Retinal Vessel Diameter and Open-Angle Glaucoma

The Blue Mountains Eye Study

Paul Mitchell, MD, PhD,[1] Harry Leung, MBBS (Hons),[1] Jie Jin Wang, MMed, PhD,[1] Elena Rochtchina, BSc, MApplStat,[1] Anne J. Lee, BSc (Med), MBBS,[1] Tien Y. Wong, FRCS, PhD,[2,3] Ronald Klein, MD, MPH[4]

Purpose: To examine the relationship between open-angle glaucoma (OAG) and retinal vessel diameter among baseline participants in the Blue Mountains Eye Study.

Design: Population-based cross-sectional study.

Participants: The study included 3654 persons older than 49 years, representing 82.4% of permanent residents living in an area west of Sydney.

Methods: Participants had a detailed eye examination, including automated perimetry and stereo optic disc photography. A computer-assisted program measured retinal vessel diameters from digitized photographs of right eyes.

Main Outcome Measures: Open-angle glaucoma was diagnosed from matching visual field defects and optic disc cupping, without reference to intraocular pressure (IOP) level. Ocular hypertension was defined as IOP of >21 mmHg in either eye, without matching glaucomatous optic disc and field changes. Average retinal vessel diameters, measured from right eyes, were summarized as arteriolar and venular equivalents. The lowest quintile of the arteriolar equivalent or arteriole-to-venule ratio was used to define generalized retinal arteriolar narrowing.

Results: The study included 3314 participants, after excluding those with incomplete data or nonglaucomatous optic nerve disease. Of persons included, 59 (1.8%) had evidence of glaucomatous damage affecting the right eye, 3065 (92.5%) had no damage to either eye, and 163 (4.9%) had ocular hypertension. Right eyes with glaucomatous damage had significantly narrower retinal arteriolar diameters (183±2.6 μm) than eyes without glaucoma (194±0.4 μm, $P = 0.0001$) or eyes with ocular hypertension (195±1.6 μm, $P = 0.0002$), after adjusting for age, mean arterial blood pressure, and other confounding variables, including refraction. Right eyes with glaucomatous damage were at least 2 times more likely to have generalized retinal arteriolar narrowing than eyes without glaucoma (odds ratio, 2.7; 95% confidence interval, 1.5–4.8).

Conclusions: These population-based data suggest that generalized retinal arteriolar narrowing, an indicator of localized vascular change, is significantly associated with optic nerve damage caused by OAG. It is not clear whether such a retinal arteriolar change reflects an ischemic process leading to optic nerve damage or results from loss of retinal neurons secondary to glaucoma. *Ophthalmology 2005;112:245–250 © 2005 by the American Academy of Ophthalmology.*

The pathogenesis of open-angle glaucoma (OAG) remains uncertain. Although elevated intraocular pressure (IOP) has long been identified as a major risk factor for glaucoma, increasing evidence suggests that vascular mechanisms may play a role in this disease. Evidence for this postulate includes findings on the associations between glaucoma and systemic blood pressure[1]; perfusion pressure (blood pressure minus IOP)[1]; vasospasm[2,3] or diseases with vascular manifestations, such as diabetes[4]; and migraine.[5]

Using manual measurements of vessel diameter from projected images of the retina, Jonas et al[6] demonstrated significantly smaller parapapillary retinal vessel diameters

Originally received: February 6, 2004.
Accepted: August 9, 2004. Manuscript no. 240095.

[1] Centre for Vision Research, Department of Ophthalmology and the Westmead Millennium Institute, University of Sydney, Sydney, Australia.

[2] Centre for Eye Research Australia, Department of Ophthalmology, University of Melbourne, Melbourne, Australia.

[3] Singapore Eye Research Institute, National University of Singapore, Singapore.

[4] Department of Ophthalmology & Visual Science, University of Wisconsin–Madison, Madison, Wisconsin.

Presented at: Association for Research in Vision & Ophthalmology meeting, April, 2004; Fort Lauderdale, Florida.

Supported by the Australian National Health & Medical Research Council, Canberra, Australia (grant no.: 153948), and the National Institutes of Health, Bethesda, Maryland (grant nos.: EY06594, HL 59259) (RK and coworkers).

Correspondence to Paul Mitchell, MD, FRACO, Centre for Vision Research, Department of Ophthalmology, University of Sydney, Westmead Hospital, Hawkesbury Road, Westmead, NSW 2145, Australia. E-mail: paul_mitchell@wmi.usyd.edu.au.

