Abnormalities of Retinal Microvascular Structure and Risk of Mortality From Ischemic Heart Disease and Stroke

Nicholas Witt, Tien Y. Wong, Alun D. Hughes, Nish Chaturvedi, Barbara E. Klein, Richard Evans, Mary McNamara, Simon A. McG Thom, Ronald Klein

Abstract—Abnormalities of the retinal microcirculation are found in hypertension and diabetes and predict cardiovascular mortality. This study examined the relationship between abnormalities of the retinal microvasculature and death from ischemic heart disease (IHD) and stroke. A population-based, nested case-control study was undertaken within the Beaver Dam Eye Study. Subjects (43 to 74 years) who died of IHD (n=126) or stroke (n=28) over a 10-year period were age and gender matched with controls subjects (n=528; case:control matching, 1:4). Retinal photographs of cases and controls were digitized and analyzed using a computer-based technique. Increased risk of IHD death was associated with a suboptimal relationship of arteriolar diameters at bifurcation (P=0.02 unadjusted) and decreased retinal arteriolar tortuosity (P=0.011 unadjusted). These associations remained significant after adjustment for age, sex, past history of cardiovascular disease, and other known cardiovascular risk factors. Increased arteriolar length:diameter ratio, a measure of generalized arteriolar narrowing, was associated with increased stroke mortality (P=0.02 unadjusted). This association was independent of age and gender but was attenuated by adjustment for systolic blood pressure (P=0.15). Other quantitative measures of the retinal microvascular network (eg, venular tortuosity and arteriolar and venular bifurcation angle) were not associated with death from IHD or stroke. Retinal microvascular abnormalities are predictive of death from IHD and stroke. A detailed assessment of the retinal microvascular network from digitized photographs may be useful in the noninvasive assessment of target organ damage and cardiovascular risk.

Key Words: stroke ■ cardiovascular diseases ■ coronary diseases ■ microcirculation

Abnormalities of the retinal microcirculation, such as microaneurysms, arteriolar-venular nicking, and focal and generalized arteriolar narrowing predict future cardiovascular events independent of measured risk factors.1-3 This suggests that the retinal vasculature may provide a lifetime summary measure of exposure to cardiovascular insults and could act as a valuable marker for future cardiovascular risk. However, previous studies have largely used nonquantitative measures, such as clinical ophthalmoscopy, or used a photographic grading technique that is labor intensive. Furthermore, although the exact mechanisms of these associations are unclear, there are indications that certain retinal abnormalities, such as microaneurysms and hemorrhages, predict stroke but not ischemic heart disease (IHD),4,5 indicating that different measures of the retinal microvasculature could predict different outcomes, which is plausible given that IHD and stroke do not share identical etiologic mechanisms.

We have recently developed a computer-based robust method for the semiautomated analysis of digitized retinal images, based on the measurement of changes in the retinal microvascular network using, in the main, dimensionless parameters6-11: these include arteriolar and venular length:diameter ratio (LDR), tortuosity, bifurcation optimality, and bifurcation angles. We have previously demonstrated associations between some of these measures and age,12 hypertension,12 peripheral vascular disease,10 and low birth weight.8 We have not, however, examined associations with cardiovascular events or compared our techniques with previously reported and widely used measures. We now report the predictive ability for our methods in terms of IHD and stroke mortality using data from the Beaver Dam Eye Study cohort. This cohort has high-quality images, and conventional measures have previously demonstrated predictive power for cardiovascular disease (CVD) mortality.

Methods

Study Population
The study was designed as a nested case-control study within an existing prospective population-based study: the Beaver Dam Eye Study. Details of the study design and population have been published.
Retinal Microvascular Analyses

At baseline, all of the subjects had 30° color stereoscopic fundus photographs taken of both eyes. Photographic positives were digitized using a commercial photographic scanner (Nikon LS1000) at a resolution of 2700 dpi (yielding images of 2500 pixels) and were converted to monochrome by extraction of the green layer from the digital red, green, and blue images. Retinal microvascular and branching parameters were measured from the digitized images using a custom written program running within the Matlab programming environment on a personal computer. The reproducibility of this technique has been reported previously.11 Measurements were made from 7 informative vessel segments and ≥5 bifurcations in both arteriolar and venular arcades from each subject. An informative vessel segment was defined to be either linking 2 clearly visible bifurcations or else traversing a linear distance of ≥1.5 disc diameters (the width of an average optic disc in photographic images) from the optic disc boundary without bifurcating (Figure 1). The number of informative vessel segments and bifurcations (median [range]) measured per eye were 8 (range, 7 to 18) and 6 (range, 3 to 15), respectively.

