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Scanning laser Doppler flowmetry in glaucoma *

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

Abstract

Scanning laser Doppler flowmetry is a new means for the measurement of capillary perfusion. We studied the retinal and neuroretinal rim capillary perfusion with the Heidelberg Retina Flowmeter in one randomly selected eye of 31 healthy volunteers, 42 primary open angle glaucoma (POAG) patients and 17 normal pressure glaucoma (NPG) patients. The reproducibility of the measurements on the temporal and nasal retina and on the disc rim was 19%, 26% and 28% in the unselected control group, 12% in the POAG and 12%, 13% and 10% in the NPG group, respectively. Optic disc flow was significantly higher than retinal flow ($p < 0.000001$). Differences in corresponding flow values between healthy volunteers and glaucoma patients as well as between POAG and NPG patients were not statistically significant. There was no correlation between the temporal and nasal flow values of the same eyes. The average variation in flow between adjacent frame positions was 18.5%. Actual intraocular pressure and the type of treatment had no influence on the retinal flow. The results suggest that the position of the test-frame is very important for the final result. We could not find any significant difference in the perfusion between glaucomatous and control eyes with the Heidelberg Retina Flowmeter.

Introduction

According to the vascular concept of glaucoma [1–6], local circulatory disturbance of the optic nerve head plays a role in the pathogenesis of at least part of primary open-angle glaucoma (POAG) and normal pressure glaucoma (NPG). Using colour Doppler imaging a decreased end diastolic and an increased peak systolic blood flow velocity as well as an increased resistive index were found in the ophthalmic, central retinal and short posterior ciliary arteries in POAG and especially in NPG patients compared with controls [7–11].

Filling defects of the optic disc observed with fluorescein angiography are considered an important sign of vascular glaucoma [12–17]. Increased retinal arteriovenous fluorescein passage time [18] as well as increased choroidal filling time [3–5, 19, 20] were also noted in glaucoma patients.

Optic nerve head circulation was also studied with a non-invasive method, laser Doppler velocimetry, a method based on the Doppler-shift caused by moving red blood cells [21–24]. Velocity was reduced immediately after a significant elevation of the intraocular pressure [21]. Although optic disc blood velocity was significantly reduced in optic atrophy [25], the calculated flow per unit volume was considered unchanged both in optic atrophy and glaucoma [26, 27]. In POAG and NPG, coexistence of a decreased blood velocity in the optic nerve head and an increased blood viscosity has been found [28, 29].

Another non-invasive method, scanning laser Doppler flowmetry with the Heidelberg Retina Flowmeter, claims to provide a new approach for capillary blood flow measurement. The brightness-coded two-dimensional surface maps of the circulation help the investigator to select the locations for the measurements and to avoid large vascular branches. This study was designed to investigate retinal and optic nerve head

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

capillary flow in healthy volunteers, in POAG and in NPG patients with the Heidelberg Retina Flowmeter. Reproducibility and the effects of age, intraocular pressure, treatment and location of the measurement on capillary flow were also evaluated.

Subjects and methods

Subjects

Thirty-one healthy volunteers (age: 33–76, mean 52.9), 42 POAG patients (age: 40–84, mean 60.1) and 17 NPG patients (age: 42–81, mean 63) were involved in the study after informed consent was obtained from all subjects. Two healthy subjects and 12 glaucoma patients originally planned to be involved were excluded due to bad image quality. Exclusion criteria were history of diabetes mellitus, any autoimmune vascular disease, retinal vascular occlusion and severe systemic hypertension. Also, eyes with dense corneal, lens or vitreous opacities were excluded. The controls had a normal optic nerve head and retinal nerve fibre layer. They underwent a detailed ophthalmological examination with a negative result. Eleven of them were myopic up to - 7.0 D and 20 were emmetropic or hyperopic. All glaucoma patients had glaucomatous visual field defects. POAG was defined as an optic neuropathy with typical cupping of the disc, glaucomatous visual field defects, open anterior chamber angles and mean 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 without treatment on diurnal curve examination, but one isolated measurement up to 26 mmHg was accepted. Thirty-five of the patients were myopic up to - 6.0 D, and 24 were emmetropic or hyperopic. Actual intraocular pressure varied between 12 and 21 mmHg (mean 16.9 mmHg) in the control group, 7 and 37 mmHg (mean 19.1 mmHg) in POAG and 2 and 22 mmHg (mean 15.1 mmHg) in NPG. Fifteen glaucoma patients were off treatment because of recently detected glaucoma or stopped medication before filtering surgery, 12 subjects required no medication due to previous successful trabeculectomy, and 23 patients were on topical beta blocker medication. Three patients received topical beta blocker medication after filtering surgery, 2 patients used different cholinergic drops, 3 patients had undergone argon laser trabeculoplasty and one cataract surgery.