ISSN 0161-6420/05/$–see front matter
doi:10.1016/j.ophtha.2004.08.015

in eyes with OAG (n = 281, 473 eyes) than in age-matched normal eyes (n = 173, 275 eyes). Also, Rader et al[7] found general narrowing of retinal arterial calibers in 53% of eyes with moderate glaucomatous optic nerve damage (n = 57 patients) and in 71% of eyes with severe glaucomatous optic nerve damage (n = 56 patients), compared with only 15% in normal eyes (n = 39 subjects). However, these previous studies were limited by use of subjective methods in measuring retinal vessel diameters: selection of subjects from clinic-based samples rather than from a population, lack of adjustment for factors such as blood pressure in the analyses (which was found to be significantly related to retinal arteriolar diameter in population-based studies),[8–10] and measurements taken in only parts of the retina.[6]

Recently, a computer-assisted method developed by investigators from the Atherosclerosis Risk in Communities Study[11] has permitted reliable measurements of retinal vessel diameter from digitized photographs.[12,13] Using this technique, the current study aimed to examine the relationship between OAG and retinal vessel diameter among baseline participants of the Blue Mountains Eye Study, after adjusting for age, gender, blood pressure, and other possible confounders.

Materials and Methods

Study Population

The Blue Mountains Eye Study is a population-based cohort study of vision, common eye diseases, and other health outcomes, in an urban Australian population 49 years or older. Baseline participants (n = 3654) represented 82.4% of those eligible living in 2 postcode areas of the Blue Mountains, west of Sydney. This study was approved by the Western Sydney Area Human Ethics Committee. Written informed consent was obtained from all participants. Details of the methods and glaucoma prevalence findings have been reported.[14]

Procedures and Definitions

At the baseline examinations (1992–1994), a detailed eye examination was performed, including Goldmann applanation IOPs and Humphrey 30° suprathreshold 76-point screening tests (Humphrey Visual Field Analyser 630 with Statpac 2, Humphrey Instruments, Inc., San Leandro, CA). Dilated 30° stereoscopic retinal photographs of the macula, optic disc, and other retinal fields of both eyes were taken, using a Zeiss FF3 fundus camera (Carl Zeiss, Oberkochen, Germany). The magnification of the eye camera system is $0.056/(1-0.0016)$.[15] Participants with a history of glaucoma or ocular hypertension, or optic disk signs suggesting glaucoma, or a glaucomatous hemifield difference of ≥5 points on the 76-point screening test were asked to return for Humphrey 30-2 full-threshold visual field (VF) tests.[14]

Open-angle glaucoma was diagnosed when typical glaucomatous VF loss on a Humphrey 30-2 test was present, combined with matching optic disc rim thinning and an enlarged cup-to-disc (C/D) ratio (>0.7) or C/D asymmetry between the two eyes (≥0.3).[14] Gonioscopy excluded angle closure, rubeosis, and secondary glaucoma (other than pseudoexfoliation). Vertical optic disc diameter, optic cup diameter, and C/D ratio were reproducibly measured from stereo optic disc photographs, as described previously,[14] using the method described by Klein et al.[16] Low-pressure glaucoma was defined as OAG with IOP in both eyes of ≤21 mmHg, the patient not receiving ocular hypotensive treatment and having no history of glaucoma surgery. Other OAG cases were defined as high-pressure glaucoma. Ocular hypertension was diagnosed in participants with IOP in either eye of >21 mmHg but with no glaucomatous VF and no optic disc changes.[14]

Blood pressure was measured once using a mercury sphygmomanometer after participants had been comfortably seated for at least 5 minutes. Mean arterial blood pressure was calculated as $0.33 \times$ systolic blood pressure $+ 0.67 \times$ diastolic blood pressure. Body weight and height were measured, and body mass index was calculated as weight (kg)/height $(m)^2$. Diabetes was diagnosed from either medical history or a fasting blood glucose level of ≥7.0 mmol/l at the baseline examination. Hypertension was defined as present in persons currently using antihypertensive medications or found to have systolic blood pressure of ≥160 mmHg or diastolic blood pressure of ≥95 mmHg at the time of the examination.

Retinal Photography and Grading Methods

Details of image digitization of the retinal photographs and the grading protocols have been described.[8,11,13] In brief, a grid was placed over the 35-mm image. All vessels passing completely through a circumferential zone 0.5 to 1 disc diameters from the optic disc margin were measured. Each vessel was identified as an arteriole or a venule by the grader, using the original photograph for reference.

