The Force Required to Induce Hemivein Pulsation Is Associated with the Site of Maximum Field Loss in Glaucoma

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Purpose. To determine the factors associated with central retinal vein pulsation changes in glaucoma and identify any hemiretinal vein pulsation changes and their association with sectoral visual field loss.

Methods. One hundred twenty-six patients with glaucoma and 40 normal subjects had automated perimetry, blood pressure, and intraocular pressure measured. A hemifield sensitivity loss was calculated from the upper and lower halves of each field. Those without spontaneous venous pulsation on the optic disc had an ophthalmodynamometer applied, to measure the minimum ophthalmodynamometric force (ODF) necessary to induce venous pulsation. When ODF was restricted to the hemiveins, the force needed to induce pulsation in each hemivein was measured.

Results. Eighty-three patients with glaucoma had no spontaneous venous pulsation. The minimum ODF was strongly correlated with mean deviation (Spearman rank $r = -0.475$, $P < 0.0001$). Mixed linear regression analysis showed that mean deviation ($P < 0.0001$) and pulse blood pressure ($P < 0.0001$) were significantly associated with minimum ODF. There was a strong association between differences in hemifield sensitivity loss and in hemivein ODF (rank $r = 0.369$, $P < 0.0001$, $n = 80$). Multiple linear regression modeling demonstrated that lower hemivein ODF was independently associated with upper field loss ($P = 0.003$) and upper hemivein ODF with lower field loss ($P < 0.0001$).

Conclusions. These venous pulsation findings in glaucoma are independent of blood pressure. The hemifield and hemivein association suggests that the major hemivein change is adjacent to the site of major disc damage. (*Invest Ophthalmol Vis Sci.* 2005;46:1307–1312) DOI:10.1167/iovs.04-1126

Blood flow changes are known to occur in glaucoma.[1,2] In addition, the observation of disc rim hemorrhages indicates the presence of altered circulation within the optic disc.[3,4] It is not known where the major vascular changes occur within the vascular tree in glaucoma. However, venous collaterals are commonly seen on the optic disc,[5] and there is a strong relationship between glaucoma and central retinal vein occlusion and also hemiretinal vein occlusion.[6,7] Most previous work has tended to concentrate on the arterial side of the circulation.[8] In the present study, we examined in more detail the retinal vein pulsation changes that occur in glaucoma[9] and attempted to identify the factors associated with these changes.

Extensive previous work has been conducted to model the blood flow through the eye, which resembles that through a modified Starling resistor apparatus, taking into account the pulsatile character of the intraocular and cerebrospinal fluid pressures.[10–12] Clinical observation and modeling work demonstrate that various factors influence the minimum intraocular pressure (IOP) necessary to induce vein pulsation, termed venous pulsation pressure (VPP). An increase in cerebrospinal fluid pressure is known to elevate VPP,[13,14] as is an increase in systemic blood pressure.[11] A decrease in pulse blood pressure also elevates VPP.[15] Modeling experiments show that increasing the resistance of the vessel before entering the pressurized chamber, in a manner analogous to increased arterial resistance, reduces VPP.[11] This work also demonstrates that increasing the resistance of the vessel at its outlet from the chamber increases the chamber pressure necessary to cause vessel collapse. This effect is analogous to anastomosis or narrowing of the central retinal vein, and it has been observed in patients with central retinal vein occlusion.[16,17]

