Retinal Emboli and Stroke

The Beaver Dam Eye Study

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Objective: To describe the prevalence at baseline and the 5-year incidence of retinal emboli, associated risk factors, and the relationship of retinal emboli at baseline to stroke and ischemic heart disease mortality.

Methods: The Beaver Dam Eye Study is a large (N = 4926) population-based study of persons aged 43 to 86 years at the baseline examination. Retinal emboli were detected at baseline (1988-1990) and at a 5-year follow-up (1993-1995) by grading of stereoscopic 30° color fundus photographs using standardized protocols. Cause-specific mortality was determined from death certificates.

Results: The prevalence of retinal arteriolar emboli was 1.3%, and the 5-year incidence was 0.9%. After adjustments were made for age and sex, the prevalence of retinal emboli was associated with higher pulse pressure, hypertension, diabetes mellitus, past and current smoking, cardiovascular disease, and the presence of retinopathy. After adjustments were made for age and sex, the incidence of retinal emboli was associated with past and current smoking and a history of coronary artery bypass surgery. After age, sex, and systemic factors were controlled for, people with retinal emboli had a significantly higher hazard of dying with a mention of stroke on the death certificate (hazard ratio = 2.61, 95% confidence interval = 1.12-6.08) than those without retinal emboli.

Conclusions: Persons with retinal emboli are at an increased risk of stroke-related death. Data also show an association of smoking, hypertension, and cardiovascular disease with the prevalence of retinal emboli.

Clinical Relevance: Data from this population-based study suggest that after discovery of retinal emboli in the asymptomatic patient, referral for possible medical intervention to control hypertension, if present, may be beneficial.


Retinal arteriolar emboli are associated with an increased risk of cerebrovascular disease morbidity and mortality.1-9 Hollenhorst4 and Pfaffenbach and Hollenhorst,5 in a case-series follow-up of 208 patients seen with retinal emboli in an eye clinic, found that 15% of this group had died within 1 year and 54% had died within 7 years. Strokes or cerebral transient ischemic attacks were present in 63% of this group before or at the baseline examination in that study, and stroke or a cerebral transient ischemic attack developed in another 34% in the follow-up period.1,4,5 In another study, Savino et al6 reported 4 stroke-related deaths in 49 persons with retinal emboli compared with an expected stroke death of about 1 of 72 patients with visible emboli. These emboli may originate from ulcerations of atheromatous plaques in the internal or common carotid artery; from mural thrombi in the carotid artery; and from cardiac valvular structures, the left atrium of persons with fibrillation, and the left ventricle after a myocardial infarction.1,2,8-14 Most observations regarding these emboli and their clinical significance have come from clinic-based studies.1-15 To date, only 1 population-based study16 has provided cross-sectional data describing the prevalence of retinal emboli and associations with risk factors for cardiovascular disease and stroke. We describe the prevalence and incidence of retinal emboli, examine associated risk factors, and describe the relationship of retinal emboli to stroke and ischemic heart disease mortality in a large population-based cohort in Beaver Dam, Wis.

PREVALENCE OF RETINAL EMBOLI

At baseline, the overall prevalence of retinal arteriolar emboli was 1.3% (61/4856). Bilateral involvement was found in only 1 participant (0.02%). The prevalence of retinal emboli varied with age and was more frequent in men than in women (Table 1). Persons aged 75 years or older at baseline were 9.4 times (95% confidence interval [CI] = 5.8-15.2) as likely to...
have retinal emboli as persons aged 43 to 54 years. The overall prevalence of retinal emboli in right eyes was higher than in left eyes (0.8% [40/4865]) vs 0.5% [22/4877]; P = .02). Of those eyes with retinal emboli, only 1 embolus was found in 32 (80.0%) of the 40 right eyes and 20 (90.9%) of the 22 left eyes. 2 emboli in 5 right eyes (12.5%) and 2 left eyes (9.1%), and 3 or more emboli in 3 right eyes (7.5%) and none in the left eyes. Emboli were described as dull in 17 right eyes (42.5%) and nonreflective dull, that were defined by the graders to detect retinal emboli—lesions that appeared as reflective bright or nonreflective dull, that were rhombooidal, rectangular, or round, and that were lodged in retinal arterioles—which were classified as cholesterol, fibrin-platelet, or calcific in origin from the appearance on the fundus photographs. Instead, emboli reflectance (dull vs bright, based on a reference standard photograph) was directly classifying the embolus as cholesterol, fibrin-platelet, or calcific in origin from the appearance on the fundus photographs. Similar procedures were used at both baseline and follow-up examinations and have been described in detail elsewhere.17-22