Retinal Analysis[17] measures the central width and calculates the average width from 5 equidistant measures of each vessel or branch (in micrometers). The branches of arterioles (regardless of their position on the grid) were measured if the trunk measured ≥85 μm. Branch measurements were declined if either of the branches could not be measured accurately. The Parr–Hubbard formula was used to standardize arteriolar and venular calibers of each eye, summarized as central retinal arteriolar equivalent (CRAE) or central retinal venular equivalent (CRVE).[18] The formula used to calculate CRAE was

$$W_t = (0.87\ W_a^2 + 1.01\ W_b^2 - 0.22\ W_a\ W_b - 10.76)^{1/2},$$

where W_t was calculated as the trunk arteriole caliber and included calibers from the smallest (W_a) to largest (W_b) branches. A similar formula was used to calculate the CRVE. The CRAE was divided by the CRVE to obtain the arteriole-to-venule ratio (AVR). Eyes were considered ungradable if any vessels with a diameter of >45 μm could not be measured accurately. Vessels measuring <25 μm were excluded.

Generalized retinal arteriolar narrowing was defined as the narrowest quintile of CRAE or the lowest quintile of AVR. Intragrader reliability and intergrader reliability of this method were found to be high in our previous study.[13] Only retinal vessel diameters from right eyes were measured in this study, as right and left eye measurements were found to be correlated highly.[19]

Statistical Methods

SAS[20] was used for data analysis. We used right eye data to assess eye-specific associations between OAG and retinal arteriolar narrowing. Adjusted means of the retinal vessel parameters were obtained using covariance analysis (general linear model). Potential confounding variables, including age, gender, smoking, body mass index, mean arterial blood pressure, and refractive error of the right eyes (expressed as spherical equivalent) were adjusted for in logistic regression models. We did not adjust for IOP, as it was not found associated with any retinal vessel parameters in this population, even after adjusting for age, gender, and systolic blood pressure (data not shown). We also assessed the person-specific

Table 1. Baseline Characteristics by Glaucoma Group

	No Glaucomatous Damage in Either Eye	Ocular Hypertension	Glaucomatous Damage in Right Eye	Glaucomatous Damage in Either Eye
n	3065	163	59	86
Mean age (yrs)	65.2	67.4	74.4	74.7
Body mass index (kg/m^2)	26.2	26.1	25.5	25.2
Right eye mean refraction (diopters)*	0.77	0.83	0.51	0.52
Right eye mean IOP (mmHg)	15.8	21.5	19.3	19.3
Mean systolic BP (mmHg)	145	156	157	158
Mean diastolic BP (mmHg)	83	87	85	85
Mean arterial BP (mmHg)	103	110	109	109
Hypertension (%)	44.0	55.9	66.1	68.6
Diabetes (%)	7.4	9.8	11.9	9.3
Typical migraine (%)	16.8	19.6	18.6	17.4
Cigarette smoking, current (%)	15.6	11.7	6.8	4.7
Cigarette smoking, past (%)	36.1	40.9	44.1	39.5

BP = blood pressure; IOP = intraocular pressure.
*Expressed as spherical equivalent.

association between glaucoma and retinal arteriolar narrowing, by comparing retinal arteriolar diameters of the right eye between persons with glaucomatous damage that affected the left eye only and persons with no glaucomatous damage in either eye (after excluding persons with glaucoma affecting the right eye). Means, standard errors, odds ratios (ORs), and 95% confidence intervals (CIs) are presented. A P value of <0.05 indicated statistical significance.

Results

At baseline, 340 participants were excluded because they had missing or ungradable retinal photographs or had optic nerve diseases such as anterior ischemic optic neuropathy, optic disc drusen or coloboma, severely tilted discs, or other optic disc pathologies. The remaining 3314 were included in this study. Among these participants, 3065 (92.5%) had no glaucomatous damage affecting either eye, and 163 (4.9%) had ocular hypertension. Of the 72 participants who had glaucomatous damage affecting the right eye (with or without damage in their left eye), 59 (81.9%) had gradable photographs. Of these 59 right eyes with glaucomatous damage, 21 were classified as having low-pressure and 38 as having high-pressure glaucoma. There were 27 participants in whom glaucomatous damage affected the left eye only.

Table 1 shows the baseline characteristics by glaucoma category. Compared with persons without glaucoma, those with glaucomatous damage were older, had similar mean arterial blood pressure, and a higher prevalence of diagnosed hypertension or diabetes.