Instrument

The Heidelberg Retina Flowmeter is a scanning laser Doppler flowmeter which scans the retina over a 2.7 × 0.7 mm (256 point × 64 lines) area in an approximately 0.3 mm deep layer for Doppler-shift caused by moving red blood cells (Operation Software Release 1.01, Heidelberg Engineering GmbH, 1995, Heidelberg, Germany). The wavelength of the diode laser source is 780 nm, its power is 100 μW. Dilated pupils are not required. The digital resolution is 10 μm. The acquisition time is 2.048 sec. During this period each line is scanned 128 times by the confocal optical system, i.e. the line repetition frequency is 4000 Hz.

After a fast Fourier transformation a topographical image and three corresponding, brightness-coded perfusion images ('volume', 'flow' and 'velocity' surface maps) are provided automatically. The perfusion maps are derived from the Doppler-shift, and they can be used for detailed analysis. Mean red blood cell 'volume' (a value which is proportional to the number of the 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 all the moving red blood cells inside the sample volume per unit time) and 'velocity' ('flow' divided by 'volume') values belonging to the actual position of the measuring frame are provided immediately in arbitrary units. It is important to emphasize that the meaning of 'flow' obtained with scanning laser Doppler flowmetry is not identical to the conventional meaning of flow (velocity times cross sectional area).

The default size of the measuring frame is 10 × 10 pixel (approximately 100 × 100 μm). The Fourier transformed entire images can be used for detailed examination. However, vessels larger than precapillaries are to be avoided, because the Doppler frequency in such vessels is higher than 2000 Hz, the upper limit for exact measurement. Low values under 125 Hz are automatically excluded from the analysis to reduce the influence of heart action and breathing. Eye movements are represented by horizontal lines. Blinking causes black frames in the image series before fast Fourier transformation. Based on these features the incorrect recordings can be easily excluded from the evaluation.

Our method of flowmetry

One randomly selected eye (without pupillary dilatation) was tested in each person with five consecutive image acquisitions. To reduce eye movements a red light was used for fixation. A 10 × 2.5 degrees field size was applied. The optic nerve head was positioned in the center, and the image was focused on the retinal surface. Image series were checked for blinking and eye movements. The default 10 × 10 pixel-sized frame was applied for the measurements.

To determine the reproducibility, the first two technically correct and good quality images per eye were evaluated. Flow was measured in an area defined by a superficial retinal capillary crossing on the temporal and nasal retina, respectively, outside the 300 μm peripapillary area and any peripapillary atrophy, if present. The neuroretinal rim was tested in a single temporal position avoiding large vessels. Reproducibility was defined by the coefficient of variation calculated as standard deviation divided by the mean.

To study the effect of the location on the flow result, the frame was moved along the horizontal meridian (one image per person) in randomly selected 34 control subjects, 27 POAG and 10 NPG patients. The frame was placed adjacent to its previous location, and the flow values belonging to each studied position were registered. Large retinal vessels and cilioretinal arteries were avoided. By this method one to four temporal and nasal retinal locations were measured. These locations were outside the 300 μm peripapillary area, and any peripapillary atrophy, if present. Interlocation variation was defined by the coefficient of variation belonging to the first two locations on the temporal and nasal retina, respectively. It was calculated as standard deviation divided by the mean.

Intraocular pressure was measured either with a Goldmann applanation tonometer or an Ocular Blood Flow Tonograph (OBF Labs, U.K.) immediately after flowmetry.

Spearman Rank Order Correlations were applied when the effects of age and actual intraocular pressure were investigated. Three-way analysis of variance (ANOVA) was applied when the effects of patient groups and type of treatment were analysed. Temporal and nasal retinal as well as disc rim flow were compared with Wilcoxon Matched Pairs Test. P values of less than 0.05 were considered significant.

