

# Prolonged retinal arteriovenous passage time is correlated to ocular perfusion pressure in normal tension glaucoma

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## Abstract

**Background** The pathogenesis of normal tension glaucoma (NTG) might be related to impaired autoregulation of ocular blood flow. The purpose of the study is to evaluate retinal haemodynamics by fluorescein angiography and to correlate arteriovenous passage times (AVP) with ocular perfusion pressure in patients with NTG and controls.

**Methods** Thirty-five patients with NTG without any topical treatment (mean age  $53 \pm 11$  years) and 35 age-matched controls (mean age  $53 \pm 11$  years) were included in this study. Retinal AVP was assessed by video fluorescein angiography using a scanning laser ophthalmoscope (Rodenstock, Germany). Dye dilution curves of temporal superior and inferior arterioles and venules were evaluated by digital image analysis. AVP was correlated to mean arterial blood pressure and ocular perfusion pressure.

**Results** The AVP was significantly prolonged in patients with NTG compared to controls ( $1.82 \pm 0.57$  versus  $1.42 \pm 0.46$ ,  $p=0.002$ ). Patients with NTG and controls showed no significant differences in intraocular pressure, mean arterial pressure and mean and diastolic ocular perfusion pressure. The AVP was significantly correlated to mean arterial pressure and mean and diastolic ocular perfusion pressure in patients with NTG ( $r=-0.54$ ;  $p=0.0006$ ,  $r=-0.51$ ;  $p=0.002$ ,  $r=-0.49$ ,  $p=0.002$ ), but not in controls ( $r=-0.21$ ;  $p=0.23$ ,  $r=-0.19$ ;  $p=0.27$ ,  $r=0.02$ ,  $p=0.93$ ).

**Conclusions** Patients with NTG exhibit prolonged retinal AVP compared to controls. A significant correlation of retinal haemodynamics to mean arterial blood pressure and ocular perfusion pressure might reflect impaired autoregulation in NTG.

**Keywords** Normal tension glaucoma · Ocular blood flow · Arteriovenous passage time · Ocular perfusion pressure · Autoregulation

## Introduction

Disorders of ocular haemodynamics are a major factor in the pathogenesis of glaucomatous optic neuropathy [1–4]. The arteriovenous passage time (AVP), characterizing retinal haemodynamics, may be determined by fluorescein angiography. The retinal AVP represents the shortest passage time from the first influx of fluorescein dye in retinal arterioles to the first arrival in corresponding retinal venules passing retinal microcirculation [5, 6]. Previous studies have shown that the measurement of AVP is reproducible and prolonged in ischemic retinal disease and glaucoma [1, 7–11]. In asymmetric glaucomatous visual field loss, the AVP is significantly prolonged in the hemifield with the larger visual field defect, suggesting a link between retinal haemodynamics and visual function in glaucoma [12].

In healthy subjects, retinal blood flow is autoregulated to provide a constant blood flow regardless of changes in ocular perfusion pressure [13–18]. Endothelium derived vasoactive agents and pericyte contractility are important actors of local blood flow regulation, as well as smooth muscle cells of blood vessels and vessel anatomy. The mechanisms of blood-flow autoregulation are only effective

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in a certain range of perfusion pressure [19–21]. Ocular perfusion pressure is determined by systemic blood pressure and intraocular pressure (IOP). Decreased ocular perfusion pressure due to high IOP or low arterial blood pressure might result in decreased ocular haemodynamics if autoregulation is impaired. This could be a risk factor for progression in glaucoma [2].

In 1981, Riva et al. showed that retinal blood flow is autoregulated up to IOP values of 30 mmHg in healthy subjects using the blue field simulation technique [16]. Macular blood flow is maintained down to an IOP low as 7 mmHg [13]. Riva et al. confirmed these findings on retinal autoregulation using the laser Doppler phenomenon in 1986 [15]. However, retinal AVP is significantly prolonged when IOP reaches values of 34 mmHg [22]. Zetlan et al. showed that blue field macular blood flow parallels changes found in visual evoked potentials during increases in IOP. A relationship between retinal haemodynamics and visual pathway activity as measured by visual evoked potentials was suggested, and patients with glaucoma failed to demonstrate these associations [18, 23]. Retinal blood flow determined by laser Doppler velocimetry maintains stable during increases in mean arterial blood pressure of up to 40% [17]. Harris et al. found a constriction of retinal arterioles and an increase in mean dye velocity during dynamic exercise. Calculated retinal blood flow remained unchanged [14].

