Optic Nerve and Choroidal Circulation in Glaucoma

Juan E. Grunwald, Jody Piltz, Seenu M. Hariprasad, and Joan DuPont

PURPOSE. To investigate the circulation of the optic nerve head and choroid in patients with glaucoma.

METHODS. Laser Doppler flowmetry was used to determine optic nerve head relative blood velocity (ONVel), volume (ONVol), and flow (ONFlow) in 19 primary open-angle glaucoma patients and 15 age-matched healthy control subjects. In each subject, determinations were obtained from four sites on the neuroretinal tissue and from the center of the cup. A mean of the ONVel, ONVol, and ONFlow for these five measurement sites were calculated for each subject and defined as ONVel5, ONVol5, and ONFlow5. Circulatory parameters were correlated with measures of disease progression such as cup-to-disc ratio and Humphrey visual field indices. Measurements of relative choroidal blood velocity, volume, and flow were also obtained from the foveola.

RESULTS. In glaucoma patients, mean ONFlow5 was significantly lower than in control subjects (24%; P = 0.001; independent, two-tailed Student’s t-test). This decrease was caused by a significant decrease in ONVol5 (15%; P = 0.04) and a nonsignificant decrease in ONVel5 (10%; P = 0.07). In glaucomatous eyes, mean ONFlow was significantly reduced from normal, by 28% in the inferior temporal neuroretinal rim location (P = 0.001) and by 24% in the superior temporal location (P = 0.001). Although mean ONFlow was also decreased by 33% in the cup, the difference was not statistically significant after a Bonferroni correction was applied. No significant differences from normal were observed in the superior and inferior nasal rim tissues. In glaucoma patients, ONFlow5 was significantly and inversely correlated with the corrected pattern standard deviation (R = -0.53; P = 0.02) and with the cup-to-disc ratio (R = -0.65; P = 0.002). Choroidal blood flow measurements obtained in the foveola of glaucomatous eyes showed no statistically significant differences from normal.

CONCLUSIONS. ONFlow5 is reduced by approximately 24% in glaucoma patients. In the inferior temporal rim, the area in which nerve bundle defects most commonly occur, blood flow is reduced by 28%. Patients with more advanced glaucomatous damage, as detected by visual field corrected pattern standard deviation and measurement of the cup-to-disc ratio, tend to have lower ONFlow5. These results suggest a decrease in optic nerve blood flow that is correlated with functional and morphologic measures of glaucomatous progression. However, from these results we cannot conclude whether this decrease in flow has a primary role in the etiology of glaucoma or whether it is the result of the loss of neural components caused by this disease. (Invest Ophthalmol Vis Sci. 1998;39:2329-2336)

Glaucoma, one of the main causes of visual impairment,1-3 is a condition that results in typical morphologic optic nerve head changes and visual field loss. The mechanisms by which this disease develops are not clearly understood. Abnormalities of the circulation of the optic nerve head, retina, and choroid have been suggested to have a possible role in the etiology of glaucoma.4-27

The purpose of this study was to investigate the circulation of the optic nerve head and choroid in patients with glaucoma and to correlate circulatory findings with measures of glaucomatous damage such as visual field indices and extent of optic nerve cupping.

For this purpose, we used laser Doppler flowmetry to assess the optic nerve and choroidal circulation in a group of glaucoma patients. These results were compared with those of age-matched healthy volunteers.

METHODS

Nineteen eyes of 19 patients with primary open-angle glaucoma (POAG; 8 women and 11 men), ranging in age from 36 to 76 years (mean ± SD, 61 ± 12 years), were included in this study. The diagnosis of POAG was based on clinical observation and photographic documentation of characteristic optic disc changes, usually with typical optic nerve fiber bundle defects on Humphrey automated perimetry. Only one patient who exhibited progressive optic nerve head damage was
found not have a definitive glaucomatous visual field defect. Optic disc changes included localized notching, saucierization, and generalized rim loss. No patients had a cup-to-disc ratio larger than 0.9 or a bare lamina cribrosa. Visual field defects included focal, paracentral, arcuate, or nasal step defects using the Humphrey program 24-2. Localized defects were defined as an abnormal glaucoma hemifield test or a minimum of three adjacent defective locations in one hemifield of the pattern deviation plot, with one point having a probability of abnormality of $P < 1\%$ and two adjacent points having a probability of abnormality of $P < 2\%$. The three points of the cluster, including the $P < 1\%$ nucleus, were not located on the peripheral ring of test locations. Subjects had no pathology other than glaucoma that could account for the visual field defects.