The analysis was performed on a sequence of complete trees, generally from a single eye, continuing on the second eye if necessary to achieve the required number of vessel segments and bifurcations. Vessel path length was measured along the vessel center line between bifurcations. Arteriolar and venular diameters were measured at a series of intensity cross-sections normal to the vessel at 2-pixel intervals along the entire length of the vessel segment. At each cross-section, the vessel diameter was measured to subpixel accuracy using a sliding linear regression filter technique as described previously and an average calculated for each vessel.11 To derive a measure of vessel narrowing that is applicable to both arterioles and venules [unlike arteriovenous ratio (AVR)] and is unaffected by the refractive properties of the eye, the LDR was calculated as the ratio of the length of a vessel segment between 2 branching points to its average diameter.

The relationship of arteriolar diameters at a bifurcation has been shown previously to relate to fluid power losses and endothelial function.14 This relationship was quantified by calculating an optimality ratio and the optimality deviation, which measure the extent to which the optimality ratio deviates from the theoretically predicted optimum.13 Departures away from theoretically predicted optimum are predicted to be associated with increased power losses at bifurcations and are indicative of endothelial dysfunction. The optimality ratio is calculated from the mean daughter vessel diameter divided by the parent vessel diameter multiplied by a correction factor, which renders it independent of bifurcation asymmetry.15 For a theoretically optimal bifurcation, the optimality ratio yields a value of 0.79, and the optimality deviation is defined as the absolute difference from this value.

Two measures of vessel tortuosity were used. Simple tortuosity was estimated as the difference between the actual path length of the vessel segment (measured by tracking) and the straight line length of the segment divided by the straight line length. Because simple tortuosity does not distinguish between increased length because of bowing and that because of multiple points of inflection (Figure 2), another distinct measure of tortuosity based on vessel curvature was derived from the integral of the square of curvature along the path of the vessel, normalized by the total path length.16

Previously Reported Retinal Data

Measurement of AVR has been described previously.5 In brief, arteriolar and venular diameters were measured on digitized images from the optic disc boundary without bifurcating (Figure 1). The number of informative vessel segments and bifurcations (median [range]) measured per eye were 8 (range, 7 to 18) and 6 (range, 3 to 15), respectively.

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![Figure 1. Measurement of a single arteriolar tree, illustrating inner grid (solid and dashed lines) centered on the optic disc and the outer grid line separated by 1.5-disc diameters. Vessel tracking of centerline and diameter with bifurcations circled is also shown.](image_url)
in a prescribed area surrounding the optic disc margin. Using formulas from Parr and Spears\(^{17,18}\) and from Hubbard et al.,\(^9\) a summary measure of both arteriolar and venular diameter was estimated, from which the AVR was calculated. Because this was a key predictor of outcomes in previous reports, it is also included here for comparison.

Other Baseline Characteristics

A standardized interview and examination was performed at each examination. Questions were asked relating to household income, a history of CVD, medication use, and cigarette smoking. BP was measured with a random-zero sphygmomanometer according to the Hypertension Detection and Follow-Up Program protocol,\(^{20}\) and the average of 2 measurements was used for analysis. Hypertension was defined as systolic BP ≥140 mm Hg, diastolic BP ≥90 mm Hg, or the combination of self-reported high BP diagnosis and use of antihypertensive medications at the time of examination. Nonfasting bloods were obtained from all of the participants and serum glucose levels, plasma glycosylated hemoglobin, serum total cholesterol, and high-density lipoprotein (HDL) cholesterol determined as described previously.\(^5\) Diabetes mellitus was defined as a past history of diabetes or the presence of elevated glycosylated hemoglobin and a random blood sugar >200 mg/dL. Body mass index (BMI) was calculated as weight/height\(^2\).