In contrast, impaired autoregulation might lead to a higher susceptibility of ocular tissues to decreased perfusion pressure in glaucoma [2, 24, 25]. Epidemiological trials found that low perfusion pressures were associated with a higher prevalence of primary open-angle glaucoma [26, 27]. Diastolic perfusion pressures below 30 mmHg were related to a 6-fold higher risk for glaucoma compared to higher perfusion pressures [27].

The present study investigates the correlation of systemic blood pressure and ocular perfusion pressure with the retinal AVP in patients with normal tension glaucoma (NTG) and controls.

## Materials and methods

### Methods

All patients with NTG and control subjects had a detailed ophthalmological examination and visual field testing. Visual field examinations were performed with the Humphrey Field Analyzer (Model 750, Humphrey-Zeiss, San Leandro, CA, USA: 24-2 full-threshold or SITA program). One eye was randomly selected for the study in patients with bilateral NTG (coin toss). In patients with unilateral NTG, the diseased eye was included in the study.

Adherence to the Declaration of Helsinki for research involving human subjects is confirmed. Informed consent was obtained from all subjects. Data accumulation was carried out with Institutional Review Board approval.

Video fluorescein angiograms were obtained with a scanning laser ophthalmoscope (Rodentstock, Ottobrunn, Germany). The methods are described in detail elsewhere [1, 5, 6]. The 40-degree observation mode was used with the optic nerve head centred. To start the angiography, 10% sodium-fluorescein dye (2.5 cc) was injected into an antecubital vein. The image acquisition parameters (video gain and laser intensity) were kept constant until the maximum intensity levels in the retinal venules were passed over to avoid artefacts. Dynamic sequences were acquired with a frequency of 25 images per second. The angiograms were analysed off-line by means of digital image analysis (Matrox Inspector, Matrox Inc., Quebec, Canada) in a masked manner. The retinal AVP was determined using dye dilution curve analysis. The intensity level for each image was determined at a fixed region of interest (ROI) located on the arterioles respective venules. The extent of the ROI (circle) was chosen to correspond to the vessel diameter. Measurements were performed in the superotemporal and inferotemporal arterioles and venules. The mean retinal AVP was used for analysis.

Before fluorescein angiography, intraocular pressure was measured in a sitting position using Goldmann applanation tonometry. Systolic and diastolic blood pressure and heart rate were measured after a rest of 5 minutes (Dinamap, Criticare Systems Inc., USA). Mean ocular perfusion pressure (PP) was calculated as:  $PP = 2/3 (MAP) - IOP$ , where mean arterial pressure (MAP) is defined as: diastolic blood pressure  $+1/3$  (systolic blood pressure - diastolic blood pressure). Diastolic ocular perfusion pressure (dPP) was calculated as:  $dPP = 2/3$  (diastolic blood pressure) - IOP.

### Patients

Thirty-five patients with NTG and 35 age-matched controls were included in the study. All patients with NTG had glaucomatous optic nerve head cupping and glaucomatous visual field defects as defined by the European Glaucoma Society in absence of retinal or neurological disease affecting the visual field [28]. Visual field loss was considered significant when: (a) the glaucoma hemifield test was abnormal, (b) three points were confirmed with  $p < 0.05$  probability of being normal, not contiguous with the blind spot, or (c) corrected pattern standard deviation (CPSD) was abnormal with  $p < 0.05$ . All parameters were confirmed on two consecutive visual fields performed with the Humphrey Visual Field Analyzer (full threshold program 24-2) within 6 weeks. Patients with NTG never had IOP values above 21 mmHg, confirmed with IOP

**Table 1** Clinical data of the patients with untreated NTG and controls

	NTG	Controls	<i>P</i> value
Sex (male/female)	8/27	10/25	<i>p</i> =0.70
Age (years)	53±11	53±11	<i>p</i> =0.97
Intraocular pressure (mmHg)	16±3	16±2	<i>p</i> =0.85
Systolic blood pressure (mmHg)	131±18	132±17	<i>p</i> =0.73
Diastolic blood pressure (mmHg)	81±14	77±10	<i>p</i> =0.23
Mean deviation (dB)	-6.8±5.6	-0.4±1.1	<i>p</i> <0.0001
Pattern standard deviation (dB)	7.3±4.4	1.8±0.5	<i>p</i> <0.0001

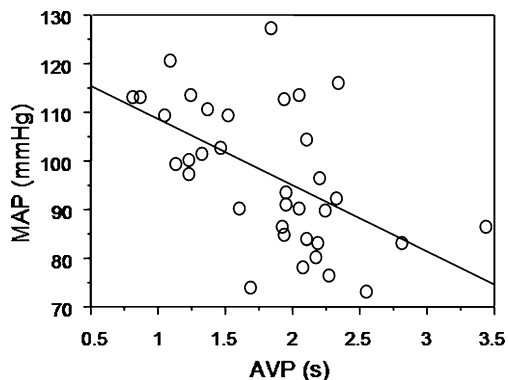
Mean and standard deviations are given

measurements at 8 a.m., 12 a.m., 4 p.m, 8 p.m., 12 p.m. (1 day IOP profile) without any IOP-lowering medication. 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 diopters, or with diabetes mellitus were excluded from this study. The control subjects did not have any ophthalmologic disease, presented with IOP values below 22 mmHg and normal visual field examinations.

