

# Capillary density and retinal diameter measurements and their impact on altered retinal circulation in glaucoma: a digital fluorescein angiographic study

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**Aim:** Normal pressure glaucoma (NPG) patients exhibit prolonged retinal arteriovenous passage times in fluorescein angiography and colour Doppler imaging suggests increased resistance downstream from the central retinal and posterior ciliary arteries. The aim of the study was to elucidate the morphological source of decreased perfusion and increased resistance of the ocular circulation in NPG.

**Methods:** Retinal arteriovenous passage time (AVP) and peripapillary arterial and venous diameters were measured in digital scanning laser fluorescein angiograms. For estimation of retinal capillary density the area of the foveal avascular zone (FAZ) and the perifoveal intercapillary area (PIA) was quantified. 36 patients with NPG (mean age 57 (SD 13) years) and 21 healthy subjects (mean age 51 (13) years) were enrolled in the comparative study.

**Results:** In NPG patients the AVP (2.55 (1.1) seconds) was significantly prolonged ( $p < 0.001$ ) when compared with healthy subject data (AVP: 1.70 (0.39) seconds). No differences for arterial or venous diameter, FAZ, and PIA were observed in NPG patients compared with healthy subjects. FAZ, PIA, arterial and venous diameter were not correlated with visual field indices (except venous diameter with PSD,  $r = 0.35$  ( $p < 0.05$ )) or cup to disc ratios. AVP was significantly correlated ( $p < 0.05$ ) with the size of the optic nerve head ( $r = -0.28$ ), visual field indices (MD:  $r = -0.3$ ; PSD:  $r = 0.3$ ; CPSD:  $r = 0.3$ ), and contrast sensitivity ( $r = -0.34$ ).

**Conclusion:** AVP times are significantly prolonged in NPG. The slowing of the retinal transit does not result from capillary dropout, or changes of peripapillary arterial or venous diameters with increased vascular resistance.

In normal pressure glaucoma (NPG) patients, a direct correlation of increased intraocular pressure (IOP) and optic nerve head damage remains controversial. For example, in a large study of an asymmetric NPG population, the more affected eye did not show higher IOP.<sup>1</sup> Circulatory studies in NPG patients find prolonged retinal circulation times,<sup>2</sup> decreased retrobulbar flow velocities,<sup>3</sup> and lower pulsatile ocular blood flow<sup>4</sup> when compared with healthy subjects. Colour Doppler studies in NPG patients reveal increases in vascular resistance downstream from the central retinal and posterior ciliary arteries.<sup>5</sup> Capillary dropout or vasoconstriction of the retinal vasculature could contribute to increased resistance.

Other signs in NPG patients indicating vascular dysregulation are gliosis-like lesions,<sup>6</sup> silent myocardial ischaemia,<sup>7</sup> and increased incidence of ischaemic cerebral lesions.<sup>8</sup> These findings suggest a more general vascular dysfunction than just ocular disturbances in NPG patients. One could speculate from these studies that pathological alterations of arterial or venous diameter or macular vasculature might occur in NPG, causing gliosis-like repair mechanisms, or that retinal capillary density is reduced as a sign of ischaemic disease.

This study was designed to examine whether a macular capillary density reduction and/or peripapillary diameter changes account for the pathological retinal circulation in patients with NPG. Further, clinical correlation of the dynamic and morphological measurements with visual field indices, contrast sensitivity, and optic nerve head morphology were performed to determine how vascular, visual functional, and morphological changes are correlated.

## MATERIAL AND METHODS

Digital scanning laser fluorescein angiography (Rodentock Instruments, Ottobrunn, Germany) was performed to assess

retinal arteriovenous passage time (AVP). The methodology has been presented in detail elsewhere.<sup>9, 10</sup> The angiograms were recorded on NTSC Sony videotapes. A self developed digital recording system was used to grab the fluorescein angiographic sequence and perform the image processing. In short, fluorescein intensity curves were registered (Matrox frame grabber, Matrox Inc, Quebec, Canada) and the first entry of fluorescein was detected.<sup>10</sup> The AVP time characterises the passage from the retinal artery through the capillary formation and arrival in the vein and is correlated with macular capillary blood velocities.<sup>10</sup>

Diameter measurements of the temporal superior and inferior vessels at the measuring location of the AVP were assessed from mid-transit fluorescein angiograms. A density profile was performed perpendicular to the vessel and by identification of the half height from maximum height of the ascending and descending slope diameter measurements.<sup>11</sup> To reach sub-pixel accuracy the measurement was performed five times and was averaged. In this study, the mean of the AVP and the diameters from the temporal superior and inferior vessel formation are given to characterise the posterior pole circulation.

