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Hollo, G.; Greve, E.L.; van den Berg, T.J.T.P.; Vargha, P.

Publication date
1997

Published in
International ophthalmology

International Ophthalmology **20:** 71–77, 1997.

Evaluation of the peripapillary circulation in healthy and glaucoma eyes with scanning laser Doppler flowmetry *

Gábor Holló[1,2], Erik L. Greve[1], Thomas J.T.P. van den Berg[3] & Péter Vargha[4]
[1] *Glaucoma Center, University of Amsterdam, The Netherlands;* [2] *1st Department of Ophthalmology, Semmelweis University School of Medicine, Budapest, Hungary;* [3] *Medical Physics and Informatics Department, University of Amsterdam, The Netherlands;* [4] *Unit of Biometry, Semmelweis University School of Medicine, Budapest, Hungary*

Key words: blood flow, glaucoma, Heidelberg Retina Flowmeter, myopia, peripapillary atrophy, scanning laser Doppler flowmetry

Abstract

In order to study peripapillary perfusion, one randomly selected eye of 34 healthy volunteers and 40 glaucoma patients (27 suffering from primary open-angle glaucoma (POAG) 10 from normal pressure glaucoma (NPG) and three from other types of glaucoma) was studied with a Heidelberg Retina Flowmeter. Temporal flow adjacent to the disc edge was significantly higher than the nasal flow ($p < 0.01$). It was reduced significantly in myopia both in controls ($p < 0.05$) and in glaucoma patients ($p < 0.001$). However, there was no difference between either controls and glaucoma patients or between POAG and NPG patients. It was independent of treatment type in glaucoma. Within the temporal peripapillary area extremely high flow values (values higher than the mean + 2 SD of the corresponding individual retinal flow) seemed to represent deep peripapillary vascular rings. They were significantly more frequent in glaucoma (72%) than in healthy volunteers (44%, $p < 0.05$). Their frequency was 83% in myopic and 23% in non-myopic eyes in the control group ($p < 0.001$). However, in glaucoma patients they were common both in myopic eyes (71%) and in non-myopic ones (75%). The results suggest that capillary perfusion adjacent to the temporal edge of the disc is significantly reduced in myopia. Deep peripapillary vascular structures can be measured on images focused on the surface of the retina, especially if the retina is thinner than normal (healthy myopic eyes and glaucomatous eyes independently of the refraction). This may mask a deficient function of the retinal capillary bed.

Introduction

Peripapillary circulatory disturbances are important in the pathogenesis of vascular glaucoma [1–7]. In glaucoma a high prevalence of watershed zones was discovered with fluorescein angiography [4, 5, 8], as well as a slow blood refreshment rate of the peripapillary choroid with scanning laser angiography [1, 3]. In this study a new, non-invasive technical approach, involving the Heidelberg Retina Flowmeter, was utilized to map and evaluate the peripapillary circulation in healthy volunteers and in glaucoma patients.

Subjects and methods

Randomly we selected one eye of 34 healthy volunteers (age: 23–76, mean: 49.2) and one eye of 40 glaucoma patients (age: 40–81, mean: 61.0). These were studied with a Heidelberg Retina Flowmeter after informed consent was obtained from all subjects. Twenty-seven patients suffered from primary open angle glaucoma (POAG, age: 40–79, mean 59.4), 10 from normal pressure glaucoma (NPG, age: 47–81, mean: 64.6) and 3 (age: 62–75, mean 70.6) from traumatic and combined mechanism glaucoma. Exclusion criteria were history of diabetes mellitus, any autoimmune vascular disease, retinal vascular occlusion and severe systemic hypertension. Also, eyes with dense corneal,

* The authors have no financial interest in the Heidelberg Retina Flowmeter.