Figure 1 shows mean retinal vessel diameter by glaucoma category using right eye data, after adjusting for age, gender, body mass index, smoking status, mean arterial blood pressure, blood glucose level, and refraction. The mean arteriolar diameter of the right eye was significantly narrower in eyes with glaucomatous damage (183±2.6 μm) than in eyes without glaucoma (194±0.4 μm, $P = 0.0001$) or in eyes with ocular hypertension (195±1.6 μm, $P = 0.0002$). There was no statistically significant difference in the multivariate-adjusted mean arteriolar diameter of the right eye between eyes that were normal and eyes with ocular hypertension ($P = 0.39$), or between eyes with low-pressure (188±4.3 μm) and high-pressure (180±3.3 μm) glaucoma ($P = 0.14$). Eyes with high-pressure glaucoma had a significantly narrower mean arteriolar diameter than eyes with ocular hypertension ($P<0.0001$).

A similar pattern was also found in adjusted mean venular diameters, measured from the right eye, as shown in Figure 1. Right eyes with glaucomatous damage had a significantly narrower mean CRVE than normal eyes ($P = 0.0005$) or eyes with ocular hypertension ($P = 0.002$). The multivariate-adjusted mean AVR of the right eye was similar in eyes without glaucoma (0.86±0.002) and eyes with ocular hypertension (0.87±0.006). Right eyes with glaucomatous damage had a smaller mean AVR (0.85±0.01) than eyes with ocular hypertension ($P = 0.13$) or normal eyes ($P = 0.28$). Figure 2 shows the relationship between generalized arteriolar narrowing (mean CRAE) and C/D ratio (right eyes)[14,21] in the entire baseline population used in this study. A strong trend for narrower retinal arterioles with an increasing C/D ratio is shown, particularly for C/D ratios of >0.6.

Table 2 shows both eye- and person-specific associations between generalized retinal arteriolar narrowing and OAG, after adjusting for age, gender, body mass index, smoking, mean arterial

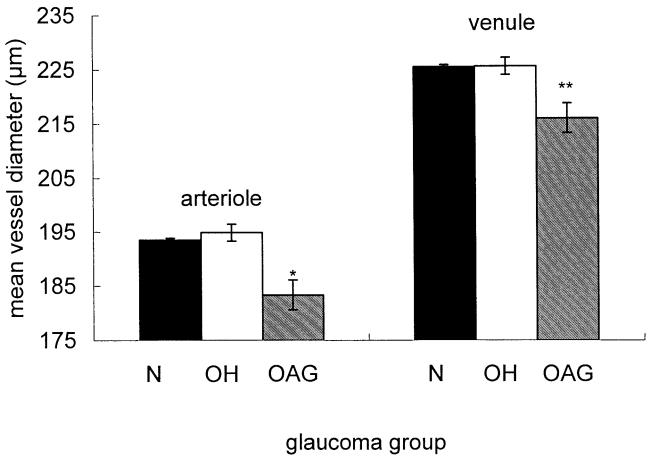

Figure 1. Mean (standard error) retinal vessel diameter by glaucoma group (right eyes), adjusted for age, gender, body mass index, smoking, mean arterial blood pressure, blood glucose level, and spherical refractive error in the right eye. N = no glaucoma; OAG = open-angle glaucoma; OH = ocular hypertension. *$P = 0.0001$ and $P = 0.0002$; OAG compared with N and OH, respectively. **$P = 0.0005$ and $P = 0.002$; OAG compared with N and OH, respectively.

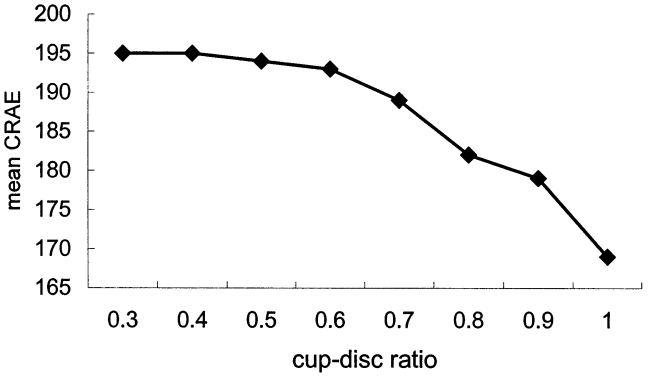

Figure 2. Relationship between mean central retinal arteriolar equivalent (CRAE) and cup-to-disc ratio (≤0.3–1.0) in right eyes of the baseline study population.

blood pressure, and refractive error. Open-angle glaucoma affecting the right eye was significantly associated with generalized arteriolar narrowing, defined by the narrowest quintile of the CRAE (OR, 2.7; CI, 1.5–4.8). Right eyes with the narrowest quintile of CRAE were 5 times more likely to have glaucomatous damage than right eyes with the widest quintile, after multivariate adjustment (data not shown).