Photographs were graded using the Wisconsin Age-Related Maculopathy grading scheme.11,21 As part of this scheme, all photographic fields of each eye were examined by the graders to detect retinal emboli—lesions that appeared as reflective bright or nonreflective dull, that were rhombooidal, rectangular, or round, and that were lodged in retinal arterioles—which were classified as present or questionable, or present.20 When present, the number of emboli (1, 2, or ≥3) were counted. In addition, emboli locations were indicated by which field it first appeared, listing an appearance only once if the same embolus appeared in several fields. Different types of emboli were not specified in the grading because of the difficulty in correctly classifying the embolus as cholesterol, fibrin-platelet, or calcific in origin from the appearance on the fundus photographs. Instead, emboli reflectance (dull vs bright, based on a reference standard photograph) was

The relation of cardiovascular disease and its risk factors to the prevalence of retinal emboli at baseline is presented in Table 2. After adjustments were made for age and sex, retinal emboli were associated with a higher
indicated. One of us (R.K.) examined all the photographs of persons with questionable or definite retinal emboli.

The presence of retinal microaneurysms only; blot hemorrhages only; hemorrhages, microaneurysms, or both; cotton-wool spots; hard exudates; intraretinal microvascular abnormalities; venous beading; arteriovenous nicking; new vessels on the disc and elsewhere; and preretinal and vitreous hemorrhages were graded in a masked manner using an abbreviated modified Airlie House classification scheme.29 Focal arteriolar narrowing was graded using a standard photograph from the Wisconsin Age-Related Maculopathy Grading30 protocol in which focal narrowing of small arterioles in the posterior pole (field 2) involves a total length of one third the disc diameter. Arteriolar narrowing was graded as absent, questionable, less than the standard, and equal to or greater than the standard for all arterioles more than 750 µm from the disc margin in all 3 standard fields. When there were multiple but separate areas of focal arteriolar narrowing, the composite length of involvement was compared with the standard. For the analyses, 2 categories were used: absent or questionably present, and present. Arteriovenous nicking was graded for all arteriovenous crossings that were more than 750 µm from the disc margin in all 3 fields. Arteriovenous nicking was graded as present if there was a decrease in the diameter of the venule on both sides of the arteriole that was crossing it. The presence of other retinal disease, such as central and branch retinal arterial or venous occlusion and surface wrinkling retinopathy, was graded using a detailed protocol.20,21

When 2 eyes of a participant were discrepant regarding the presence of a lesion, the grade assigned for the participant was that of the more severely involved eye. For example, in assigning the presence of a retinal embolus, if the retinal embolus was present in one eye but not the other, the participant would be considered to have a retinal embolus. When lesions could not be graded in one eye and the other eye had no lesions present, the participant’s information was classified as missing.

DEFINITIONS

Current age was defined as the age at the time of the baseline examination. The mean systolic and the mean diastolic blood pressures were of the 2 systolic and 2 diastolic blood pressure measurements, respectively. The pulse pressure was computed by taking the difference between the mean systolic and the mean diastolic blood pressures. Hypertension was defined as one or all of the following findings: a mean systolic blood pressure that was 160 mm Hg or greater, a mean diastolic blood pressure that was 95 mm Hg or greater, or a history of hypertension with the use of anti-hypertensive medication at the time of examination. Uncontrolled hypertension was defined as a systolic blood pressure of 160 mm Hg or greater or a diastolic blood pressure of 95 mm Hg or greater. Cardiovascular disease was defined as a history of angina pectoris, myocardial infarction, or stroke or currently taking heart medication such as digitalis or nitroglycerin. Cigarette smoking status was defined as follows: subjects were classified as having never smoked if they reported having smoked fewer than 100 cigarettes in their lifetime, as former smokers if they had smoked more than 100 cigarettes in their lifetime but had stopped smoking before the examination, and as currently smoking if they had not stopped. There were 373 people with a previous history of diabetes mellitus, treated with either insulin or oral hypoglycemic agents and/or diet. There were also 48 people with newly diagnosed diabetes mellitus.22