No patient with NTG received topical IOP-lowering treatment. Patients were either newly diagnosed NTG patients or had a washout period of 3 weeks without any IOP-lowering medication. No control subject received any topical treatment. The clinical and demographic data of all individuals included in the study are presented in Table 1.

#### Statistical analysis

An unpaired *t*-test was applied for comparisons between patients with NTG and controls. Correlations were tested using the Fisher's *r* to *z* test. In all analyses, *p*<0.05 was regarded as statistically significant.



**Fig. 1** The arteriovenous passage time (AVP) is correlated to mean arterial blood pressure (MAP) in patients with NTG ( $r=-0.54$ ,  $p=0.0006$ )

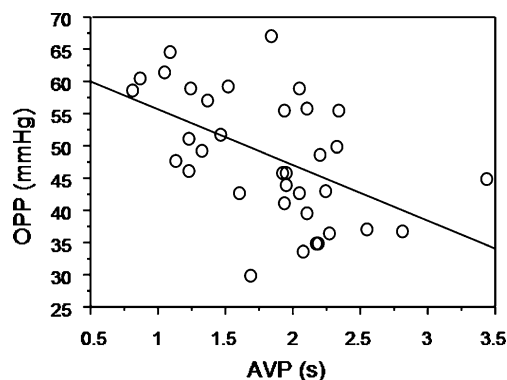
## Results

The retinal AVP was significantly prolonged in patients with NTG compared to controls. Intraocular pressure, systolic, diastolic, mean arterial pressure and calculated mean and diastolic ocular perfusion pressure were not significantly different between groups (Table 1).

The AVP was significantly correlated to mean arterial pressure, mean ocular perfusion pressure, and diastolic ocular perfusion pressure in NTG. Control subjects exhibited no correlation of systemic blood pressure, mean ocular perfusion pressure or diastolic ocular perfusion pressure with AVP. No correlation of AVP to IOP or age was found in patients with NTG or controls. The results are presented in Tables 2 and 3 and Figs. 1 and 2. The comparison of the correlation coefficients revealed a significantly different correlation for the diastolic ocular perfusion pressure and AVP between patients with NTG and controls ( $p=0.026$ ).

## Discussion

Past studies provide evidence that the retinal vasculature is autoregulated to maintain constant blood flow regardless of changes in ocular perfusion pressure in healthy subjects [13–18]. In contrast, an impaired ocular blood flow regulation is apparent in glaucomatous optic neuropathy. In primary open-angle glaucoma (POAG), a defective autoregulation of macular blood flow compared to controls was shown by Grunwald et al. in 1984 after artificial IOP increase by a suction cup [24]. Pillunat et al. found a different pattern of visually evoked response during IOP increase in patients with NTG. In contrast to healthy controls, patients with NTG exhibit a linear decrease of visual evoked response amplitudes during IOP elevation [25]. Robert et al. suggested that the optic nerve head brightness is an expression of capillary blood volume, and



**Fig. 2** The arteriovenous passage time (AVP) is correlated to ocular perfusion pressure (OPP) in patients with NTG ( $r=-0.51$ ,  $p=0.002$ )

**Table 2** Data of the retinal AVP and systemic blood pressure and ocular perfusion pressure for patients with NTG and controls

	NTG	Controls	<i>P</i> value
AVP (s)	1.82±0.57	1.42±0.46	<i>p</i> =0.002
Mean arterial pressure (mmHg)	97±14	96±10	<i>p</i> =0.55
Ocular perfusion pressure (mmHg)	48±10	47±7	<i>p</i> =0.60
Diastolic ocular perfusion pressure (mmHg)	38±9	36±7	<i>p</i> =0.27

Mean and standard deviations are given

found that during IOP elevation the optic nerve head brightness persisted for a shorter time in patients with POAG than in controls [29]. Retinal vessel diameters tend to show a smaller reaction upon intraocular pressure provocation up to suprasystolic values in patients with POAG than in controls [30].