For quantification of capillary density of the macular region within a circle of 5 degrees, centred over the foveal avascular zone (FAZ), perifoveal intercapillary areas (PIA), are chosen randomly and interactively marked by the cursor<sup>12</sup> (Matrox

**Abbreviations:** AVP, arteriovenous passage time; cpd, cycles/degree; CPSD, corrected pattern standard deviation; FAZ, foveal avascular zone; IOP, intraocular pressure; MD, mean defect; NPG, normal pressure glaucoma; PIA, perifoveal intercapillary area; PSD, pattern standard deviation; SF, short term fluctuation

**Table 1** Clinical and demographic data (mean (SD)) of the patients with NPG (n=36) and healthy subjects (n=21)

	Normal pressure glaucoma	Healthy subjects	Significance*
Age (years)	57 (13)	51 (13)	NS
Intraocular pressure (mm Hg)	16 (3)	16 (3)	NS
Systolic blood pressure (mm Hg)	119 (14)	127 (17)	NS
Diastolic blood pressure (mm Hg)	73 (10)	76 (11)	NS
Heart rate (beats/min)	73 (11)	74 (12)	NS
CDR (area)	0.51 (0.13)	0.32 (0.15)	p=0.0001
Optic nerve head area (mm <sup>2</sup> )	1.70 (0.41)	1.77 (0.34)	NS
MD (dB)	-4.7 (4.6)	-0.4 (1.3)	p<0.0001
PSD (dB)	6.8 (5)	1.7 (0.6)	p<0.0001
SF (dB)	2 (1)	1.2 (0.5)	p=0.0001
CPSD (dB)	6.6 (5)	0.89 (0.72)	p<0.0001
Contrast sensitivity 3 (cpd)	1.47 (0.3)	1.78 (0.36)	p=0.006
Contrast sensitivity 6 (cpd)	1.72 (0.25)	1.88 (0.5)	NS
Contrast sensitivity 12 (cpd)	1.24 (0.28)	1.52 (0.47)	p=0.04
Contrast sensitivity 18 (cpd)	0.84 (0.37)	1.14 (0.48)	p=0.04

\*Unpaired Student's *t* test.

MD = mean deviation, PSD = pattern standard deviation, SF = short term fluctuation, CPSD = corrected pattern standard deviation, CDR = cup to disc ratio, NS = not significant.

Inspector, Matrox Inc, Quebec, Canada). The mean value of 100 measurements is given as mean PIA. Further, the area of the FAZ was quantified by surrounding the area of interest with the cursor and calculating the number of pixels enclosed in this area. The dynamic and morphological readings were masked to the diagnosis for analysis.

Best corrected visual acuity was tested with objective refractometry. The visual field indices (MD: mean defect, PSD: pattern standard deviation, SF: short term fluctuation, CPSD: corrected pattern standard deviation) were obtained from standard Humphrey field analyser (Humphrey Inc, San Leandro, CA, USA; program 24-2, full threshold). The static contrast sensitivity (CSV 1000, Vector vision, Dayton, OH, USA) was performed in all subjects at four spatial frequencies (3, 6, 12, 18 cycles/degree (cpd)).<sup>13</sup> The cup to disc ratio was calculated from red-free photographs (argon blue laser illumination). Therefore, a number of pictures at different planes (by changing the focus) were taken. The cup and the optic disc were then marked interactively and the area was calculated with knowledge of the magnification from an image processing program (Matrox Inspector 2.1). Intraocular pressures were measured before angiographic examination with Goldmann tonometry for statistical purpose. Heart rate and blood pressures were determined with an automatic device (Vital Daten Monitor, Criticon Inc, Tampa, FL, USA). All morphological measures were corrected for individual refractive error by using ultrasonic A-scan length for calculation of Littmann factors.<sup>14, 15</sup>

### Patients

Prospectively, patients with open angle glaucoma (based on gonioscopy) with repeated IOP measurements below 21 mm Hg (diurnal IOP curves at 7 am, noon, 4 pm, 10 pm, midnight) were included. The measurements were obtained without any antiglaucomatous medication. Ophthalmological examination, medical history as well as neurological investigation did not show any other reason for visual field loss. Glaucomatous visual field loss was defined on the basis of Humphrey 24-2 full threshold visual field examination. A glaucomatous field defect was considered in the absence of retinal or neurological disease, when one of the following criteria was confirmed on two consecutive visits: (1) abnormal glaucoma hemifield test, or (2) three points confirmed with p<5% probability of being normal, one of which should have p<1%, and points should not be contiguous with the blind spot, or (3) CPSD<5% if the visual field is otherwise normal.<sup>16</sup> Patients with myopia >-8 dioptres, a history of fluorescein allergy, and dense lens opacities precluding detailed fundus visualisation were excluded.