All POAG patients had open anterior chamber angles. Sixteen of these patients had pretreatment intraocular pressures (IOPs) greater than 21 mm Hg, without any detectable ophthalmic or systemic cause for the elevated IOP. Three patients had pretreatment IOPs less than or equal to 21 mm Hg. Visual acuity was 20/40 or better in all subjects. Other patient characteristics are summarized in Table 1. Two of these subjects were receiving the following topical therapies: $\beta$-adrenergic blocking agents (12 patients), dorzolamide (8 patients), pilocarpine (4 patients), and latanoprost (5 patients). Four of these 19 patients had a history of systemic hypertension and were receiving systemic antihypertensive therapy. Patients with systemic hypertension were not excluded from the study because of the high prevalence of this condition in the glaucoma and healthy populations older than 40 years of age. In the Baltimore Eye Survey, for example, 42% of control subjects and 50% of POAG patients had systemic hypertension.28

Results from the glaucoma patients were compared with those of 15 eyes of 15 control subjects (9 women and 6 men) who had normal slit lamp, external eye, and funduscopic eye examinations. Control subjects ranged in age from 32 to 76 years (mean ± SD, 60 ± 13 years), had IOPs < 21 mm Hg, and had a cup-to-disc ratio of $\pm 0.4$. Other control subject characteristics are summarized in Table 1. Two of these subjects were receiving systemic therapy for systemic hypertension and elevated blood cholesterol levels.

Glucoma patients and control subjects with refractive errors greater than 4.00 diopters, cataract, aphakia, pseudophakia, unsteady fixation, or poor pupillary dilatation were excluded from this study.
Figure 1. Typical measurement sites on the optic nerve head. Site 2 is on the superior temporal rim, site 3 is on the inferior temporal rim, site 4 is on the inferior nasal rim, site 5 is on the superior nasal rim, and site 6 is on the cup. Site 1 is on the foveola (not shown in this figure).

The highlighted section depicts a segment of approximately 2 seconds selected for analysis.

In seven POAG patients and four control subjects, the procedure described above was repeated, and three separate determinations were made during the same experimental session to assess the reproducibility of the measurements. From these three measurements a coefficient of variability (CV) was calculated as $CV = (\text{mean/SD}) \times 100$.

Brachial artery systolic and diastolic blood pressures ($BP_s$ and $BP_d$, respectively) were determined by sphygmomanometry after blood flow measurements. IOP was measured by applanation tonometry. The mean brachial artery pressure...
(BP_m) was calculated according to the following formula: BP_m = BP_d + 1/3 (BP_h - BP_l).

Perfusion pressure (PP) for the study eye was estimated according to the following formula: PP = 2/3BP_m - IOP.

Humphrey visual field testing was performed in all glaucoma groups for the main comparisons was calculated based on an analysis of the results. The assumption of normality of the data was assessed by the Shapiro-Wilk test. On a small number of parameters, linear regression coefficients were used in the statistical analysis of the results. The Wilcoxon rank sum test was performed. No significant differences from normal were observed in our study in the superior and inferior nasal rim tissues.

In glaucomatous eyes, significant reductions of mean ONVel, ONVol, and ONFlow (Tables 2, 3, and 4) in glaucoma patients were not statistically significant after a Bonferroni correction was applied. No significant differences from normal were observed in the superior and inferior nasal rim tissues.

In glaucomatous eyes, significant reductions of mean ONVel were detected in the inferior temporal neuroretinal rim (24%; P = 0.005) and in the cup (28%; P = 0.005; Table 2). All other differences in ONVel between healthy control subjects and glaucoma patients were not statistically significant. Although our primary outcome ONVol was significantly reduced in glaucoma patients (15%; P = 0.04; Table 3) and a nonsignificant decrease in ONVe5 (10%; P = 0.07; Table 2).