Previous work has demonstrated that patients with glaucoma have less frequent spontaneous venous pulsation than their normal counterparts and that patients with glaucoma with more severe disease have less frequent spontaneous venous pulsation than their less-affected counterparts.[9] Greater force must also be applied to their eyes to induce vein pulsation, and hence they have a greater VPP.[9,18] In this early work, we did not measure systemic blood pressure and so were unable to identify the likely cause of the alteration in pulsation characteristics. While conducting that work, we noted that most subjects had pulsation within their hemiveins and that the hemiveins joined to form the central retinal vein as it passed into the lamina cribrosa. Generally, the central retinal vein did not pulsate, but the pulsation was restricted to the hemiveins. In this study, we examined a group of patients with glaucoma and measured the ophthalmodynamometric force (ODF) necessary to induce venous pulsation in hemiveins that were not observed to be pulsating spontaneously, to allow a comparison with glaucoma severity and correlation with blood pressure and other variables. When it is possible to measure the ODF in both hemiveins in the same eye, one can subtract the results and examine the difference, thereby eliminating the influence of factors acting equally on both hemiveins. Such factors are IOP, blood pressure, pulse pressure, cerebrospinal fluid pressure, and other systemic factors. By examining the relationship between hemivein ODF difference and visual field sector difference, we can test whether local optic disc changes are associated with hemivein changes.

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VPP can be measured directly in normal subjects with spontaneous venous pulsation by lowering IOP to a level where pulsation ceases and is then observed to recur.[11] However, we have found that such IOP lowering by ocular compression in glaucoma is too difficult to be feasible. In subjects who do not have spontaneous venous pulsations, ODF can be measured with an ophthalmodynamometer. The VPP can be calculated by using an empiric relationship derived from experiments in pigs in which VPP = IOP + 0.72 × ODF.[19] This relationship makes several assumptions and so, in this work, the measured variable ODF was used in our analysis. We assume that subjects with spontaneous venous pulsation have an unknown negative ODF. In the first analysis, we examined the relationship between the minimum central retinal vein or hemivein ODF and total visual field defect and other variables. In the second analysis, we examined the hemivein and hemifield difference in subjects without spontaneous venous pulsation.

Methods

One hundred twenty-six patients with glaucoma and 40 normal subjects were examined. Some of the data from the normal subjects have been published,[9] whereas none of the data from this glaucoma cohort have been described. All those with glaucoma were eligible patients who were in follow-up at a glaucoma practice and were examined consecutively over a 12-month period by one clinician. These subjects had at least a −4-dB mean deviation field defect in one eye. The normal subjects were invited to participate separately. This research adhered to the tenets of the Declaration of Helsinki in accordance with the University of Western Australia's human ethics committee, with measurements taken after informed consent had been obtained from the subjects.

Patients with glaucoma were defined as subjects with a repeatable Humphrey 24-2 full-threshold field (Carl Zeiss Meditec, Dublin, CA), consistent with glaucoma and congruent excavation of the optic disc with neuroretinal rim loss. All patients with glaucoma had at least two visual field tests performed, the second being performed within 3 months of the examination. This visual field was divided into an upper and lower hemifield across the horizontal midline, and the total deviations were added together to determine the total sensitivity loss for each hemifield. The difference between the upper and lower total sensitivity loss was then calculated.

Non–blood relatives or friends of patients with glaucoma were invited to participate as normal subjects. They were required to have a normal ophthalmic examination including a Humphrey visual field test with normal results, with reliability indices better than 25%. Subjects with IOP of >21 mm Hg or any other abnormal ocular feature were excluded.

To be included in the study, all subjects had to have sufficient ocular media clarity and pupil dilation to allow clear visibility of the optic disc and retinal vessels. All eyes were examined after dilation. IOP was measured in a complete ophthalmic examination, including visualization of the optic disc and blood vessels. Pulsation of the hemiretinal veins or branch retinal veins on the disc surface was classified as pulsation of the contiguous hemivein (Fig. 1). The state of pulsation of the hemiveins and central retinal vein were noted. If any of the hemiveins and/or central retinal vein were pulsating spontaneously, it was documented. If spontaneous venous pulsation was absent, an ophthalmodynamometer (American Optical, Buffalo, NY)[20] was applied, and the force gradually increased on the corneal surface until pulsation was observed. If the veins could not be induced to pulsate, then this result was recorded, and the data were excluded from the analysis. If the central retinal vein pulsated before either hemivein, then this minimum ODF was documented, and the patient's data were included only in the first segment of the analysis. If one hemivein was induced to pulsate, then this minimum ODF was recorded and the force increased until the opposite hemivein pulsated, at which point