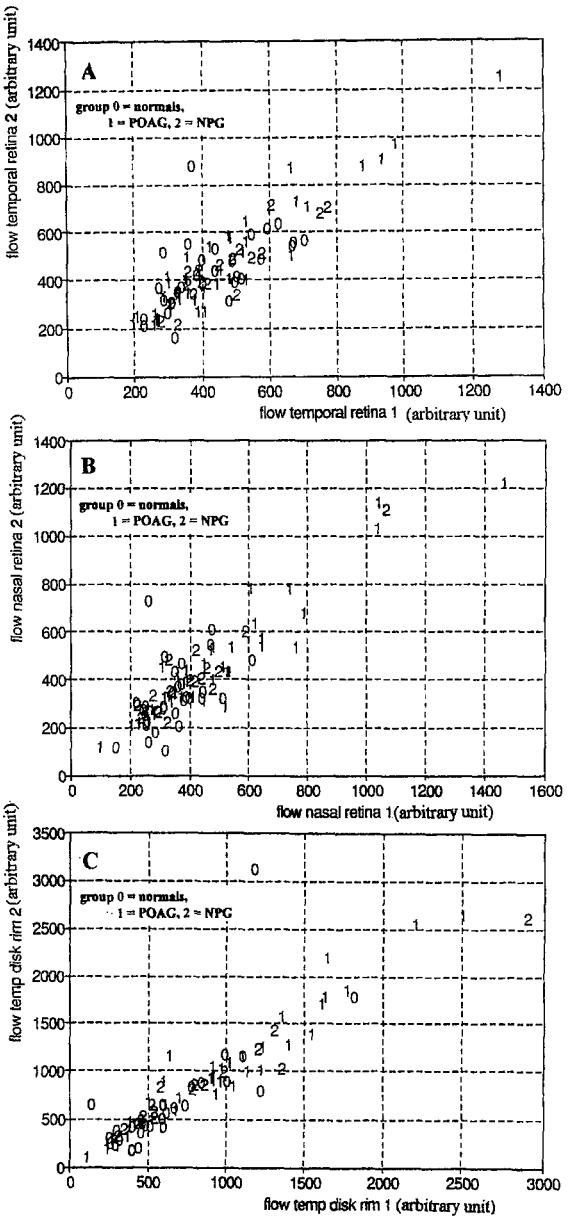

Figure 1. Flow measured at identical capillary crossings of two consecutive images. The corresponding readings are plotted against each other. (*A*): temporal retinal flow, (*B*): nasal retinal flow, (*C*): temporal neuroretinal rim flow.

Results

Because of the relatively long duration (2.048 sec) of image acquisition, it was not easy to obtain repeated image series without significant eye movements especially in glaucoma patients, who were on average 7 years older in the POAG and 10 years older in the

Table 1. Reproducibility of flow measurements

	Reproducibility (%)		
	Temporal retina	Nasal retina	Temporal disc rim
Controls, uncorrected	19 (N = 31)	26 (N = 30)	28 (N = 28)
Controls, corrected	17 (N = 30)	19 (N = 28)	18 (N = 26)
POAG	12 (N = 42)	12 (N = 40)	12 (N = 38)
NPG	12 (N = 17)	13 (N = 17)	10 (N = 17)

NPG group than the control persons. Dry eyes, severe visual field deterioration of the fixating fellow eye as well as failure to co-operate diminished the ability to obtain satisfactory images. Small pupils due to pilocarpine medication, fine posterior subcapsular cataract and mucus clumps on the corneal surface caused low quality of the perfusion images.

Two control subjects (6.4% of the original sample) and 12 glaucoma patients (20.3% of the original sample) had to be excluded from the study due to low quality images. Also, in 27 control persons (87%) and 55 glaucoma patients (93%) it was not possible to identify exactly all three selected locations of interest in all five consecutive image series. To eliminate this problem only the first two technically optimal images with the three clearly visible locations of interest were analysed for reproducibility.

Most flow values measured at identical points on two consecutive images were similar in all groups (Figure 1). The few outlying measurements of healthy volunteers may represent unrecognized technical problems. The reproducibility coefficients are shown in Table 1. Reproducibility was similar in both glaucoma groups: in POAG it was 12% at all sites. In NPG its value varied between 10% and 13% depending on the location. In healthy volunteers, however, the coefficient of variation was higher: it varied between 19% and 28% when outlying values were included but varied still between 17% and 19% when the most prominent outlying readings were excluded (Table 1).