No clinically or statistically significant differences in age, BP_m, IOP, or PP were observed between glaucoma patients and control subjects (Table 1).

Mean values of relative ONVel, ONVol, and ONFlow for each measurement site in healthy subjects and glaucoma patients are shown in Tables 2, 3, and 4, respectively. In each subject, average ONVel, ONVol, and ONFlow were calculated from the five measurement sites (four sites on the rim and one site on the cup) and were defined as ONVel5, ONVol5, and ONFlow5 (Tables 2, 3, and 4).

### Table 2. Relative Optic Nerve Head Blood Velocity

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects</th>
<th>Glaucoma Patients</th>
<th>Nominal P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ONVel5</td>
<td>0.41 ± 0.07</td>
<td>0.37 ± 0.05</td>
<td>0.07</td>
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<tr>
<td>Superior temporal rim</td>
<td>0.41 ± 0.11</td>
<td>0.38 ± 0.07</td>
<td>0.31</td>
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<tr>
<td>Inferior temporal rim</td>
<td>0.43 ± 0.13</td>
<td>0.33 ± 0.06</td>
<td>0.005</td>
</tr>
<tr>
<td>Superior nasal rim</td>
<td>0.38 ± 0.10</td>
<td>0.40 ± 0.09</td>
<td>0.48</td>
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</table>

### Table 3. Relative Optic Nerve Head Blood Volume

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects</th>
<th>Glaucoma Patients</th>
<th>Nominal P*</th>
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<tbody>
<tr>
<td>ONVol5</td>
<td>0.47 ± 0.13</td>
<td>0.40 ± 0.07</td>
<td>0.04</td>
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<tr>
<td>Superior temporal rim</td>
<td>0.45 ± 0.12</td>
<td>0.40 ± 0.22</td>
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<tr>
<td>Inferior temporal rim</td>
<td>0.45 ± 0.12</td>
<td>0.40 ± 0.09</td>
<td>0.22</td>
</tr>
<tr>
<td>Superior nasal rim</td>
<td>0.53 ± 0.33</td>
<td>0.38 ± 0.14</td>
<td>0.11</td>
</tr>
<tr>
<td>Superior nasal rim</td>
<td>0.41 ± 0.17</td>
<td>0.33 ± 0.12</td>
<td>0.16</td>
</tr>
<tr>
<td>Cup</td>
<td>0.48 ± 0.20</td>
<td>0.46 ± 0.18</td>
<td>0.79</td>
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### Table 4. Relative Optic Nerve Head Blood Flow in Arbitrary Units

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects</th>
<th>Glaucoma Patients</th>
<th>Nominal P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ONFlow5</td>
<td>16.1 ± 3.5</td>
<td>12.3 ± 2.4</td>
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<tr>
<td>Superior temporal rim</td>
<td>16.4 ± 3.7</td>
<td>12.4 ± 2.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Inferior temporal rim</td>
<td>16.3 ± 2.8</td>
<td>11.7 ± 3.2</td>
<td>0.001</td>
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<tr>
<td>Superior nasal rim</td>
<td>15.7 ± 5.6</td>
<td>13.2 ± 4.0</td>
<td>0.17</td>
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<tr>
<td>Superior nasal rim</td>
<td>13.6 ± 4.9</td>
<td>12.4 ± 4.1</td>
<td>0.45</td>
</tr>
<tr>
<td>Cup</td>
<td>18.0 ± 9.3</td>
<td>12.1 ± 5.0</td>
<td>0.028†</td>
</tr>
</tbody>
</table>

Values, except probabilities, are means ± SD, ONFlow5, optic nerve head blood flow; average of five optic nerve head measurement sites.