All patients were washed out of any antiglaucomatous medication for 3 weeks before examination. The washout period of 3 weeks is considered sufficient to eliminate the effects of topical antiglaucomatous drugs.<sup>16</sup> Thirty six patients with NPG (mean age 57 (SD 13) years; 12 male, 24 female) were included in this examination and underwent fluorescein angiographic studies. None of the patients was suffering from diabetes mellitus; however, 12 subjects were diagnosed with arterial hypertension (four patients untreated, three patients  $\beta$  blockers, three patients calcium channel blocking agents, two patients angiotensin converting enzyme inhibitors).

The healthy subjects (n=21) recruited for this study had no history or evidence of any ocular or systemic disease. Their ages ranged from 30 to 73 years (mean 51 (13) years; seven male, 14 female). The ophthalmic examination for all participants included a medical and ocular history, visual acuity, external and slit lamp examination, Goldmann applanation tonometry, Humphrey visual field and fundus ophthalmoscopy. The eye for study was selected at random in all subjects.

Informed consent was obtained from each subject including detailed explanations of all procedures before participation in this study. The protocol for the study was reviewed and approved by the institutional review board. The tenets of the Helsinki Declaration were followed throughout the study.

### Statistical analysis

Mean value and standard deviation are given for all samples with normal distributions (Kolmogorov-Smirnov test) and non-normal distributions, median, and percentiles (10% and 90%). The Student's *t* test was used to assess the significance of the differences for unpaired comparisons. Findings with a *p* value of less than 0.05 were considered to be statistically significant. Pearson correlation coefficients were calculated to evaluate the relation between the parameters. *p* Values were obtained after carrying out Fisher's *r* to *z* transformations.

### RESULTS

The clinical and demographic data of the patients with NPG and the healthy subjects are presented in Table 1. The patients with NPG showed significantly increased visual field indices (PSD, SF, CPSD), cup to disc ratios, a decreased MD, and contrast sensitivity (3, 12, and 18 cpd) when compared with healthy subjects.

The dynamic (AVP) and morphological measurements (PIA, FAZ, arterial and venous diameters) of the patients with NPG and the healthy reference values are shown in Table 2. The AVP time of NPG patients was significantly prolonged

**Table 2** Dynamic data of the arteriovenous passage time (AVP) of the patients with NPG and healthy subjects. Morphological data of the foveal avascular zone (FAZ), mean perifoveal intercapillary area (PIA), and arterial and venous diameters of NPG patients and healthy subjects are presented (mean (SD))

	Normal pressure glaucoma	Healthy subjects	Significance*
AVP (seconds)	2.54 (1.19)	1.70 (0.39)	p<0.0001
Arterial diameter (µm)	101 (15)	100 (8)	NS
Venous diameter (µm)	140 (21)	139 (15)	NS
FAZ (mm <sup>2</sup> )	140 (21)	139 (15)	NS
PIA (µm <sup>2</sup> )	140 (21)	139 (15)	NS

\*Unpaired Student's *t* test.  
NS = not significant.

when compared with healthy subject data. The morphological data of FAZ and PIA did not differ from healthy subjects, neither did peripapillary arterial and venous diameter measurements.

When correlating morphological measurements (PIA, FAZ, arterial and venous diameter), dynamic measurements (AVP), IOP, blood pressure and heart rate, the following significant correlations were detected (Table 3): (1) systolic and diastolic blood pressure, (2) between diastolic blood pressure and heart rate, (3) between arterial and venous diameters, (4) between arterial diameters and systolic blood pressure (Table 3).

Morphological measurements (PIA, FAZ, arterial and venous diameter) and dynamic measurements (AVP) were correlated with the perimetric indices (MD, PSD, SF, CPSD) of conventional 24-2 full threshold visual fields and contrast sensitivity as follows: (1) AVP with MD, PSD, CPSD, and (2) venous diameter with PSD (Table 4).

AVP was significantly correlated with the size of the optic nerve head, but not with the cup to disc ratio (Table 5). No correlations were found between PIA, FAZ, arterial and venous diameter, and optic nerve head parameters.