Distribution of temporal retinal, nasal retinal and disc rim flow values (readings applied for reproducibility calculations) plotted against age is given in Figure 2. An increase with age both in the temporal and nasal retinal flow was observed when all persons were involved in the analysis ($p < 0.05$). Analysing the groups separately, a borderline significance was found in the POAG group ($p < 0.03$, $p < 0.01$, $p = 0.05$ and $p = 0.08$ when values measured the first and second time on the temporal and nasal retina were analysed, respectively). No correlation was observed within the control and NPG groups.

Table 2. Age-corrected mean flow values and standard deviations

	Controls	POAG	NPG
	mean (SD) in arbitrary units		
Temporal retina	438(139)	453(238)	470(144)
Nasal retina	338(100)	467(278)	416(194)
Disc rim	617(369)	983(556)	844(624)

Age-corrected mean (SD) flow results are summarised in Table 2. Temporal retinal flow was 438(139) in the controls, 453(238) in POAG and 470(144) in NPG in arbitrary units. The corresponding nasal retinal flow results were 338(100), 467(278) and 416(194) unit. Flow belonging to the temporal neuroretinal rim was 617(369) unit in healthy volunteers, 983(556) unit in POAG and 844(624) unit in NPG. The difference in flow between the study groups was not statistically significant ($p = 0.11$). Mean temporal retinal flow was higher than the corresponding mean nasal retinal flow in all groups. A borderline significance was found when temporal and nasal retinal flow were compared ($p = 0.068$ when values measured first time and $p < 0.02$ when values measured second time were compared). Disc rim flow was significantly higher than retinal flow ($p < 0.000001$).

A positive correlation with a borderline significance was found between the neuroretinal rim flow and actual intraocular pressure ($p = 0.065$ when flow values measured first time and $p < 0.03$ when flow values measured second time were investigated). No correlation was noted between retinal flow and actual intraocular pressure as well as between flow and type of treatment.

Measurements of adjacent frame positions along the horizontal meridian were performed to estimate the local effects within a large (temporal or nasal) retinal sector. In Figure 3 flow results belonging to the first two adjacent temporal and nasal locations are plotted

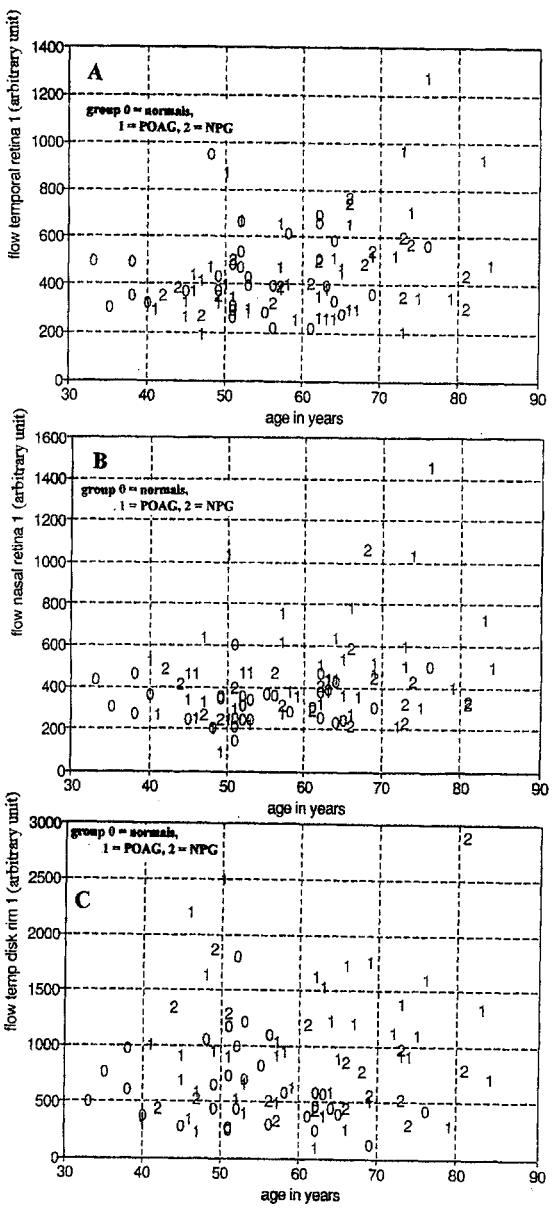

Figure 2. Flow plotted against age. The values reflect one reading per subject used also for the reproducibility calculations. (*A*): temporal retinal flow, (*B*): nasal retinal flow, (*C*): temporal neuroretinal rim flow.