Stratified analyses (Table 2) showed that the magnitude of the eye-specific association between glaucoma and generalized arteriolar narrowing was slightly greater in women than in men and was relatively similar in those with high-pressure and those with low-pressure glaucoma, and in those treated and not treated with glaucoma medications. There were also no major differences in the magnitude of the association between persons with and without diabetes (apart from the AVR) and between smokers and nonsmokers. Presence of ocular hypertension was not significantly associated with generalized arteriolar narrowing (OR, 0.8; CI, 0.5–1.2). We found no statistically significant eye-specific association when generalized retinal arteriolar narrowing was defined using the lowest quintile of the AVR.

There were no statistically significant person-specific associations found between OAG and retinal arteriolar narrowing (Table 2). Compared with persons without glaucomatous damage in either eye, those with glaucoma affecting the left eye only had no increased likelihood of generalized arteriolar narrowing, when this was measured from photographs of the right eye.

Discussion

The vascular theory of glaucoma has been supported by clinic-based studies showing an association between glaucoma and retinal arteriolar narrowing,[6,7,22,23] as well as by studies suggesting altered ocular hemodynamics in eyes with OAG.[24–26] Retinal artery narrowing has also been observed in nonglaucomatous optic atrophy.[27] In the current population-based cross-sectional study, using a reliable computer-assisted method to quantify retinal vessel diameter, right eyes with OAG had significantly narrower adjusted

Table 2. Associations in Right Eyes between Generalized Retinal Arteriolar Narrowing and Glaucoma, Stratified as High or Low Pressure, Age, Gender, Diabetes, and Smoking Status

	Generalized Retinal Arteriolar Narrowing, Right Eye				
		Narrowest Quintile of CRAE		*Narrowest Quintile of AVR*	
	n	*% Affected*	*Odds Ratios* (95% CI)*	*% Affected*	*Odds Ratios* (95% CI)*
Eye-specific association					
No glaucomatous damage	3065	19.1	1.0	19.7	1.0
Ocular hypertension	163	21.5	0.8 (0.5–1.2)	19.6	0.8 (0.6–1.3)
Glaucomatous damage affecting right eye†	59	54.2	2.7 (1.5–4.8)	33.9	1.4 (0.8–2.5)
Stratified analyses					
Low-pressure glaucoma	21	52.4	2.7 (1.1–6.7)	28.6	1.2 (0.4–3.1)
High-pressure glaucoma	38	55.3	2.7 (1.3–5.5)	36.8	1.5 (0.7–3.1)
Age < 65 yrs	9	55.6	4.0 (0.9–18.3)	33.3	1.2 (0.2–6.3)
Age ≥ 65 yrs	50	54.0	2.5 (1.4–4.6)	34.0	1.4 (0.8–2.7)
Men	25	56.0	2.5 (1.0–6.2)	36.0	1.0 (0.4–2.6)
Women	34	52.9	2.7 (1.3–5.8)	32.4	1.6 (0.8–3.4)
Persons with diabetes	7	42.9	2.8 (0.5–16.0)	57.1	6.2 (1.2–32.9)
Persons without diabetes	52	55.8	2.6 (1.4–4.9)	30.8	1.0 (0.5–2.0)
History of smoking‡	30	56.7	2.9 (1.3–6.6)	36.7	1.2 (0.5–2.7)
No history of smoking	29	51.7	2.5 (1.1–5.6)	31.0	1.6 (0.7–3.6)
Not using glaucoma medication§	33	54.6	2.7 (1.3–5.8)	27.3	0.9 (0.4–2.1)
Using glaucoma medication	25	52.0	2.6 (1.1–6.1)	44.0	2.4 (1.0–5.5)
Person-specific association					
Glaucomatous damage affecting left eye only‖	27	40.7	1.4 (0.6–3.3)	18.5	0.7 (0.3–1.9)

AVR = arteriole-to-venule ratio; CI = confidence interval; CRAE = central retinal arteriolar equivalent.
*Adjusted for age, gender, body mass index, smoking, mean arterial blood pressure, and right eye refraction.
†Comparison of retinal arteriolar diameters in the right eye between persons with glaucomatous damage in this eye and persons with no glaucomatous damage in either eye (eye-specific association).
‡Including current and past smokers.
§Represents undiagnosed glaucoma (1 person who had only surgical treatment for glaucoma excluded).
‖Comparison of retinal arteriolar diameters in the right eye between persons with glaucomatous damage in the left eye only and persons with no glaucomatous damage in either eye (person-specific association).

mean retinal arteriolar diameters in a zone outside the immediate peripapillary zone. These eyes were also at least 2 times more likely to have generalized arteriolar narrowing than eyes without glaucoma, after controlling for age, blood pressure, and other glaucoma risk factors. The association was generally similar for high- and low-tension glaucoma, in younger and older persons, in men and women, in persons with and without diabetes, and in those with and without a history of cigarette smoking. This study therefore provides the first population-based data to support an association between narrowing retinal vessel caliber and the presence of glaucomatous damage that is independent of blood pressure and other glaucoma risk factors.