STATISTICAL METHODS

Commercial statistical software (SAS, version 6; SAS Institute, Inc, Cary, NC) was used for analyzing the data, including producing proportions, χ² statistics, and logistic regression. Trends in proportions across age groups were tested for significance using the Mantel-Haenszel procedure.31 The McNemar test,31 a special case of the Cochran-Mantel-Haenszel statistic, was used to test the differences in incidence and progression rates between eyes. Liang-Zeger models32 were used to assess relationships with data from both eyes when a risk factor was specific to eyes (ie, retinopathy, focal retinal arteriolar narrowing, and arteriovenous nicking). The relation of retinal embolus to overall mortality and to mortality in which ischemic heart disease and stroke were listed as causes of death was examined after age and sex adjustments using the Cox proportional hazards regression model.33

INCIDENCE OF RETINAL EMBOLI

The incidence of retinal embolus during the 5 years was 0.9% (32/3489). The incidence of retinal emboli varied with age, and they were more likely to occur in men than
in women (Table 1). The overall incidence was similar in right and left eyes (0.5% [17/3535] vs 0.4% [16/3559]; \(P = .85\)). Retinal emboli developed in both eyes in only 2 people. Of those eyes that had retinal emboli, 1 embolus was found in 14 (82.3%) of the 17 right eyes and 11 (68.8%) of the 16 left eyes, 2 emboli in 2 right eyes (11.8%) and 2 left eyes (12.5%), and 3 or more emboli in 1 right eye (5.9%) and 3 left eyes (18.8%). Emboli were described as dull in 10 of the right eyes (58.8%) and 7 of the left eyes (43.8%). Both dull and bright emboli developed in the same eye in only 1 right eye and 2 left eyes. Emboli disappeared (present at baseline and absent at follow-up) in 36 (90.0%) of 40 eyes.

The relation of cardiovascular disease and its risk factors to the incidence of retinal emboli is presented in Table 2. After adjustments were made for age and sex, the incidence of retinal emboli was associated with past and current smoking, alcohol use, and a history of coronary artery bypass surgery. An odds ratio of greater than 2 for the incidence of retinal emboli was found for a history of carotid artery bypass surgery at baseline. This relation was not statistically significant, however (\(P > .05\)). Smoking and a history of coronary artery bypass surgery were also associated with the incidence of retinal emboli.

### Table 2. Age- and Sex-Adjusted Relations of Various Characteristics to the Prevalence and 5-Year Incidence of Retinal Emboli in the Beaver Dam Eye Study

<table>
<thead>
<tr>
<th>Characteristic or History</th>
<th>Prevalence Odds Ratio (95% CI) (P)</th>
<th>Incidence Odds Ratio (95% CI) (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, per 10 mm Hg</td>
<td>1.10 (0.98-1.23) .11</td>
<td>1.11 (0.93-1.32) .25</td>
</tr>
<tr>
<td>Diastolic blood pressure, per 10 mm Hg</td>
<td>0.99 (0.79-1.26) .96</td>
<td>0.92 (0.66-1.30) .65</td>
</tr>
<tr>
<td>Pulse pressure, per 10 mm Hg</td>
<td>1.14 (1.00-1.31) .05</td>
<td>1.19 (0.97-1.46) .09</td>
</tr>
<tr>
<td>Serum total cholesterol level, per mmol/L</td>
<td>1.16 (0.93-1.45) .19</td>
<td>1.12 (0.82-1.53) .46</td>
</tr>
<tr>
<td>Serum HDL cholesterol level, per mmol/L</td>
<td>0.77 (0.41-1.45) .44</td>
<td>0.78 (0.32-1.86) .57</td>
</tr>
<tr>
<td>Hematocrit, per 0.10</td>
<td>1.51 (0.74-3.09) .26</td>
<td>1.19 (0.41-3.45) .75</td>
</tr>
<tr>
<td>Leukocyte count, &gt; 10⁹/L</td>
<td>1.07 (0.99-1.15) .09</td>
<td>1.05 (0.92-1.21) .48</td>
</tr>
<tr>
<td>Platelet count, 100×10⁹/L</td>
<td>0.90 (0.63-1.27) .53</td>
<td>1.20 (0.77-1.87) .42</td>
</tr>
<tr>
<td>Body mass index, per kg/m²†</td>
<td>0.99 (0.94-1.05) .79</td>
<td>0.96 (0.89-1.04) .31</td>
</tr>
</tbody>
</table>