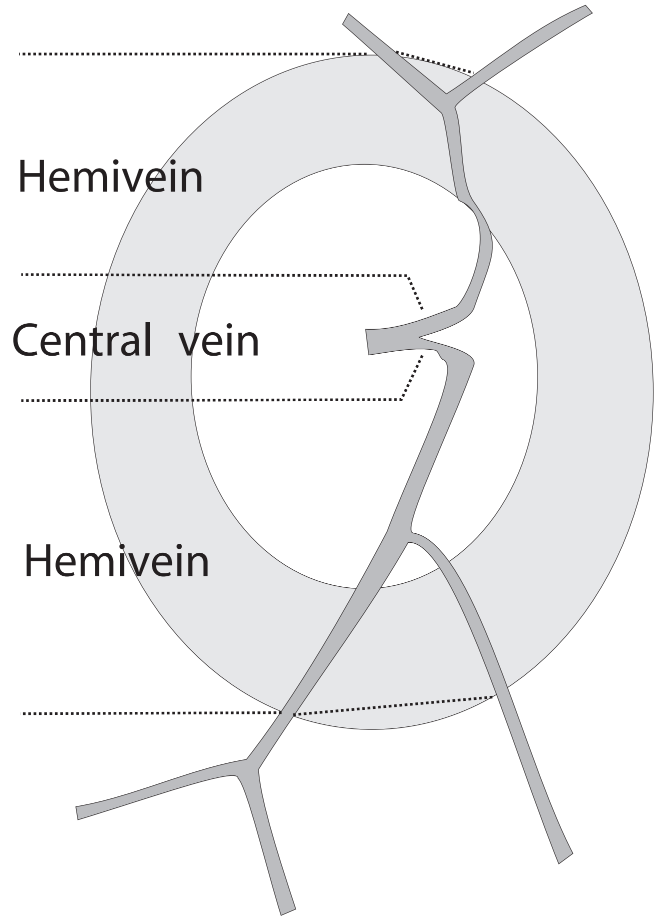

Figure 1. Illustration of the branch vein draining into the hemiveins and into the central retinal vein. Pulsation at the hemiveins or branch veins was classified as hemivein pulsation.

the greater ODF was recorded. The difference between the ODF from each hemivein was recorded and compared to the difference between ODF in the upper and lower visual fields.

Blood pressure was measured with the cuff around the humerus and the arm elevated so that the cuff was maintained at the same horizontal level as the eye, so that the measured arterial pressure would be close to the internal carotid artery pressure.[21,22] The mean blood pressure and the pulse blood pressure were calculated in each instance. The vertical distance between the suprasternal notch and the horizontal level of the eye was also measured. This measurement was taken as a substitute for cerebrospinal fluid pressure to see whether this indirect and approximate measurement from the hydrostatic-indifferent point[23] to the eye was related to the presence of glaucoma and/or influenced spontaneous venous pulsation.

Reproducibility of the ODF measurements was assessed by taking multiple measurements at one time and taking measurements on two separate occasions. First, nine measurements of hemivein ODF were taken in patients with glaucoma who had no spontaneous venous pulsation. The technique described herein was used, with the ophthalmodynamometer pulled back from the patient's eye and the force dial set to zero between measurements. The ophthalmodynamometer was reapplied and the force increased until the pulsation end point was reached, at which stage it was read by a separate observer. A group of patients with glaucoma were invited back to the clinic to be remeasured between 3 days and 4 weeks after the initial assessment. They had an additional measurement of hemivein ODF performed at that second visit.