An important question is whether retinal arteriolar narrowing precedes or follows the development of glaucomatous damage. Diminished blood flow in the optic nerve has been detected early in glaucoma suspects, suggesting that such vascular change may precede glaucomatous optic neuropathy.[28] Alternately, it has been suggested that loss of retinal ganglion cells may result in a decrease in retinal vessel diameter via the autoregulatory mechanisms responding to a reduction in oxygen demand. The latter argument is supported by observations that narrowing of retinal vessels is observed typically in many forms of optic nerve damage, and is not specific for glaucoma.[7,29,30] It should be noted, however, that in these 3 reports arteriolar narrowing was observed proximal to the disc (typically within the zone of peripapillary atrophy),[7] rather than further downstream in the retina.[7,29,30] Our assessments of arteriolar diameter or generalized narrowing were based on measures taken between 0.5 and 1.0 disc diameters from the edge of the optic disc.

Due to the cross-sectional nature of our data, we cannot determine temporal aspects of the association between retinal arteriolar narrowing and glaucoma. However, our findings suggest that the association between glaucoma and retinal arteriolar narrowing is eye specific and not person specific. This is indicated by the significant association found between generalized arteriolar narrowing and ipsilateral glaucomatous damage, with no similar association found for the contralateral eyes of patients with glaucomatous damage only in the fellow eye. Regardless of whether generalized retinal arteriolar narrowing is antecedent or consequential to OAG, the finding in our study of an eye-specific but not person-specific association suggests that OAG may be related to changes in the local but not the systemic circulation.

We also found that eyes with high-pressure glaucoma had significantly narrower mean retinal arteriolar diameters than eyes with ocular hypertension ($P<0.0001$). This is in keeping with the findings by Rader et al[7] that general narrowing of retinal arteries was found in 53% of eyes with high-pressure glaucoma and moderate optic nerve damage and in 71% of eyes with high-pressure glaucoma and severe optic nerve damage, compared with only 10% in eyes with ocular hypertension. Using laser Doppler flowmetry, Kerr et al[31] also observed a significant decrease in minimum blood velocity at the temporal juxtapapillary retina in untreated high-pressure glaucoma patients (n = 10) compared with age- and IOP-matched persons with ocular hypertension (n = 14). Thus, retinal arteriolar narrowing appears to be related specifically to pathologic optic nerve damage rather than to an increase in IOP.

Interestingly, in our study, no significant difference in mean arteriolar diameter was found between eyes with apparent high-pressure and low-pressure glaucoma ($P = 0.14$). This finding is supported by previous studies on ocular hemodynamics that found that blood velocities and resistance indices in the central retinal artery did not significantly differ between eyes with high-pressure and low-pressure glaucoma.[24,25] It is important to note, however, that in our study the classification of high- or low-pressure glaucoma was based on only 2 IOP measurements taken on 2 different days. Therefore, the comparisons in retinal arteriolar diameter between these 2 groups in our study should be viewed with caution.

We also found retinal venular diameters in eyes with glaucoma significantly narrower than those in normal eyes. This contrasts with recent findings by Jonas[32] that central retinal vein collapse pressure, as measured by ophthalmodynamometry, was significantly higher ($P = 0.001$) in eyes with OAG (n = 19) than in age-matched nonglaucomatous eyes (n = 27), suggesting a larger retinal vein diameter in glaucomatous eyes. Our study findings, however, are not directly comparable to Jonas's data, as we did not measure central retinal vein collapse pressure.