* By independent, two-tailed Student's t-test.
† Not statistically significant after Bonferroni correction for multiple comparisons.
TABLE 5. Choroidal Foveolar Relative Blood Velocity, Volume, and Flow

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects</th>
<th>Glaucoma Patients</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>ChBVel</td>
<td>0.42 ± 0.07</td>
<td>0.46 ± 0.07</td>
<td>0.27</td>
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<tr>
<td>ChBVol</td>
<td>0.35 ± 0.11</td>
<td>0.32 ± 0.09</td>
<td>0.46</td>
</tr>
<tr>
<td>ChBFlow</td>
<td>13.0 ± 2.5</td>
<td>13.0 ± 3.2</td>
<td>1.00</td>
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</table>

Values, except probabilities, are means ± SD, in arbitrary units. ChBVel, ChBVol, and ChBFlow, choroidal foveolar relative blood velocity, volume, and flow, respectively.

* By independent, two-tailed Student’s $t$-test.

any of the five specific locations of the disc (Table 3). There were no statistically significant differences in average ONVel, ONVol, or ONFlow among the five different measurement locations in the neuroretinal rim and cup, in either glaucomatous or healthy (control) eyes.

ChBFlow measurements obtained in the foveola of glaucomatous eyes showed no statistically significant differences from normal in any of the circulatory parameters (Table 5).

In glaucoma patients, significant inverse correlations were detected between ONFlow$_5$ and the Humphrey visual field CPSD ($R = -0.53$, $P = 0.02$; Fig. 3) and between ONFlow$_5$ and the cup-to-disc ratio ($R = -0.65$, $P = 0.002$; Fig. 4). In other words, larger cup-to-disc ratios and greater field defects were associated with an overall lower optic nerve blood flow. Interestingly, similar significant inverse correlations were also found in glaucoma patients between ONFlow in the cup and the CPSD ($R = -0.68$; $P = 0.005$).

Average CVs for ONVel, ONVol, and ONFlow were 15%, 20%, and 15%, respectively, in POAG patients, and 16%, 16%, and 18%, respectively, in healthy control subjects. No statistically significant differences were observed between the CVs of POAG patients and those of healthy control subjects.

**DISCUSSION**

The pathophysiology of glaucoma is not clearly understood. Several reports have suggested that vascular abnormalities of the ocular circulation may play a role in the development of glaucoma.

Fluorescein angiographic evidence of optic nerve head filling defects and the presence of optic nerve hemorrhages suggest an abnormal vascular component in this disease. Hypoperfusion of the ocular circulation may also have a role in the development of glaucoma, as suggested by the report of Graham et al. showing that nocturnal blood pressure decreases are more marked in glaucoma patients with progressive visual field loss than in glaucoma patients with stable visual fields.

Glaucomatous damage has been documented in patients with acute hypotensive episodes, suggesting that ischemia may have a role in the etiology of this disease. Increased vasospastic activity is more prevalent in patients with normal tension glaucoma, a finding that is particularly intriguing because vasoactivity is a crucial element in the autoregulation of blood flow, and abnormal vasoactivity in the brain and peripheral circulations could be associated with a similar malfunction in the optic nerve head circulation. Evidence of an abnormal autoregulation of the retinal circulation in glaucoma was reported by our group in a study that suggested that the highest IOP for which the retinal circulation can efficiently autoregulate its blood flow is lower than normal in glaucoma patients.
Measurements of visually evoked potentials under increased IOPs have shown abnormal responses in glaucoma patients, suggesting that this effect may be due to abnormal ocular vascular regulation.

Evidence of decreased optic nerve head blood velocity measured by laser Doppler velocimetry and scanning laser ophthalmoscopy has also been reported in glaucoma patients.

Transcranial Doppler ultrasound measurements of the ophthalmic artery and color Doppler measurements have also shown that blood velocities in the central retinal artery and short posterior ciliary arteries are also decreased in glaucoma, suggesting again decreased blood circulation. Interestingly, this decrease seems to be present early in the disease process and before the appearance of visual field defects, hinting to a possible role in the etiology of glaucoma.

Additional studies have also suggested that hemorheological abnormalities such as increased blood viscosity and decreased red cell deformability could affect blood flow in the glaucomatous eye. More recently, Michelson et al. and Nicolela et al. have used the scanning laser Doppler flowmetry technique and have described decreases in relative blood flow in the optic nerve head neuroretinal rim tissue and lamina cribrosa of patients with glaucoma.