lens or vitreous opacities were excluded. The control persons had normal optic nerve heads and retinal nerve fibre layer. They underwent a detailed ophthalmological examination with a negative result. Twelve of the healthy volunteers were myopic up to - 7.0 D and 22 were emmetropic or hyperopic. POAG was defined as an optic neuropathy with typical cupping of the disc, glaucomatous visual field defects, open anterior chamber angles and intraocular pressure higher than 21 mmHg without treatment on diurnal curve examination. NPG was defined as typical glaucomatous optic nerve head and visual field changes with open anterior chamber angle and intraocular pressure not higher than 21 mmHg on diurnal curve examination without treatment, but one isolated measurement up to 26 mmHg was accepted. Among glaucoma patients 24 were myopic up to - 6.0 D, and 16 were emmetropic or hyperopic. The actual intraocular pressure varied between 12 and 21 mmHg (mean: 16.5 mmHg) in the control group, 7 and 28 mmHg (mean: 18.9 mmHg) in POAG, 9 and 23 mmHg (mean: 15.4 mmHg) in NPG and 7 mmHg in the miscellaneous group. At the time of the examination 12 patients were off treatment, 7 patients required no medication due to previous successful trabeculectomy, and 12 were on topical beta receptor blocker medication. Three patients received topical beta blocker medication after filtering surgery, 2 patients received different cholinergic drops, 3 patients had undergone argon laser trabeculoplasty and one cataract surgery.

For scanning laser Doppler flowmetry a Heidelberg Retina Flowmeter was used. The Heidelberg Retina Flowmeter is a new, two-dimensional optical scanner combined with an infrared laser Doppler velocimetric system (Operation Software Release 1.01, Heidelberg Engineering GmbH, Heidelberg, 1995, Germany). The instrument provides a topographical image and three brightness-coded, two-dimensional images of the retinal perfusion. 'Volume' (a value which is proportional to the total number of moving red blood cells inside the sample volume), 'flow' (a value which is proportional to the total number of red blood cells times their velocity, i.e. the total distance travelled by the moving red blood cells per unit time within the sample volume) and 'velocity' ('flow' divided by 'volume') are measured within a measuring frame of variable size which can be moved. The instrument measures only capillary blood perfusion, therefore large vessels must be avoided. The measuring depth is approximately 300 μm.

We focused the images of 10 × 2.5 degree size on the retinal surface. The optic nerve head was positioned in the center of the image. Peripapillary retinal flow was studied along the horizontal meridian with adjacent 10 × 10 pixel (100 × 100 μm) sized frames. The position of the horizontal line was determined so that large retinal vessels and cilioretinal arteries were avoided. Normal and atrophic peripapillary retinae at the instant frame position were distinguished on the basis of the retinal morphology visible on the corresponding topographic image.

Table 1. Frequency of 'high' and 'low' peripapillary flow values in control and glaucoma eyes

Peripapillary flow	Control N = 34	Total glaucoma N = 40
Temporal high value	15 (44%)	29 (72%)
	$p < 0.05$	
Temporal low value	20 (59%)	30 (75%)
	$p = 0.14$	
Temporal high + low value	5 (15%)	21 (52%)
	$p < 0.01$	
Nasal high value	6 (18%)	3 (7%)
	$p = 0.18$	
Nasal low value	21 (62%)	28 (70%)
	$p = 0.45$	
Nasal high + low value	0	0

The symbol 'high + low' represents both 'high' and 'low' flow values registered within the same peripapillary area along the horizontal meridian.

By this method, two to three temporal and nasal retinal locations outside the peripapillary retina were available for the calculation of individual mean temporal and nasal retinal flow and standard deviation, respectively. The size of the peripapillary region and atrophy differed remarkably among individuals, therefore one to four (mostly two) peripapillary frame positions per person were studied. If at least one of the peripapillary flow values was higher than the mean + 2 SD of the corresponding retinal flow on the same image, a 'high' peripapillary value was registered. If any of the peripapillary values was lower than the mean - 2 SD of the corresponding retinal flow on the same image, a 'low' value was detected.

Flow values belonging to two frame positions were used for numerical analysis. One was temporally, the other nasally adjacent to the edge of the disc. 'High' values belonging to a position adjacent to the disc were excluded from numerical analysis, as they probably reflected arterial perfusion instead of capillary flow.