In our study, a significant prolongation of the retinal AVP was confirmed in patients with NTG compared to controls [1, 11, 31]. The retinal AVP, prolonged in ischemic disease of the retina [7–10], represents the shortest passage of the fluorescein dye through the capillary formation. The retinal AVP might reflect alterations in retinal microcirculation, and is not related to capillary dropout of the posterior pole or retinal vessel diameters in glaucoma [5]. Further, the AVP is correlated to flow velocities and resistive indices of the central retinal artery and short posterior ciliary arteries [32]. Our investigation shows that AVP is correlated to mean and diastolic ocular perfusion pressure and mean arterial pressure in patients with untreated NTG, but not in controls. The direct comparison between patients with NTG and controls showed a significantly different correlation for the diastolic ocular perfusion pressure and AVP. This finding supports the concept of an impaired retinal blood flow regulation in NTG, although we did not measure AVP at baseline and after ocular perfusion pressure change. Most of the previous studies investigated the phenomenon of blood flow regula-

tion related to changes in ocular perfusion pressure in patients with POAG [24, 29, 30, 33, 34]. In POAG, an abnormal association of optic nerve head blood flow [33, 34] and choroidal blood flow [34] with systemic blood pressure or ocular perfusion pressure was shown. This phenomenon is also present in patients with NTG, as shown by our study on retinal haemodynamics. The results emphasise the impact of a deficient blood flow regulation during changes in ocular perfusion pressure and systemic blood pressure. The diastolic ocular perfusion pressure represents the lowest perfusion pressure levels during the heart cycle, and can be interpreted as the steady component of perfusion pressure. The presented data suggest that decreased diastolic perfusion pressure due to low diastolic blood pressure levels is relevant for decreased retinal haemodynamics in NTG. Interestingly, the AVP was not correlated to IOP in the present study. Therefore, the control of systemic blood pressure as the major component of calculated ocular perfusion pressure seems to be highly relevant to maintaining constant ocular blood flow in patients with NTG. In a recent investigation on 24-hour blood pressure monitoring in glaucoma, more profound night-time blood pressure fluctuations could be found in patients with NTG [35]. Such alterations in systemic blood pressure result in ocular perfusion pressure fluctuations. A defective blood flow regulation in glaucoma might then be relevant for recurring ischemic episodes of ocular tissues. The therapeutic lowering of IOP in glaucoma increases the ocular perfusion pressure, and might reduce the risk of an impairment of ocular haemodynamics. However, it is essential to evaluate the systemic blood pressure data in glaucoma patients in order to limit the risk of low diastolic perfusion pressures, e.g. in the case of extensive antihypertensive treatment. In the future, agents that interact with vascular resistance might contribute to diminishing the rate of progression in glaucoma.

The considerable overlap of AVP times between the patients with NTG and controls limits the interpretation of our results with regard to an individual patient. Prospective longitudinal studies are required to investigate the individ-

**Table 3** Correlation coefficients and corresponding *p*-values of the retinal AVP with mean arterial pressure and ocular perfusion pressure in patients with NTG and controls

AVP with	NTG		Controls	
	Correlation coefficient	<i>P</i> value	Correlation coefficient	<i>P</i> value
Intraocular pressure (mmHg)	-0.07	<i>p</i> =0.69	-0.04	<i>p</i> =0.84
Mean arterial pressure (mmHg)	-0.54	<i>p</i> =0.0006	-0.21	<i>p</i> =0.23
Ocular perfusion pressure (mmHg)	-0.51	<i>p</i> =0.002	-0.19	<i>p</i> =0.27
Diastolic ocular perfusion pressure (mmHg)	-0.49*	<i>p</i> =0.002	0.02	<i>p</i> =0.93

\*The correlation is significantly different in NTG compared to controls (*p*=0.026)

ual risk of progression when prolonged AVP times are present. Another limitation is the possible influence of systemic vascular disease in the patients with NTG, which might confound the results of our study. However, large-scale studies are necessary to investigate the potential role of systemic disease and medications in the relation between blood pressure and retinal haemodynamics. A certain selection bias of the patients with NTG sent to our clinic cannot be excluded.

In conclusion, our study showed that retinal AVP is prolonged in patients with NTG, suggesting decreased retinal haemodynamics. In addition, retinal AVP was correlated with ocular perfusion pressure and systemic blood pressure in NTG. A defective blood flow regulation may account for this association, which is not present in healthy subjects. A higher susceptibility of ocular tissues in glaucoma to fluctuations in ocular perfusion pressure may be related to recurring ischemic episodes [2,20]. This may be a relevant factor in the pathogenesis of glaucomatous optic neuropathy.

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