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TABLE 1. Characteristics of the Glaucoma and Normal Study Groups

	Age	IOP R	IOP L	Pulse BP	Mean BP	Sternal Notch	Females
Glaucoma							
Mean	67.3	15.8	16.7	58.6	80.34	19.8	70
n	126	83	84	126	126	126	126
SE	1.09	0.43	0.57	2.1	1.2	0.15	
Normal							
Mean	65.6	15.9	16.1	69.4	85.7	19.7	23
n	40	36	36	40	40	40	40
SE	1.8	0.53	0.52	3.0	2.4	0.22	
p	0.43	0.91	0.52	0.01	0.04	0.57	0.97

Pressure data are expressed in mm Hg; sternal notch data are expressed in centimeters. R, right eye; L, left eye.

Data Analysis

We used χ^2 tests (2 × 2 contingency tables) to analyze the difference between spontaneous and absent venous pulsation ratios and the male-to-female ratios between the normal and glaucoma groups. Student's *t*-test was used to examine the difference between the mean measured continuous variables of each of the two groups. Use of the *t*-test was judged appropriate by appeal to the Central Limit Theorem, having inspected the distributions of the variables concerned. The reproducibility data were analyzed, and the mean, standard deviation, and coefficient of variation were calculated.[24]

The influence of various variables on the minimum ODF was analyzed in a linear mixed (regression) model.[25] Data from both eyes (when available) were modeled by using patient-specific random effects to account for the intereye correlation in the manner described by Rosner.[26] The ODF was modeled as a normally distributed response, left-hand censored at zero in cases with spontaneous venous pulsation. This censoring can be interpreted in terms of unknown negative values of ODF in such cases and has been described previously.[9] The specific variables mean deviation, IOP, pulse blood pressure, mean blood pressure, and sternal notch-to-eye distance were used, in addition to age, as predictors of ODF. The model was fitted using Gibbs sampling[27,28] and implemented with the software package BUGS (Bayesian inference using Gibbs sampling; Medical Research Council Biostatistics Unit, Cambridge UK).[29] Vague Bayesian priors were applied to all unobservables.[30]

Mean deviation was correlated directly with ODF by using Spearman's rank correlation method. Data from the right eye were used if available; otherwise, left eye data were used.

The difference between the hemivein ODF was correlated with the difference between hemifield sensitivity loss using Spearman's rank correlation method. In addition, a nonparametric regression of hemifield difference on hemivein ODF difference was fitted by spline smoothing[31] extended to a semiparametric (multiple) regression incorporating linear terms in IOP, mean BP, age, and sex, as well as a spline term in hemivein ODF difference, as predictors for hemifield difference.[32]

RESULTS

One hundred twenty-eight patients with glaucoma were examined; however, two had noninducible venous pulsation and so were excluded. The remaining 126 patients and 40 normal subjects were examined, and their respective ages, IOPs, blood pressures, and sternal notch measurements are described in Table 1. The average mean deviation in right glaucomatous eyes was −13.6 ± 0.93 dB (SE) and in left glaucomatous eyes was −11.8 ± 0.72 dB. There was no significant difference in the age, IOP, sternal notch measurement, or sex ratios between groups. The pulse blood pressure and mean blood pressure were significantly lower in the glaucoma group than in the normal group.

Only 43% of patients with glaucoma had spontaneous venous pulsation in the right eye, whereas it was observed in 97% of normal right eyes. This difference in proportions was statistically significant (χ^2 with Yates correction, 28.1, $df = 1$, $P < 0.001$). The mean ODF in the patients with glaucoma was 18.4 ± 21.1 g (SD; $n = 47$) in the right eye and 13.5 ± 18.2 g, $n = 50$) in the left eye. Only one normal right eye did not have spontaneous venous pulsation, with an ODF of 8 g, whereas only two left eyes did not (mean ODF, 11 g).

Eleven pairs of hemivein ODF measurements, from 11 patients, were repeated nine times, with a mean SD of 2.4 (mean ODF, 17.4) and a mean coefficient of variation of 21% ± 11.5% (SD). Twenty-one eyes of 21 individuals were examined on two separate occasions, with mean hemivein ODF of 7.8 g ($n = 84$). The mean difference between initial and second ODF measurements was 4.1 ± 4.9 g.