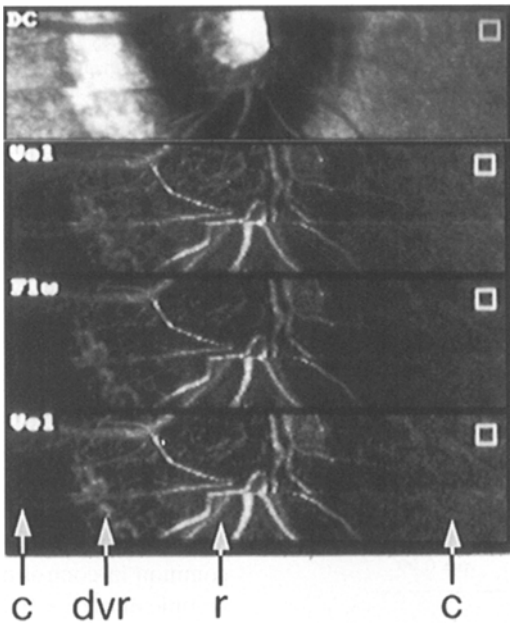

Figure 1. Topographic image and the corresponding perfusion maps of a - 7.0 D myopic control eye. c = retinal capillaries, dv = deep vascular ring, r = neuroretinal rim.

Table 2. Frequency of 'high' and 'low' peripapillary flow values in myopic and in non-myopic eyes

Peripapillary flow	Control		Total glaucoma		Total myopes (control + glaucoma) N = 36	Total non-myopes (control + glaucoma) N = 36
	myopes N = 12	non-myopes N = 22	myopes N = 24	non-myopes N = 16		
Temporal high value	10 (83%)	5 (23%)	17 (71%)	12 (75%)	27 (75%)	17 (47%)
		$p < 0.001$		$p = 0.99$	$p < 0.05$	
Temporal low value	3 (25%)	17 (77%)	20 (83%)	10 (62%)	23 (64%)	27 (75%)
		$p = 0.05$		$p = 0.26$	$p = 0.31$	
Temporal high + low value	3 (25%)	2 (9%)	14 (58%)	7 (44%)	17 (47%)	9 (25%)
		$p = 0.32$		$p = 0.37$	$p = 0.05$	
Nasal high value	1 (8%)	5 (23%)	1 (4%)	2 (12%)	2 (6%)	7 (19%)
		$p = 0.29$		$p = 0.55$	$p = 0.07$	
Nasal low value	9 (75%)	12 (54%)	18 (75%)	10 (62%)	27 (75%)	22 (61%)
		$p = 0.46$		$p = 0.49$	$p = 0.21$	
Nasal high + low value	0	0	0	0	0	0

The symbol 'high + low' represents both 'high' and 'low' flow values registered within the same peripapillary area along the horizontal meridian.

Table 3. Frequency of 'high' and 'low' peripapillary flow values on normal and atrophic peripapillary area

Peripapillary area	Peripapillary flow	
	Temporal high value	Temporal low value
Normal N = 14	6 (43%)	8 (57%)
Atrophic N = 60	39 (65%)	41 (68%)
	p = 0.13	p = 0.99
	Nasal high value	Nasal low value
Normal N = 38	5 (13%)	26 (68%)
Atrophic N = 35	4 (11%)	24 (69%)
	p = 0.99	p = 0.99

Two and three-way (one of them intraindividual) analysis of variance (ANOVA) was applied for statistical analysis. Paired comparison was performed using the Duncan-test. Chi-square test and Fisher's exact test were applied when the frequency of 'high' and 'low' peripapillary values was studied. P values less than 0.05 were considered significant.

Results

'High' peripapillary flow values were up to 6.5 times higher than the corresponding retinal flow outside the peripapillary area. Thus, they by far exceeded mean retinal flow plus 2 SD. The 'high' peripapillary flow values mostly correlated with locations over deep vascular rings clearly visible on the perfusion images especially in myopia (Figure 1). The criterion of 'low' peripapillary flow value was created to identify the significantly reduced peripapillary perfusion, i.e. flow lower than the corresponding mean retinal flow minus 2 SD outside the peripapillary area.