It is possible that the ocular hypotensive medications used by participants with glaucoma could have vasodilating effects, so that the association between glaucoma and retinal arteriolar narrowing may have been underestimated. In our study, magnitudes of association between glaucoma and retinal arteriolar narrowing in eyes with glaucomatous damage were similar in treated (using glaucoma medication) and untreated eyes. The effect of topical hypotensive medications on retinal vessel diameter, however, remains controversial. Collignon and Collignon-Brach[33] reported a significant increase in mean retinal arterial diameter (+7.4%, $P = 0.000$) after 12 months of betaxolol treatment, but no persistent change after a further 12 months of timolol treatment in 13 persons with OAG or ocular hypertension. Grunwald[34] reported no significant change in retinal venous diameter 2 hours after instillation of timolol in 14 persons with ocular hypertension, whereas a double-masked randomized trial in 37 persons with ocular hypertension found a relative increase in retinal vessel diameter in eyes treated with timolol for 18 to 24 months compared with a placebo.[35]

There has been considerable recent evidence suggesting that retinal microvascular signs, including retinal vessel narrowing, may predict the development of stroke,[36] dementia,[37] and subclinical cerebral diseases.[38] Retinal arteriolar narrowing may also be a marker of microvascular disease occurring in people with preclinical diabetes.[39] Our data indicate that glaucoma needs to be considered an important ocular confounder in the assessment of such systemic relationships with retinal vessel diameter.

In summary, using a previously validated computer-assisted method to quantify retinal vessel diameters, we found that eyes with glaucomatous damage had significantly smaller mean retinal vessel diameters and were at least 2 times more likely to have generalized arteriolar narrowing than normal eyes, after adjusting for age, mean arterial blood pressure, and other possible confounders. In contrast, there was no statistically

significant difference in mean retinal arteriolar diameter between eyes with ocular hypertension and normal eyes. These findings provide further support for the concept that glaucoma is associated with retinal vessel narrowing and possible altered ocular hemodynamics. Whether such vascular changes reflect an ischemic pathologic process leading to glaucomatous damage or result from an autoregulatory response to the loss of retinal neurons secondary to glaucomatous damage needs further investigation.