When data from both eyes were examined in the mixed linear regression model, gender, age, and sternal notch measurement were not independently associated with ODF. Mean deviation was shown to be the most statistically significant predictor of ODF ($P < 0.0001$, Table 2). Pulse blood pressure was the other significant predictor ($P < 0.0001$). A lower-pulse blood pressure was associated with a greater ODF. A greater mean blood pressure tended to be associated with greater ODF, but this relationship did not reach formal statistical significance ($P = 0.08$). In addition, a lower IOP tended to be associated with a greater ODF but again did not reach formal statistical significance ($P = 0.08$). When blood pressure and pulse blood pressure were excluded from the linear model, lower age was found to be significantly associated with an increased ODF ($P = 0.03$). There was a significant linear correlation between age and mean blood pressure ($r = 0.3$, $P < 0.0001$), so that, with increasing age, there tended to be an increased mean blood pressure. In addition, age was even more strongly associated with pulse blood pressure ($r = 0.45$, $P < 0.0001$), and thus an increased age was associated with an increased pulse pressure. The intereye correlation with the original linear mixed model was 0.25 ± 0.20 (SE).

TABLE 2. Mixed Linear Regression Results

	Estimate	SE	*P*
Intercept	−11.98	10.44	0.25
Mean deviation	−2.07	0.21	<0.0001
IOP	−0.73	0.41	0.0765
Pulse BP	−0.38	0.09	<0.0001
Mean BP	0.24	0.14	0.0796

Data model the influence of key parameters on minimum ODF.

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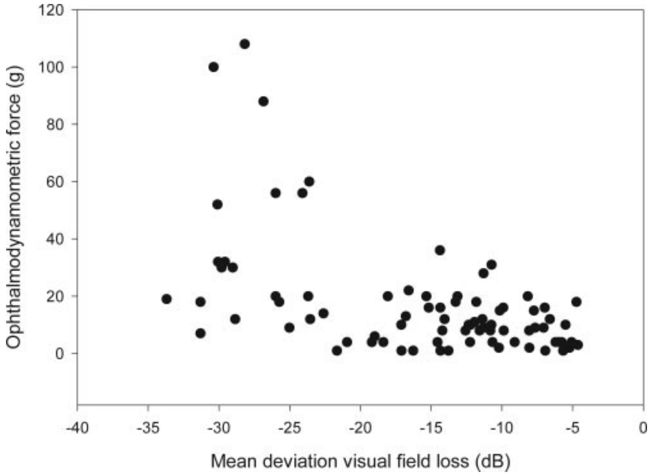

Figure 2. Glaucoma severity versus venous pulsation force. In 83 patients with glaucoma without spontaneous venous pulsation, the ODF necessary to induce venous pulsation was greater in those with more visual field loss, when measured by the mean deviation (MD; Spearman rank, $r = -0.475$, $P < 0.0001$).

Of the 126 patients with glaucoma examined, 83 had no spontaneous pulsation in one or both eyes. When no spontaneous pulsation was present in both eyes, only data from the right eye were analyzed. A direct correlation of ODF and mean deviation demonstrated a Spearman rank correlation coefficient of -0.475 ($P < 0.0001$). Figure 2 demonstrates the relationship between visual field severity and ODF in the patients with glaucoma.

Of the 83 patients with glaucoma with no spontaneous venous pulsation, 3 had induced pulsation in the central retinal vein and were excluded from subsequent analysis. The remaining 80 subjects had separate induced pulsation in each hemivein. Figure 3 demonstrates the relationship between the hemivein ODF difference and hemifield difference. The y-axis is the upper hemifield sensitivity loss minus the lower hemifield sensitivity loss. A positive value reflects a worse lower visual field. Data to the right of the x-axis indicate that greater force was needed to induce pulsation in the upper hemivein than in the lower hemivein. Spearman's rank correlation coefficient was 0.369 ($P < 0.0001$). Both linear (adjusted $r = 0.26$, $df = 2$) and spline curve fit (adjusted $r = 0.46$, estimated $df = 4.4$, $P < 0.0001$) models were applied, with the spline curve being a significantly better fit than the linear model ($P = 0.001$).