Table 3. Interlocation variation of the flow values

	Interlocation variation (%)	
	Temporal retina	Nasal retina
Controls	18 (N = 30)	23 (N = 29)
POAG	19 (N = 24)	19 (N = 27)
NPG	8 (N = 6)	24 (N = 9)

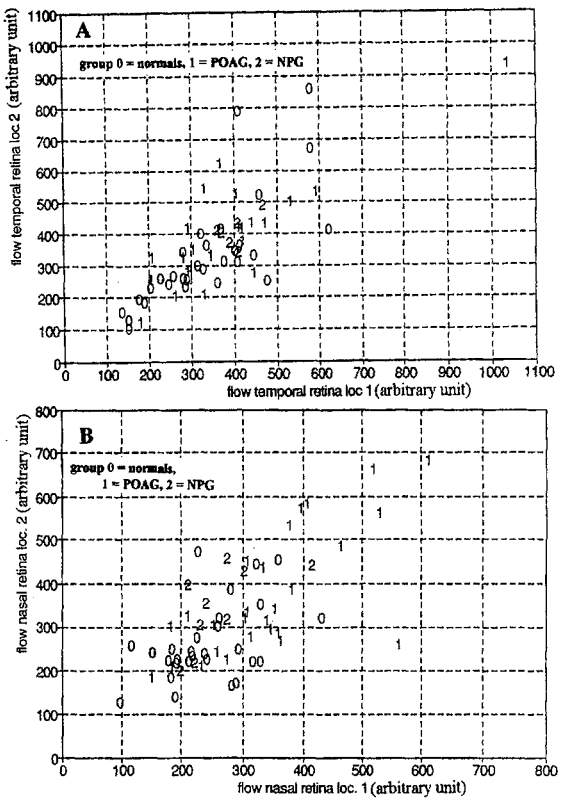

Figure 3. Retinal flow values belonging to adjacent frame positions plotted against each other. (*A*): first two readings on the temporal retina, (*B*): first two readings on the nasal retina.

against one another, respectively. The graphs show considerable differences. Interlocation differences are shown in Table 3. Mean interlocation variation was 20.5% in healthy volunteers, 19% in POAG and 16% in NPG. The overall interlocation variation was 18.5%.

It was interesting to study the tendency of the location-dependent flow changes inside the two retinal sectors. In the temporal retina (Figure 4), when moving the frame from the periphery to the disc, both increases and decreases occurred frequently. In the most central locations a decrease was detected in most cases. Moving the frame from the disc to the nasal periphery, a slight increase was recorded in several subjects, however, a decrease also occurred frequently.

Temporal and nasal flow values belonging to the same images differed considerably in all groups (Figure 5). The difference in flow between the temporal and nasal sectors was even larger than between adjacent locations inside a sector (Figure 3).

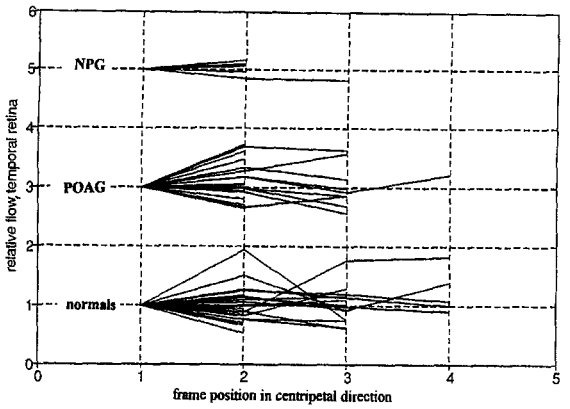

Figure 4. Flow changes along the horizontal meridian on the temporal retina. The consecutive values are compared to the first i.e. the most temporal reading. POAG is displaced by + 2, NPG is displaced by + 4 compared to normals.

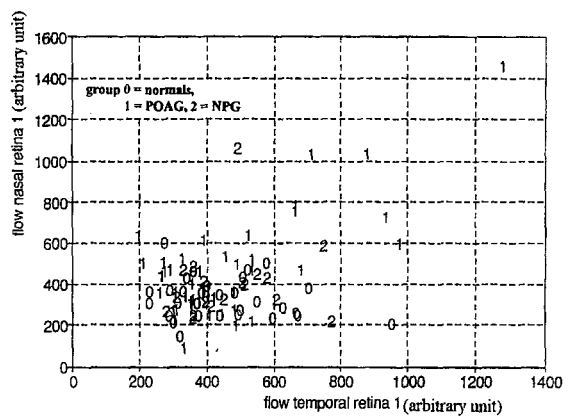

Figure 5. Temporal flow plotted against nasal flow. The corresponding temporal and nasal values belong to the same image and were used for reproducibility calculations as first measurements.