Statistical Methods and Power Calculations

Previous analyses from the younger age group in this cohort have reported odds ratios of between 1.9 and 3.3 (equivalent to a logistic coefficient between 0.64 and 1.19) when using dichotomized categories of retinal abnormality versus outcome on multivariate adjustment.\(^5\) Adopting the same approach, with 5% significance and 80% power, we had more power to detect associations than previous analyses using categorical dichotomization of the data. Mean values of retinal abnormalities were compared between IHD and stroke cases, and the number of subjects with AVR in the lowest quintile was increased in IHD and stroke cases compared with controls, but these differences did not achieve statistical significance (with or without adjustment for age and gender). Other retinal parameters did not differ significantly between controls and IHD or stroke cases.

Self-reported smoking was classified as current, exsmoker, or never smoker. AVR, as measured previously, was reported both as a continuous variable and categorized in quintiles to permit comparisons with previous reports. Skewed variables were log transformed for analysis. Mean values of baseline parameters, adjusted for age using regression techniques, were compared by outcome status (IHD death, stroke death, or control). ANOVA was used to detect significant differences between groups for continuous variables and the \(\chi^2\) test for categorical variables. Retinal vascular measures were also compared by group in this way, using Tukey Wholly Significant Difference (WSD) test for separate comparisons between IHD or stroke on the one hand, with controls on the other. Multivariate logistic regression was used to assess independence of association between retinal measures and IHD or stroke. Statistical analysis was performed using Stata 8.2 (StataCorp).

Results

Baseline characteristics of controls, IHD cases, and stroke cases are shown in Table 1. As anticipated, cases and controls differed significantly in terms of systolic BP, prevalence of hypertension, total cholesterol, HDL cholesterol, glycosylated hemoglobin, diabetes, smoking habit, proteinuria, income category, and history of CVD. Retinal parameters adjusted for age in controls, IHD cases, and stroke cases are shown in Table 2. Optimality ratio and optimality deviation were significantly increased in individuals dying from IHD, whereas arterial tortuosity (simple tortuosity and vessel curvature) were significantly reduced in IHD cases (Table 2). Arteriolar LDR was significantly increased in stroke cases, whereas the reduction in arteriolar diameter was of borderline statistical significance (Table 2). There was no significant difference in arteriolar length between IHD or stroke cases and controls. AVR was slightly reduced in IHD and stroke cases, and the number of subjects with AVR in the lowest quintile was increased in IHD and stroke cases compared with controls, but these differences did not achieve statistical significance (with or without adjustment for age and gender). Other retinal parameters did not differ significantly between controls and IHD or stroke cases.

### Table 1. Baseline Characteristics of Study Population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n = 528)</th>
<th>IHD (n = 124)</th>
<th>Stroke (n = 28)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64.4 ± 7.4</td>
<td>64.4 ± 7.2</td>
<td>66.0 ± 7.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>336 (63.5)</td>
<td>75 (60.5)</td>
<td>18 (64.3)</td>
<td>0.9</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>133 ± 19</td>
<td>138 ± 24</td>
<td>148 ± 26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>77 ± 11</td>
<td>78 ± 12</td>
<td>82 ± 15</td>
<td>0.1</td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>28.9 ± 4.9</td>
<td>29.8 ± 5.4</td>
<td>29.9 ± 5.6</td>
<td>0.090</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>233 ± 39</td>
<td>252 ± 47</td>
<td>224 ± 50</td>
<td>0.001</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>51.1 ± 18.5</td>
<td>45.1 ± 16.5</td>
<td>50.9 ± 24.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Glycosylated hemoglobin, %</td>
<td>6.03 ± 1.33</td>
<td>6.63 ± 2.32</td>
<td>6.86 ± 2.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Below median income category, n (%)</td>
<td>293 (46.4)</td>
<td>75 (56.0)</td>
<td>19 (63.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>52 (9.9)</td>
<td>23 (19.0)</td>
<td>9 (32.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No proteinuria, n (%)</td>
<td>470 (69.2)</td>
<td>98 (14.4)</td>
<td>21 (73.1)</td>
<td>0.004</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>90 (17.1)</td>
<td>38 (30.7)</td>
<td>8 (28.6)</td>
<td>0.011</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>203 (38.5)</td>
<td>69 (55.7)</td>
<td>20 (71.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of cardiovascular disease, n (%)</td>
<td>89 (17.0)</td>
<td>47 (38.5)</td>
<td>12 (42.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Data are mean ± SD. \(P\) values were calculated by ANOVA for continuous and \(\chi^2\) for categorical data.*
There was a positive association between optimality deviation (abnormal bifurcation optimality) and IHD death and a negative association between simple arteriolar tortuosity and IHD death (Table 3). Both of these effects persisted after adjustment for age, gender, and other cardiovascular risk factors (Table 3). Multivariate adjustment for age, sex, past history of CVD, and other conventional cardiovascular risk factors (systolic BP, serum total cholesterol, serum HDL cholesterol, glycosylated hemoglobin, diabetes, BMI, and smoking, history of CVD) did little to attenuate the association between optimality deviation or simple tortuosity and IHD, and exclusion of subjects with diabetes from the analysis yielded logistic coefficients of similar magnitude to the group as a whole. Optimality deviation was positively related to BMI (β coefficient = 0.002 ± 0.001; P = 0.001), and simple arteriolar tortuosity was weakly positively related to systolic BP (β coefficient = 0.00005 ± 0.00003; P = 0.06), although this was of borderline statistical significance. Neither parameter showed any significant relationship to any other conventional cardiovascular risk factor.