'High' temporal flow values were significantly more frequently observed in glaucoma than in healthy volunteers ($p < 0.05$, Table 1). Interestingly, neither temporal nor nasal 'low' values were significantly more frequent in glaucoma than in the control group (Table 1).

Table 4. Peripapillary flow in control and glaucoma eyes in arbitrary units

Peripapillary flow (arbitrary unit)	Control N = 34 Mean (SD)	Total glaucoma N = 40 Mean (SD)
Temporal	211 (82)	217 (116)
	p = 0.88	
Nasal	131 (57)	172 (78)
	p = 0.21	

'High' peripapillary flow was detected significantly more frequently on the temporal than on the nasal side of the disc ($p < 0.001$, Table 1). The frequency of 'low' peripapillary values was similar on both sides of the disc (Table 1).

A temporal 'high' value was significantly more common in control myopic eyes than in control non-myopic ones ($p < 0.001$, Table 2). However, as shown in Table 2, in glaucoma the frequency of 'high' values on the temporal peripapillary retina was high both in myopic eyes (71%) and in non-myopic ones (75%).

Flow pattern characterized by the presence of at least one 'high' flow value in the peripheral peripapillary area and at least one 'low' flow value near the disc within the same peripapillary area, probably representing the most typical anatomical variation (peripapillary deep vascular ring – peripapillary capillary zone – disc edge configuration), was not detected on the nasal side, but frequently occurred on the temporal side. This pattern was observed in 21 of the 40 glaucoma patients (52%) and in only five of the 34 control persons (15%, $p < 0.01$, Table 1). A borderline significance was noted, when all myopic subjects (controls and glaucoma patients) were compared to all non-myopic persons: this flow pattern was detected in 17 of the 36 myopic eyes (47%), but in only nine of the 36 non-myopic eyes (25%, $p = 0.05$, Table 2).

Although the frequency of 'high' as well as 'low' temporal peripapillary values was higher in clearly atrophic areas than in supposedly normal peripapillary retina (Table 3), this difference did not reach statistical significance. Nasally the frequency did not differ (Table 3).

Temporal and nasal peripapillary flow results, calculated from the values measured on the locations temporally and nasally adjacent to the disc, are shown in Tables 4–6. These results are based on measurements excluding 'high' values. Eight of the temporal and 12 of the nasal locations adjacent to the disc produced

Table 5. Peripapillary flow in myopic and non-myopic eyes in arbitrary units

Peripapillary flow	Control		Glaucoma	
	myopic	non-myopic	myopic	non-myopic
	N = 12	N = 22	N = 25	N = 15
(arbitrary unit)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Temporal	175 (79)	232 (79)	189 (101)	265 (128)
	$p < 0.05$		$p < 0.001$	
Nasal	139 (56)	127 (59)	163 (84)	189 (66)
	$p = 0.68$		$p = 0.31$	

Table 6. Peripapillary flow in POAG and NPG in arbitrary units

Peripapillary flow	POAG	NPG
	N = 27	N = 10
(arbitrary unit)	Mean (SD)	Mean (SD)
Temporal	200 (110)	226 (59)
	$p = 0.79$	
Nasal	156 (69)	207 (98)
	$p = 0.12$	

'high' values which are believed not to represent capillary flow but deep vascular rings.

Neither temporal nor nasal peripapillary flow differed between healthy subjects and glaucoma patients (Table 4).

Temporal peripapillary flow was significantly reduced in myopic eyes compared to non-myopic ones both in the controls ($p < 0.05$) and in glaucoma patients ($p < 0.001$, Table 5). The corresponding nasal values were not statistically significantly different (Table 5).

There was no difference in peripapillary flow between POAG and NPG patients (Table 6).

Temporal peripapillary flow was significantly higher than nasal peripapillary flow ($p < 0.05$).

When age was the only independent variable, excluding 'high' values, both temporal and nasal peripapillary flow increased significantly with age ($p < 0.05$ and $p < 0.01$). The type of treatment and actual intraocular pressure had no influence on peripapillary flow values.

