, the independent analysis of different blinded researchers revealed good intra-class correlations, further supporting the strength of the methodology.

To further test the hypothesis of reduced ocular blood flow rate in NTG patients, we propose two possible study designs. Firstly, based on the findings of this pilot study, where we found a mean difference of 2.3 ml/min between the groups and large inter-individual variability, we estimate that a study design with 60 subjects in each group would be needed if the same measurement technique and protocol were used assuming a standard deviation of 4.5 ml/min. Secondly, and preferably, a direct measurement of the central retinal artery and/or the ciliary arteries' trunks would provide a more precise measurement. These are end vessels that do not anastomose with the external carotid circulation. Thus, all their blood flow is conveyed to the ocular system. Measurements of blood flow rate in these arteries would therefore be more directly associated with the functional damage in glaucoma. Measurements in these small arteries could be possible with even more advanced MRI technique with better resolution. Results from a recent publication evaluating 7-Tesla PCMRI (Markenroth Bloch et al. 2018) indicate that the technique might enable a resolution of 0.2×0.2 mm^2, that is improving the current resolution by a factor of three. Hence, it is possible that the 7-Tesla PCMRI could be used to measure blood flow rate in the above-mentioned smaller ocular branches from the OA, which have a diameter up to 0.6–0.7 mm (Michalinos et al. 2015).

A limitation of this study is that the NTG group was receiving IOP-lowering treatment with eye drops. Intriguingly, there was no difference between the groups in either IOP or blood pressure at the time of examination, which indicates that these factors should have affected the PCMRI blood flow measurements equally in both groups. A potential limitation of the PCMRI technique is partial volume errors, which may lead to overestimated blood flow rates. To minimize such effects, we maximized the spatial resolution so that a typical OA, with a diameter of 1.5 mm (Lang & Kageyama 1990; Michalinos et al. 2015), corresponded to 4-5 pixels, which should keep overestimations below 10% according to earlier findings (Wahlin et al. 2012). To improve the signal-to-noise ratio at this high resolution, averaging of two separate excitations (NEX = 2) was utilized; this was deemed a sufficient number of averages based on visual inspection of pilot scans. The biomechanical measurements show a lower corneal hysteresis in the NTG group than in the healthy group. This is in accordance with previously published literature (Shah et al. 2008) indicating that the included NTG patients indeed have a typical NTG phenotype. A strength of this study is the age- and sex-matched control group, hence minimizing these potentially important confounding factors.

In conclusion, this study assessed the feasibility of using the PCMRI technique to study if blood flow rate in the OA of NTG patients is reduced compared with healthy controls. The study showed a tendency towards a lower blood flow rate in NTG, although not significant. Furthermore, it revealed a large inter-individual variability. To detect a difference of 2–3 ml/min between the groups as indicated in this study, approximately 60 subjects in each group would be required. Given such a study design, using the 3-Tesla PCMRI methodology to answer if blood flow rate is reduced in NTG patients is likely to be feasible. An alternative and more intriguing approach would be to utilize the more powerful 7-Tesla PCMRI technology for measurements of the central retinal and posterior ciliary arteries. Although OA blood flow rate is interesting for investigating potential hypoperfusion in glaucoma on a group level, in clinical care the measurements are of limited value due to effects of

extraocular inter-individual blood flow variability in the OA.

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