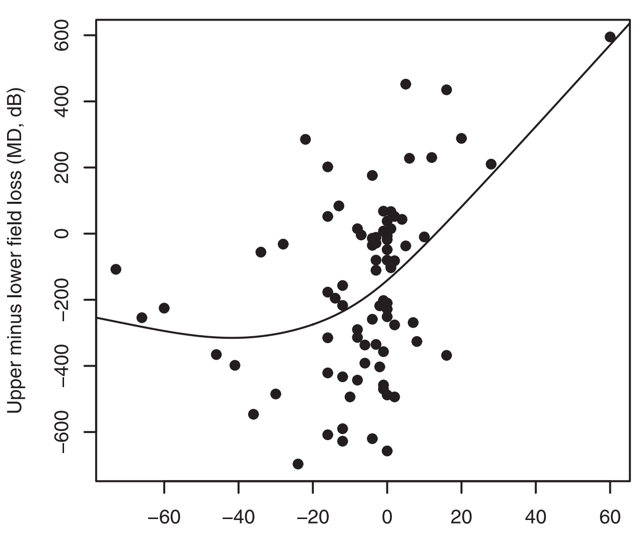

Figure 3. The relationship between hemifield and hemivein differences. The sum of the sensitivity loss in the upper half of the visual field minus the summed loss from the lower half of the visual field is represented along the ordinate, with a positive value indicating a worse lower visual field. The force necessary to induce pulsation in the upper hemivein minus that required for the lower hemivein is represented along the abscissa. A significant relationship exists between these two parameters (Spearman rank, $r = 0.369$, $n = 80$, $P < 0.0001$).

Table 3. Multiple Regression Results

	Estimate	SE	P
Intercept	−185	54.1	0.001
Upper − lower ODF	9	1.7	<0.0001
Mean deviation	−5.4	3.6	0.133
IOP	−0.001	0.0026	0.605
Mean BP	0.001	0.0026	0.703

Data model the influence of key parameters on the difference in hemifields.

A semiparametric multiple regression model, combining linear parametric and smoothing spline terms, was used to model the effect of key variables on the hemifield difference. The results for the parametric terms in the model are described in Table 3. The only parametric term found to be significantly associated with the difference between hemifield sensitivities was the difference in hemivein ODF ($P < 0.0001$). In addition, a spline function in dODF (difference between upper and lower hemivein ODF) was significant ($\chi^2 = 11.585$; estimated $df = 1$, $P = 0.0011$).

When multiple linear regression was performed modeling the effect of upper hemivein ODF, lower hemivein ODF, age, sex, IOP, and mean and pulse BP on upper hemifield loss, lower hemivein ODF was found to be independently associated with upper hemifield loss ($P = 0.004$). Upper hemivein ODF, sex, IOP, and mean and pulse blood pressure were not associated with upper field loss. Similarly, when the effect of upper hemivein ODF was modeled, lower hemivein ODF, age, sex, IOP, and mean and pulse BP on lower hemifield loss, upper hemivein ODF was found to be independently associated ($P < 0.0001$). Sex was associated with lower hemifield loss ($P = 0.001$), and males were more likely to have a worse inferior hemifield. Pulse and mean BP, IOP, and lower hemivein ODF were not associated with lower hemifield loss. Increasing age was found to be significantly associated with both upper ($P = 0.001$) and lower ($P = 0.02$) hemifield loss.