Discussion

The reduction of blood flow in the optic nerve head has been offered as one of the possible explanations for the pathogenesis of glaucoma. In order to substantiate this hypothesis it is necessary to quantify the changes in blood flow and to relate these changes to the progression of the disease. Quantification of blood flow behaviour is also necessary for the determination of the effect of topical and systemic medication on blood flow. Scanning laser Doppler flowmetry with the Heidelberg Retina Flowmeter has been offered as a new, quick and non-invasive possibility for the evaluation of the retinal capillary circulation.

Scanning laser Doppler flowmetry claims to measure values in the retinal capillaries which are representative of blood flow in these capillaries. One of these flow, values, was used for the investigation in this study. It is important to remember that the meaning of 'flow' measured by the Heidelberg Retina Flowmeter is similar but not identical with the meaning of flow measured by other methods. 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 per unit time within the sample volume.

In our series of patients the reproducibility in all locations was satisfactory, although in the normal subjects there were some outlying values for unknown reasons. In our unselected group of glaucoma patients we could not find any difference in flow between the normals and the patient groups. Thus, we were not able to reproduce the results of Michelson and colleagues [30].

How can this finding be explained? It is known from other methods that patients with glaucoma and particularly NPG may show a considerable reduction of blood flow in up to 50% of cases [3, 4, 20]. One might suppose that the patient selection in this population was the reason for the lack of significant differences between the groups. However, measurements with another blood flow technique in the same group of patients did show deficient blood flow values in the patient group [31].

There are differences between our groups and the groups of Michelson. Mean intraocular pressure values were similar in both studies; however, the mean age was 11 years higher in our normal subjects, 4 years higher in our POAG patients and 7 years higher in our NPG patients than the corresponding mean ages in Michelson's subjects. The frequency of the different types of treatment was also different: 44% of our patients received topical beta receptor blocker drops in contrast to 62% in Michelson's group. Twenty-five percent of our glaucoma patients underwent filtering surgery, in Michelson's study this rate was 16%. In contrast to our patients a considerable number of his glaucoma patients received topical alpha adrenergic and cholinergic medication and underwent argon laser trabeculoplasty. Another difference was the rate of myopes in the control and glaucoma patient groups. We evaluated the significance of myopia in another study [32]. The rate of myopic eyes was 35% in our healthy controls and 59% in our glaucoma patients. However, we have no information on the frequency of myopic subjects in Michelson's study.

The question arises whether this technique actually measures the flow within the retinal capillary layer. It is claimed that the flow in a slice of 300 μm thickness is measured. It is conceivable that if the thickness of the retina is reduced, flow values from the underlying choroid may be obtained on images focused on the retinal surface. It is known that in glaucoma patients the thickness of the retinal nerve fibre layer may be considerably reduced [33–38]. It has been shown that once choroidal measurements are involved, the obtained values may be much higher [32]. This may explain the tendency for higher values in the glaucoma groups.

Reduced retinal thickness in glaucoma patients resulting in detection of Doppler-shift from the deeper layers might also explain the positive correlation between age and retinal flow as well as between actual intraocular pressure and neuroretinal rim flow. Age was considerably higher both in the POAG and the NPG groups compared to the control subjects. Also, mean intraocular pressure was higher in POAG patients than in healthy volunteers.

One of the major problems with this technique is that the measurements are extremely location dependent as shown in Figures 3, 4 and 5. It can be seen from Figure 5 that in the individual subjects there may be substantial differences in flow between the temporal and nasal retina. In order to obtain reproducible values, the measurements have to be at exactly the same locations. It could also be seen that even in adjacent areas, flow values may be quite different as shown in Figure 3 with a coefficient of variation up to 24%.

Figure 4 demonstrates that in adjacent locations any type of difference can be found when moving along the horizontal meridian. These location-dependent differences are a handicap in obtaining reproducible results, however they do not explain the lack of differences between the patient groups and the controls.

Scanning laser Doppler flowmetry with the Heidelberg Retina Flowmeter is an interesting option for the measurement of blood flow related indices of the retinal capillary circulation. The reproducibility is satisfactory. The results are highly location dependent. This study could not find differences between controls and glaucoma patients. Further studies are needed to elucidate discrepancies between this study and the earlier reports.

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