Inclusion of the quintiled AVR (as used previously by Wong et al; Reference 3) did not significantly predict IHD in the age- and sex-adjusted model (P = 0.12) or in the multivariate model (P = 0.12). However, when AVR was used as a continuous variable in the multivariate model, including simple arteriolar tortuosity, decreased AVR was a significant predictor of IHD death (β coefficient = −2.96 ± 1.29; P = 0.02) but did not alter the strong relationship between simple arteriolar tortuosity and IHD death (Table 3).

Risk factors for IHD death, which remained significant in a stepwise multivariate model, included serum total cholesterol (P < 0.001), serum HDL cholesterol (P = 0.008), income (P = 0.032), glycosylated hemoglobin (P = 0.026), antihypertensive therapy (P = 0.01), smoking (P = 0.012), and previous history of CVD (including myocardial infarction, angina, and stroke; P = 0.004). Arteriolar LDR predicted stroke deaths (β coefficient = 0.075 ± 0.03; P = 0.02), and this relationship was unaffected by adjustment for age and gender. However, arteriolar LDR was also strongly related to resting systolic BP (β coefficient = 0.049 ± 0.009), and after adjustment for systolic BP, the relationship between arteriolar LDR and stroke deaths ceased to be statistically significant (P = 0.15). Risk factors for stroke death that remained significant in a stepwise multivariate model included systolic BP (P < 0.001), diabetes (P = 0.02), and previous history of CVD (P = 0.009).

In this population-based case control study, quantitative measures of retinal microvascular abnormalities at baseline were associated with incident IHD and stroke. Cases with incident IHD had impaired bifurcation optimality and reduced arteriolar tortuosity, independent of known cardiovascular risk factors. Stroke cases had increased arteriolar LDR (evidence of increased arteriolar narrowing), although this association was not independent of BP. Arteriolar and venular bifurcation angles or venular tortuosity were not associated with IHD or stroke death in the current study.

This is the first study to examine the relationship among quantitative measures of arteriolar bifurcation optimality, tortuosity, and CVD. Bifurcation optimality has been found previously to be impaired by ageing, atherosclerosis, and inhibition of NO synthase and is an indicator of endothelial function. The finding that impaired bifurcation optimality
Our observation of an association between increased arteriolar LDR (a measure of generalized arteriolar narrowing) and stroke deaths is in keeping with the findings of the Atherosclerosis Risk in Communities Study, where generalized arteriolar narrowing assessed by AVR was associated with incident stroke even after adjustment for BP, diabetes, hypertension in both younger and older patients, although only a weak positive relationship between BP and tortuosity was observed in a large study of 715 subjects, and retinal arteriolar tortuosity was not related to cerebral small vessel disease assessed by MRI. We found a weak positive association between systolic BP and arteriolar tortuosity, and this cannot, therefore, account for the relationship of reduced tortuosity and death from IHD which may be related to increased atherosclerosis and impaired microvascular endothelial function in subjects at risk of IHD.