**Table 5** Correlation matrix of arteriovenous passage time (AVP), perifoveal intercapillary area (PIA), foveal avascular zone (FAZ), arterial diameter (AaDia), venous diameter (VvDia) and the cup to disc ratio (CDR) and size of the optic nerve head

	CDR	Optic nerve head size
AVP	0.22	-0.3*
PIA	-0.15	0.19
FAZ	-0.14	-0.19
AaDi	0.16	0.15
VvDi	-0.02	0.05

Significance \*p<0.05, \*\*p<0.01.

**DISCUSSION**

Angiographic studies in the past showed significant differences between healthy subjects and patients with glaucoma.<sup>17-22</sup> A persisting hypoperfusion was considered highly characteristic in subjects with open angle glaucoma.<sup>22</sup> In this study, patients with NPG show a significant prolongation of arteriovenous passage time when compared with healthy volunteers. Several factors could account for these findings.

Anatomically, three sites may account for decreased retinal perfusion and increased downstream resistance from retrobulbar measurements<sup>5</sup>: (1) the retinal capillary bed, (2) retinal arterioles, and (3) anatomical-pathological properties at the lamina cribrosa. The retinal circulation, lacking of precapillary sphincters,<sup>23</sup> most probably is regulated by direct interaction at the level of the capillaries.<sup>24</sup> Modulations of the vessel width are responsible for increased or decreased resistance, thus leading to shortened or prolonged retinal circulation times. In addition, a rarefaction of the vascular network is a substantial source of increased resistance.<sup>25</sup> In vivo quantification of capillary densities in fluorescein angiograms was first described<sup>26</sup> in healthy subjects and in modification introduced for evaluation in various diseases.<sup>12 27 28</sup> In NPG patients, the perifoveal

**Table 3** Correlation matrix of arteriovenous passage time (AVP), perifoveal intercapillary area (PIA), foveal avascular zone (FAZ), arterial diameter (AaDia), venous diameter (VvDia) and the clinical data of intraocular pressure (IOP), diastolic and systolic blood pressure (diast BP, syst BP), heart rate (HR)

	PIA	FAZ	AaDi	VvDi	IOP	Syst BP	Diast BP	HR
AVP	-0.11	0.03	0.04	0.05	0.04	-0.28	-0.18	0.05
PIA	-	0.09	0.13	-0.07	-0.27	-0.26	-0.03	-0.03
FAZ	-	-	0.26	0.14	-0.26	0.1	0.2	-0.27
AaDi	-	-	-	<b>0.56**</b>	-0.21	<b>-0.39*</b>	-0.22	-0.08
VvDi	-	-	-	-	-0.29	-0.29	-0.15	0.2
IOP	-	-	-	-	-	0.16	0.02	0.11
Syst BP	-	-	-	-	-	-	<b>0.42**</b>	0.02
Diast BP	-	-	-	-	-	-	-	<b>0.4*</b>
HR	-	-	-	-	-	-	-	-

Significance \*p<0.05, \*\*p<0.01.

**Table 4** Correlation matrix of arteriovenous passage time (AVP), perifoveal intercapillary area (PIA), foveal avascular zone (FAZ), arterial diameter (AaDia), venous diameter (VvDia) and the visual field indices (MD: mean defect, PSD: pattern standard deviation, SF: short term fluctuation; CPSD: corrected pattern standard deviation) and contrast sensitivity (3, 6, 12, 18 cycles per degree (cpd))

	MD	PSD	SF	CPSD	CS 3cpd	CS 6cpd	CS 12cpd	CS 18cpd
AVP	<b>-0.3*</b>	<b>0.3*</b>	0.05	<b>0.31*</b>	-0.06	-0.13	-0.28	<b>-0.34*</b>
PIA	-0.004	-0.13	-0.11	-0.13	-0.04	0.07	0.17	0.09
FAZ	0.22	-0.27	-0.27	-0.23	0.03	0.12	-0.04	-0.04
AaDi	-0.18	0.06	0.04	0.07	0.16	-0.07	0.02	-0.06
VvDi	-0.3	<b>0.35*</b>	0.17	0.28	-0.21	-0.13	-0.06	-0.13

Significance \*p<0.05, \*\*p<0.01.

intercapillary area and foveal avascular zone showed no significant enlargement in comparison with healthy subjects. The failure of PIA and FAZ to correlate with the retinal AVP time suggests that a prolonged AVP time appears to be independent of an obstructive capillary disease of the posterior pole. Cerebral ischaemic lesions, found in NPG patients in magnetic resonance imaging examinations,<sup>8</sup> cannot be shown in the retina.