Discussion

These results confirm those in our previous report[9] that spontaneous venous pulsation is significantly less common in patients with glaucoma than in normal subjects ($P < 0.001$). Our hemivein collapse reproducibility results (mean coefficient of variation, 21%, ± 11.5% [SD]) were similar to those published by Jonas, who found a mean coefficient of variation for central retinal vein collapse of 16.3% ± 11.4%).[24]

This work confirms the strong relationship between mean deviation and minimum ODF necessary to induce vein pulsation (Spearman $r = -0.475$, $P < 0.0001$). In patients with glaucoma, subjects with worse visual fields tended to need a greater ODF. This relationship was independent of mean blood pressure, pulse blood pressure, and IOP (Table

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2, $P < 0.0001$). It is known that subjects with elevated mean blood pressure require a greater ODF to induce vein pulsation.[11] Of note, our patients with glaucoma had a lower mean blood pressure than the normal group (Table 1). Hence, this work demonstrates that elevated blood pressure is not the cause of the greater ODF necessary to induce vein pulsation in patients with glaucoma. It is not plausible to postulate that raised cerebrospinal fluid pressure is the cause of the increased ODF, because an ODF of 40 g corresponds to a 30-mm Hg increase and would require a 40-mm Hg cerebral spinal fluid pressure,[13] leading to considerable morbidity including papilledema, which was not seen in any of our subjects.

In our previous report,[9] increased age was found to be significantly associated with a reduced ODF. In this analysis when we eliminated pulse and mean blood pressure from our linear model, age was again found to be associated with ODF. Independently, age was found to be strongly correlated with pulse pressure and less so with mean blood pressure. An increasing pulse pressure was associated with a decrease in ODF, and so it is likely that this effect dominates the age effect on ODF, resulting in a decline in the ODF needed as the subject ages.

Retinal microvascular changes can lead to alterations in vein pulsation. Flow models demonstrate that reduced retinal vessel resistance will increase the ODF necessary for vein pulsation.[33] Previous work, however, demonstrates that microvascular resistance increases in glaucoma subjects.[8] Hence, it is very unlikely to be the cause of the raised ODF in our patients with glaucoma. That the greater hemifield loss is linked to greater ODF in the opposite hemivein (Fig 3, Table 3, rank correlation = 0.369, $P < 0.0001$), demonstrates that the dominant change in the optic disc occurs adjacent to the most affected hemivein. Our patients had a preponderance of upper field loss, which led to more data being on the left hand side of Figure 3. The relationship was nonlinear, with a tendency to asymptote to the left-hand side, as seen on the spline curve fit. This is not surprising, because there is a nonlinear relationship between optic disc neural tissue loss and field loss in decibels,[34] and the relationship between ODF and its causative factor(s) is likely to be nonlinear. Performing the difference analysis using hemivein and hemifield data from the same eye neutralized IOP, cerebrospinal fluid pressure, pulse blood pressure, mean blood pressure, and other systemic factors because their effect must be equal on both hemiveins. It is possible that the microvasculature in one half of the retina is predominantly affected. However, previous work demonstrates that at least one of the vascular changes in glaucoma is focal arteriolar narrowing, which would lead to a reduction in the ODF, not an increased ODF in the hemivein measured.[8,35]

A possible explanation for our observation is that resistance develops within the central retinal and hemiretinal veins in patients with glaucoma, and that patients with more severe glaucoma tend to have greater resistance within the central retinal vein and to some extent within the hemiretinal veins. The strong relationship between difference in hemifields and difference in hemivein ODF supports the hypothesis that some of the retinal vein change occurs within the hemiveins and that not all this change occurs within the central retinal vein. This conclusion is supported by the observation that upper hemifield loss is associated with lower hemivein ODF ($P = 0.004$) and is independent of upper hemivein ODF. Likewise, lower hemifield loss is associated with upper hemivein ODF ($P < 0.0001$) and is independent of lower hemivein ODF.

These results suggest that narrowing in the hemi- and central retinal veins may occur in glaucoma and that this narrowing is worse in subjects with worse glaucoma, consistent with the observation that central and hemiretinal vein occlusions are common in glaucoma and that glaucoma and raised IOP are the major predictive risk factors in these two conditions.[6,7]

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