Our results in glaucomatous eyes of decreased optic nerve head blood flow and a significant negative correlation between the overall optic nerve head blood flow and the cup-to-disc ratio are in general agreement with those of Michelson et al.

Our measurements in the cup, showing a decrease in blood velocity and a tendency toward a decrease in flow, are similar to those reported by Nicolela et al. Our determinations in the temporal neuroretinal rim, on the other hand, are somewhat different from those of Nicolela et al., who did not detect any difference from normal. In our study, however, the location of the measurements on the rim was different from that of Nicolela et al. Our measurements were obtained on the superior temporal and inferior temporal rims, whereas in their study, measurements were obtained at the 9 o'clock position.

Differences between our laser Doppler flowmetry technique and the scanning flowmetry technique may also provide some explanation for the discrepancies in the results of the different studies. In laser Doppler flowmetry, a stationary laser beam measures only one area of the disc that is approximately 200 μm in diameter, whereas a larger area of the fundus is scanned by a moving laser beam in the scanning flowmetry technique.

Differences between the two techniques have been reported and are probably related to problems with the scanning laser Doppler technique, such as those that follow: (a) a high zero value that varies from point to point on the scanning, (b) imbalances in the relationship between volume and velocity parameters, and (c) a more narrow frequency response that may not allow adequate measurement of higher blood velocities.

Another important difference between the two techniques may stem from discrepancies in the optic nerve sampling depth achieved with each instrument. The scanning instrument uses a confocal optical configuration that narrows the depth of the measurement volume, whereas our instrument does not have a confocal optical system and, therefore, probably attains a wider depth of focus.

The vascular supply of the optic nerve head derives from more than one source. The most superficial part of the nerve head originates from the retinal circulation, whereas the deeper sections are supplied by the choroidal circulation. It is important to ascertain what the depth of the tissue sampled during laser Doppler flowmetry measurements is. Estimations of the sampling depth in optic nerve head tissue have shown that the laser Doppler flowmetry method can provide a depth of tissue penetration that would allow flow measurements as deep as the lamina cribrosa. Therefore, measurements obtained with our technique in the optic nerve head probably include blood flow originating from the retinal and choroidal circulations.

Our results show a significant inverse correlation between ONFlow, and visual field function indices such as the mean defect and the CPSD. In other words, decreased optic nerve blood flows are associated with functional visual field losses. This is, to the best of our knowledge, the first report of an association between an abnormal optic nerve head circulation and visual function loss in glaucoma. It is impossible to ascertain from these results, however, whether the blood flow decreases have a primary role in the etiology of this disease and therefore precede the development of glaucomatous damage, or whether these circulatory abnormalities are the result of loss of neural tissue due to glaucoma.

Our measurements of ONFlow correspond to an average of five discrete spots (approximately 200 μm in diameter each) on the optic nerve head. This parameter, which is significantly reduced in glaucoma patients, does not represent a measure of total optic nerve head blood flow. It is of great interest that this average optic nerve flow correlates significantly with functional and anatomic measures of glaucoma damage, such as the cup-to-disc ratio and visual field indices. This suggests a decrease in the optic nerve head perfusion that is not just a localized effect in the area of the rim corresponding to the visual field defect. This is further supported by the fact that flow in the optic cup, an area of the nerve head that is not connected with any specific area of the visual field, is also correlated with visual field function abnormalities.

Most of the glaucoma patients included in our study were receiving antiglaucoma medications that could potentially have an effect on the optic nerve head circulation. Although the numbers of patients on different medications were small, we did not find any marked differences in the circulatory parameters among patients receiving the different medications. It is important to note that because of these medications IOPs and PPs both were well matched between the glaucoma and control groups; such matching is crucial when investigating circulatory differences between groups.

Laser Doppler flowmetry provides measurements of relative blood velocity, volume, and flow. When one compares measurements obtained in different persons, there are a number of factors that may introduce measurement variability. It is not known, for example, how ocular structural changes that occur in glaucoma may affect the intensity and coherence of the laser light reaching the optic nerve head and choroidal vasculatures.