The decreased retinal perfusion and increased downstream resistance, calculated from the velocities of the retrobulbar vessels,<sup>5</sup> might be caused by reduction of the capillary diameter—for example, via vasospasms or arteriosclerosis. A number of studies on peripapillary vessel diameters<sup>29–32</sup> showed arteriolar narrowing corresponding with severity of glaucomatous field damage. These measurements were performed in arterioles and venules, and therefore only partially characterise the regulatory function of the capillary bed. However, these diameter measurements are of great importance since in vivo capillary diameter imaging is not yet possible with the accuracy needed because of the limited resolution of the eye.<sup>10</sup> Peripapillary diameter measurements, in this study, did not differ from those of healthy subjects and correlated with visual field indices. The missing significance between healthy subjects and glaucoma patients in contrast with previously published data<sup>29–32</sup> might be the result of the smaller sample size or methodology. Furthermore, no patients with severe end stage glaucomatous optic neuropathy were included in this study, which than would provide an end point for statistical analysis.

Arteriovenous passage times did not correlate with peripapillary arterial and venous diameters, emphasising a greater importance of the retinal capillary vascular bed for microcirculatory regulations. Additionally, prolonged AVP times could be the results of an outflow obstruction. Thus, retinal venous outflow could be reduced as a result of mechanical alterations in the vasculature of the lamina cribrosa.<sup>33</sup> A distortion<sup>33</sup> of the laminar structure could lead to a compression of the passing vessels. This compression then could be reflected in measurements of prolonged arteriovenous passage times, resulting from obstructed venous outflow. This hypothesis is supported by prolonged arteriovenous passage times in central retinal vein occlusions (CRVO),<sup>34</sup> in which an obstruction at the level of the lamina cribrosa is suggested.<sup>35</sup> Lamina cribrosa changes in glaucoma, however, do not show increasing extracellular matrix<sup>36</sup> that would account for the obstruction. None the less, a loss of elasticity within the lamina cribrosa<sup>36</sup> could obstruct the venous outflow, generating the haemodynamic dysfunction seen in this study.

A final potential factor influencing the presented results is that of altered haemorrhology. Patients with CRVO,<sup>37–38</sup> as well as open angle glaucoma,<sup>19–39</sup> show increased plasma viscosity and haematocrit. Plasma viscosity is of particular importance in areas of obstructed flow as it would lead to decreased retinal perfusion.<sup>38</sup> Plasmapheresis studies showed that reduction of plasma viscosity significantly accelerates retinal arteriovenous passage,<sup>40</sup> so that a direct correlation is evident.

The present data underline the importance of a circulatory component in glaucomatous optic neuropathy. Of clinical interest is the correlation of haemodynamic measurements with clinical parameters such as cup to disc ratio and visual field indices. The visual field parameters of conventional perimetry (MD, PSD, CPSD) correlated significantly in this study with AVP measurements. Additionally, contrast sensitivity at higher spatial frequencies (18 cpd) was reduced in patients with prolonged AVP times. This result suggests that a prolongation of AVP times is associated with reduction of contrast sensitivity and visual field indices. However, since the significance is weak, further recruitment is needed to fully establish the relation. These correlations are in accordance with a previous report<sup>41</sup> comparing AVP and severity of field defects of the more affected hemispheres with the less affected hemi-

spheres. Further studies are required to confirm the correlations and to judge the value for predicting disease progression. Concerning systemic drugs three normal pressure glaucoma patients were on  $\beta$  blockers. Considering the possible interactions with assessed circulatory values, IOP, and cardiovascular parameters the statistics were performed without this subset. Owing to the small number of subjects no influence on the presented parameters was detected.

Additionally, decreasing size of the optic nerve head is associated with a prolongation of retinal AVP times. Among different types of glaucoma, the size of the optic nerve head differs significantly.<sup>42</sup> The size of the glaucomatous optic disc is smaller than in healthy subjects.<sup>43</sup> Although the possibility remains speculative, the association of circulatory dysfunction with optic disc size may be linked to factors creating venous obstruction at the level of the lamina cribrosa.

In summary, patients with NPG show retinal circulatory alteration despite no evidence of causative capillary dropout, or peripapillary arterial or venous diameter changes accounting for the observed changes. Consequently, diameter changes of the retinal vasculature at the capillary level, venous outflow obstruction, altered haemorrhology, or circulatory downregulation due to nerve fibre loss might explain these changes.

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