Discussion

Scanning laser Doppler flowmetry is offered as a new technique for the non-invasive in vivo evaluation and quantification of human retinal capillary perfusion. Although detection of perfused arteries and veins is possible with the Heidelberg Retina Flowmeter, due to technical reasons an exact numerical result cannot be obtained from a vascular structure larger than capillary size. The meaning of 'flow' calculated by the instrument is not identical with the conventional meaning of flow (velocity times cross sectional area). In scanning laser Doppler flowmetry 'flow' is proportional to the total number of red blood cells times their velocity, i.e. the total distance travelled by all moving red blood cells within the sample volume per unit time.

Excluding 'high' values, we did not find a quantitative difference in peripapillary capillary flow between controls and glaucoma patients. Such a difference, however, was found in the occurrence of 'high' values. 'High' flow values were significantly more frequent in glaucoma patients than in controls. 'High' values, which were up to 6.5 times higher than the corresponding mean retinal flow, generally correlated well with the position of a deep vascular ring [9–11] clearly visible on the perfusion maps. It is suggested that in such positions not only the retinal capillary flow is measured. Instead, the greatest part of the values obtained are produced by the underlying deep vascular ring. The high frequency of 'high' readings indicates that on images focused on the retinal surface, the Heidelberg Retina Flowmeter does indeed obtain values other than from the retinal capillary bed within the peripapillary region.

Evidently, thinning of the retina in the peripapillary area, which is common both in myopia [12–14] and in glaucoma [15–21], causes the instrument to measure the deep layers (e.g. chorocapillaries) in addition and not exclusively the retinal capillary bed. It is important to realize that such values may erroneously be attributed to the retina, and may mask a deficient function of the retinal capillary bed.

In control subjects the frequency of 'high' values was higher in myopic eyes than in the non-myopic

ones. However, a high frequency of 'high' values did occur both in the myopic and non-myopic glaucoma patients. Thus, in glaucoma patients the peripapillary area in myopes and in non-myopes showed a similar behaviour. We presume that this similarity of behaviour is related to a more developed and larger peripapillary atrophy that may be found also in non-myopic glaucoma patients.

It was an interesting finding that within the peripapillary area we could not find a statistically significant difference in the frequency of 'high' values between the eyes with evident peripapillary atrophy and those eyes which still seemed to have a normal retinal appearance. However, in both the evidently atrophic and the presumably normal peripapillary areas the frequency of 'high' values was by definition much higher than in the normal retina outside the peripapillary region. This indicates that even in areas that have a normal appearance, 'high' flow values can be obtained, suggesting that due to the thinning of the retina the deeper vascular layers are being measured.

The low flow values measured in myopic subjects and in myopic glaucoma patients indicate a retinal circulatory disturbance in these eyes. It has been shown that myopic eyes with glaucoma are more progressive than non-myopic ones [4, 13]. It may be postulated that the circulatory disturbance in myopic eyes plays a role in this progression. These findings also show that the inclusion of myopes may significantly affect the outcome of peripapillary flow studies.

Scanning laser Doppler flowmetry with the Heidelberg Retina Flowmeter claims to provide a new, non-invasive approach for investigations of retinal capillary perfusion. The exact value of the technique has to be judged in the light of the above mentioned findings.

'High' values were presumably derived from the deeper vessels and not from the retinal capillaries. Thus, in the peripapillary area flow values may be derived either from the retinal capillaries or from the deeper vascular layers. It is very difficult to distinguish between these sources if the choroidal effect on the measured value is not extremely high. In a temporal position adjacent to the disc, the flow was lower in myopes than in non-myopes. However, in the myopic normal subjects a high frequency of 'high' flow values was also detected similarly to glaucoma patients (both myopic and non-myopic). These findings again indicate that the deeper vascular layers may affect readings taken from thinner retinae. Peripapillary areas with a normal appearance may also have 'high' flow values, indicating that this effect is also present in the presumably normal peripapillary areas. As the Heidelberg Device incorporates both the Retina Flowmeter and the Tomograph, measuring the retinal thickness at the location of interest may help to exclude this problem.

Acknowledgement

The authors would like to thank Hylke M.N. Coevoet, M.D. for her help in collecting data for this study.

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