One hypothetical source of variability could result from a glaucoma-related change in the ocular media that would reduce the intensity of the laser light reaching the optic nerve head and choroidal vasculatures. Such an effect could decrease the penetration of light into these tissues, perhaps yielding a lower
blood volume and flow. However, our finding of very similar circulatory parameters in the center of the foveola in glaucoma patients and control subjects suggests that this scenario is unlikely.

Another concern is that the loss of ganglion cell axons within the neuroretinal rim could have changed the optical properties of the nerve tissue and, therefore, could have affected our measurements. The fact that we observed a decrease in blood velocity and a tendency toward a decreased flow in the cup, a site where there are no ganglion cells that disappear with the progression of the disease, suggests that this flow decrease is not produced by an artifact related to a change in the optical properties of the nerve due to loss of ganglion cells.

Laser Doppler flowmetry measures relative blood velocity, volume, and flow within a sampled tissue. This technique does not provide an estimate of flow per tissue like the microspheres technique. Closure of small vessels or vasoconstriction of vessels within the sampled tissue, for example, results in decreases in blood volume. A decrease in the amount of rim tissue produced by the glaucoma process could also lead to a loss of capillaries and result in decreased blood volume measurements.

We would like to stress, however, that our measurements on the neuroretinal rim were performed in areas at which relatively intact pink rim tissue was present. We avoided any areas of atrophy or localized notching. Although it is not possible to determine with certainty whether this seemingly intact neural rim was indeed normal, previous studies in glaucomatous eyes have suggested that such areas of remaining neuroretinal rim show no preferential loss of capillaries. Despite a seemingly intact capillary bed present in the remaining rim of glaucomatous eyes, our results show decreased flow, finding that supports a role for impaired circulation in the development of glaucomatous optic nerve damage. In addition, we would like to point out that because our measurements were not performed on atrophic rim tissue, the decrease in flow observed in our study could not be accounted for only by a lack of viable neuroretinal tissue.

Regarding our measurements of blood flow in the cup, it is possible that because of thinning of the prelamellar cup tissue in glaucomatous eyes, some of the signal may originate from the deeper retrobulbar optic nerve that may have a lower flow rate. This is a possibility that we cannot rule out completely at this time. However, our finding of quantitative decreases in cup flow in glaucoma are in agreement with two recent reports suggesting decreased vascularity and localized defects in the cup of glaucoma patients.

Using scanning laser Doppler flowmetry focused at the level of the lamina cribrosa, Nicola et al. detected marked qualitative differences between glaucoma patients and control subjects in the vascularity of the cup. Furthermore, they reported a high prevalence of avascular areas in the cups of the glaucoma patients but not in those of the control subjects. Similarly, Melamed et al. combined the use of confocal laser scanning ophthalmoscopy with indocyanine green angiography to evaluate the optic nerve blood supply in glaucoma patients and control subjects. Measurements were taken at multiple planes from the surface of the optic nerve down to the lamina cribrosa. Filling defects, defined as the absence of indocyanine green fluoroscein throughout the depth of the optic disc, were found in the majority of glaucoma subjects, whereas the majority of control subjects demonstrated a diffuse microvascular filling pattern throughout the rim and the cup. Both of these studies used scanning laser technology that limits the influence of changes generated outside the focal plane and, therefore, should have been minimally influenced by sampling deeper into the optic nerve. These studies demonstrated impaired vascularization at the level of the lamina cribrosa that is in concordance with our laser Doppler flowmetry measurements showing decreased blood flow in the cups of the glaucoma patients. Because the damage in glaucoma is believed to originate at the level of the lamina cribrosa, changes measured at the base of the cup may be particularly important in understanding glaucomatous optic neuropathy.

In summary, our study suggests evidence of decreased optic nerve head circulation in glaucoma that is associated with functional and anatomic measures of glaucomatous pathology. Further studies are needed to determine whether these circulatory abnormalities have an etiologic role in the development of this disease or whether they are the result of glaucomatous optic nerve damage.

Acknowledgment

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References