The relationship of reduced tortuosity and death from IHD was unexpected. A previous study of subjects undergoing coronary angiography reported that more subjects with severe coronary disease had increased tortuosity as assessed by fundoscopic evaluation. However, tortuosity is difficult to assess by fundoscopy, and possible confounding factors, such as age, hypertension, or diabetes, were not accounted for in that study. Increased arterial tortuosity is associated with hypertension in both younger and older patients, although only a weak positive relationship between BP and tortuosity was observed in a large study of 715 subjects, and retinal arteriolar tortuosity was not related to cerebral small vessel disease assessed by MRI. We found a weak positive association between systolic BP and arteriolar tortuosity, and this cannot, therefore, account for the relationship of reduced tortuosity and death from IHD which may be related to increased atherosclerosis and impaired microvascular endothelial function in subjects at risk of IHD.

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and other stroke risk factors. Although LDR may be influenced by changes in the length of arteriolar segments, we did not observe any difference in arteriolar length between control and IHD or stroke cases, suggesting that it is arterial narrowing that accounts for this relationship. Our failure to demonstrate that the association between arteriolar LDR and stroke was independent of systolic BP may be because of the relatively small number of strokes in this study. Another possible reason for the failure to demonstrate an association between arteriolar LDR and stroke deaths after adjusting for BP is that LDR may be a marker of BP damage and is on the causal pathway between elevated BP and stroke.

It is increasingly recognized that abnormalities of the microvasculature play an important role in the development and consequences of CVD. From a theoretical standpoint, the design of the microvascular network is important in determining delivery of nutrients and oxygen with maximal efficiency. Angiogenesis and increased flow in the retina is also associated with increased tortuosity, and significant alterations in retinal bifurcation geometry have been shown to be associated with age, hypertension, and peripheral vascular disease. Altered retinal bifurcation geometry has also been demonstrated to be associated with low birth weight in adult men independent of BP. In the retinal microcirculation, arteriolar LDR has been found to increase in hypertension, suggesting that evaluation of the retinal microvasculature may be a useful predictor of target organ damage and cardiovascular risk. However, we advise cautious interpretation of the study findings, because we cannot assume a perfect correlation of structural microvascular changes in the retina with coronary or cerebral microvascular disease. Although some of the histopathologic features of retinal abnormalities (arteriolar narrowing, intimal thickening, and medial hyalination) are also seen in histological studies of patients with coronary microvascular disease, there are also significant differences in the anatomy and physiology of the retinal microcirculation and the circulation in the heart and brain.

Strengths of this study include its prospective design, a community-based population, and quantitative assessment of retinal microvascular changes by graders who were masked to participant characteristics and outcome. Limitations include the following: (1) cause-of-death was not validated by examining medical records; however, death certificate information has been found to be a fairly sensitive indicator of IHD and stroke risk; (2) the effect of hypertension and diabetes on these associations is likely to be substantial and may not be completely eliminated despite our attempts to adjust for BP and diabetes status; and (3) use of medication, particularly medication affecting the microvasculature, may have affected relationships between retinal abnormalities and IHD or stroke; however, a previous study of this cohort suggests that medication has little or no effect on retinal microvascular diameters with the exception of antiglaucoma medication. Because raised intraocular pressure has been reported to be associated with raised BP, it is possible that this influenced the relationship between systolic BP and LDR, but it seems unlikely to wholly account for the relationships among bifurcation optimality, tortuosity, and risk of IHD or LDR and stroke risk.

Perspectives
This study adds to evidence that retinal microvascular abnormalities are predictive of death from IHD and stroke, respectively. The use of a semiautomated technique facilitates the measurement process and diminishes observer variability, and the derived measures of bifurcation optimality, tortuosity, and arteriolar narrowing may be able to differentiate coronary and stroke risk, providing an opportunity to study their different aetiologies. Computerized assessment of the retinal microvascular network may be useful in the noninvasive assessment of target organ damage and cardiovascular risk.

Acknowledgments
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