References

1. Tielsch JM, Katz J, Sommer A, et al. Hypertension, perfusion pressure, and primary open-angle glaucoma. A population-based assessment. Arch Ophthalmol 1995;113:216–21.
2. Drance SM, Douglas GR, Wijsman K, et al. Response of blood flow to warm and cold in normal and low-tension glaucoma patients. Am J Ophthalmol 1988;105:35–9.
3. Harris A, Sergott RC, Spaeth GL, et al. Color Doppler analysis of ocular vessel blood velocity in normal-tension glaucoma. Am J Ophthalmol 1994;118:642–9.
4. Mitchell P, Smith W, Chey T, Healey PR. Open-angle glaucoma and diabetes: the Blue Mountains Eye Study, Australia. Ophthalmology 1997;104:712–8.
5. Wang JJ, Mitchell P, Smith W. Is there an association between migraine headache and open-angle glaucoma? Findings from the Blue Mountains Eye Study. Ophthalmology 1997;104:1714–9.
6. Jonas JB, Nguyen XN, Naumann GO. Parapapillary retinal vessel diameter in normal and glaucoma eyes. I. Morphometric data. Invest Ophthalmol Vis Sci 1989;30:1599–603.
7. Rader J, Feuer WJ, Anderson DR. Peripapillary vasoconstriction in the glaucomas and the anterior ischemic optic neuropathies. Am J Ophthalmol 1994;117:72–80.
8. Leung H, Wang JJ, Rochtchina E, et al. Relationships between age, blood pressure and retinal vessel diameters in an older population. Invest Ophthalmol Vis Sci 2003;44:2900–4.
9. Wong TY, Hubbard LD, Klein R, et al. Retinal microvascular abnormalities and blood pressure in older people: the Cardiovascular Health Study. Br J Ophthalmol 2002;86:1007–13.
10. Sharrett AR, Hubbard LD, Cooper LS, et al. Retinal arteriolar diameters and elevated blood pressure: the Atherosclerosis Risk in Communities Study. Am J Epidemiol 1999;150:263–70.
11. Hubbard LD, Brothers RJ, King WN, et al. Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the Atherosclerosis Risk in Communities Study. Ophthalmology 1999;106:2269–80.
12. Couper DJ, Klein R, Hubbard LD, et al. Reliability of retinal photography in the assessment of retinal microvascular characteristics: the Atherosclerosis Risk in Communities Study. Am J Ophthalmol 2002;133:78–88.
13. Sherry LM, Wang JJ, Rochtchina E, et al. Reliability of computer-assisted retinal vessel measurement in a population. Clin Experiment Ophthalmol 2002;30:179–82.
14. Mitchell P, Smith W, Attebo K, Healey PR. Prevalence of open-angle glaucoma in Australia. The Blue Mountains Eye Study. Ophthalmology 1996;103:1661–9.
15. Bengtsson B, Krakau CE. Correction of optic disc measurements on fundus photographs. Graefes Arch Clin Exp Ophthalmol 1992;230:24–8.
16. Klein BE, Magli YL, Richie KA, et al. Quantitation of optic disc cupping. Ophthalmology 1985;92:1654–6.
17. Retinal Analysis [computer program]. Version 3.0. Madison, WI: Optimate.
18. Parr JC, Spears GF. General caliber of the retinal arteries expressed as the equivalent width of the central retinal artery. Am J Ophthalmol 1974;77:472–7.
19. Leung H, Wang JJ, Rochtchina E, et al. Computer-assisted retinal vessel measurement in an older population: correlation between right and left eyes. Clin Experiment Ophthalmol 2003;31:326–30.
20. SAS [computer program]. Version 8.2. Cary, NC: SAS Institute; 1999.
21. Healey PR, Mitchell P, Smith W, Wang JJ. Relationship between cup-disc ratio and optic disc diameter: the Blue Mountains Eye Study. Aust N Z J Ophthalmol 1997; 25(suppl):S99–101.
22. Whelton PK, He J, Cutler JA, et al. Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. JAMA 1997;277:1624–32.
23. Rankin SJ, Drance SM. Peripapillary focal retinal arteriolar narrowing in open angle glaucoma. J Glaucoma 1996;5:22–8.
24. Rankin SJ, Walman BE, Buckley AR, Drance SM. Color Doppler imaging and spectral analysis of the optic nerve vasculature in glaucoma. Am J Ophthalmol 1995;119:685–93.
25. Butt Z, O'Brien C, McKillop G, et al. Color Doppler imaging in untreated high- and normal-pressure open-angle glaucoma. Invest Ophthalmol Vis Sci 1997;38:690–6.
26. Nicolela MT, Drance SM, Rankin SJ, et al. Color Doppler imaging in patients with asymmetric glaucoma and unilateral visual field loss. Am J Ophthalmol 1996;121:502–10.
27. Frisen L, Claesson M. Narrowing of the retinal arterioles in descending optic atrophy. A quantitative clinical study. Ophthalmology 1984;91:1342–6.
28. Piltz-Seymour JR, Grunwald JE, Hariprasad SM, Dupont J. Optic nerve blood flow is diminished in eyes of primary open-angle glaucoma suspects. Am J Ophthalmol 2001;132:63–9.
29. Jonas JB, Fernandez MC, Naumann GO. Parapapillary atrophy and retinal vessel diameter in nonglaucomatous optic nerve damage. Invest Ophthalmol Vis Sci 1991;32:2942–7.
30. Papastathopoulos KI, Jonas JB. Focal narrowing of retinal arterioles in optic nerve atrophy. Ophthalmology 1995;102:1706–11.
31. Kerr J, Nelson P, O'Brien C. A comparison of ocular blood flow in untreated primary open-angle glaucoma and ocular hypertension. Am J Ophthalmol 1998;126:42–51.
32. Jonas JB. Central retinal artery and vein collapse pressure in eyes with chronic open angle glaucoma. Br J Ophthalmol 2003;87:949–51.
33. Collignon NJ, Collignon-Brach JD. Effect of topical betablockers on human retinal vessels diameters. Int Ophthalmol 1997;21:199–203.
34. Grunwald JE. Effect of timolol maleate on the retinal circulation of human eyes with ocular hypertension. Invest Ophthalmol Vis Sci 1990;31:521–6.
35. Schwartz B, Lavin P, Takamoto T, et al. Decrease of optic disc cupping and pallor of ocular hypertensives with timolol therapy. Acta Ophthalmol Scand Suppl 1995;73:5–21.
36. Wong TY, Klein R, Couper DJ, et al. Retinal microvascular abnormalities and incident stroke: the Atherosclerosis Risk in Communities Study. Lancet 2001;358:1134–40.
37. Wong TY, Klein R, Sharrett AR, et al. Retinal microvascular abnormalities and cognitive impairment in middle-aged persons: the Atherosclerosis Risk in Communities Study. Stroke 2002;33:1487–92.
38. Wong TY, Klein R, Sharrett AR, et al, ARIC Investigators. Cerebral white matter lesions, retinopathy, and incident clinical stroke. JAMA 2002;288:67–74.
39. Wong TY, Klein R, Sharrett AR, et al, ARIC Investigators. Retinal arteriolar narrowing and risk of diabetes mellitus in middle-aged persons. JAMA 2002;287:2528–33.