### Table 3. Multivariate Relationships Between Prevalence of Retinal Emboli and Various Characteristics of the Population

<table>
<thead>
<tr>
<th>Characteristic or History</th>
<th>Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per 10 y</td>
<td>1.71 (1.30-2.25)</td>
</tr>
<tr>
<td>Sex, male vs female</td>
<td>1.71 (0.96-3.02)</td>
</tr>
<tr>
<td>Smoking history</td>
<td>2.33 (1.18-4.60)</td>
</tr>
<tr>
<td>Current vs never</td>
<td>3.61 (1.66-7.87)</td>
</tr>
<tr>
<td>Diabetes mellitus, present vs absent</td>
<td>1.93 (1.02-3.65)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.81 (1.77-8.23)</td>
</tr>
<tr>
<td>Uncontrolled vs normotensive</td>
<td>3.81 (1.77-8.23)</td>
</tr>
<tr>
<td>Controlled vs normotensive</td>
<td>2.32 (1.28-4.23) .003</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2.41 (1.26-4.61)</td>
</tr>
<tr>
<td>Coronary artery bypass surgery</td>
<td>3.75 (1.72-8.17) &lt;.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.79 (0.74-4.32)</td>
</tr>
<tr>
<td>Carotid artery bypass surgery</td>
<td>3.16 (0.74-13.59)</td>
</tr>
</tbody>
</table>

* CI indicates confidence interval; HDL, high-density lipoprotein.
†Calculated as weight in kilograms divided by the square of height in meters: weight (kg)/[height (m)]².
artery bypass surgery remained significant when included together in a multivariate model (Figure).

After age and sex were controlled for, neither retinopathy (OR = 2.12, 95% CI = 0.75-5.98) nor focal retinal arteriolar narrowing (OR = 1.18, 95% CI = 0.34-4.17) was associated with the incidence of retinal arteriolar emboli. Retinal emboli did not develop in any of the eyes that at baseline had arteriovenous nicking.

**RELATION OF RETINAL EMBOLI TO CARDIOVASCULAR DISEASE AND MORTALITY**

From the baseline examination (1988-1990) through 1996, there were 794 total death certificates in the cohort. Of those in the cohort who died, 247 persons (5.0%) had ischemic heart disease and 105 persons (2.1%) had stroke listed on the death certificate as 1 of the causes of death. People with retinal emboli at baseline had an 8-year age- and sex-adjusted overall survival rate of 89.3% in persons who did not have retinal emboli (P = .06). Although adjustment was made for age (61.9 years), there was no interaction between sex and emboli status for overall mortality. The relation of the retinal emboli status at baseline to stroke and ischemic heart disease death is shown in Table 4. After adjustments were made for age and sex, persons with retinal emboli at baseline had an increased risk of dying with stroke mentioned as a cause (hazard ratio = 2.93, 95% CI = 1.28-6.72) compared with those without emboli. After age, sex, pulse pressure, hypertension status, pulse rate, diabetes status, body mass index, cardiovascular disease history, and sedentary lifestyle were controlled for, persons with retinal emboli had a significantly greater hazard ratio for dying with stroke listed as a cause (hazard ratio = 2.6, 95% CI = 1.12-6.08) than did persons who did not have retinal emboli.

The addition of a history of stroke or carotid surgery did not change these relations. The presence of retinal emboli was not related to the incidence of fatal myocardial infarction (data not shown). There were no significant interactions between retinal emboli and systemic risk factors for stroke mortality (data not shown).

Most information about the frequency of retinal emboli has been derived from studies of clinic populations, in which patients with severe manifestation of disease may be over-represented. The Beaver Dam Eye Study provides unique data on the prevalence and incidence of retinal emboli using standardized protocols for the recording and grading of these lesions with stereoscopic color fundus photographs.

Retinal emboli were infrequent (1.3%) in the population, and their prevalence increased with age, as they affected 3.1% of persons aged 75 years or older. The prevalence of retinal emboli in the Beaver Dam population was similar to that found in male veterans seen in an ophthalmology clinic in Albuquerque, NM (0.8%), and to that reported in the Blue Mountains Eye Study population (1.4%). On the basis of the Beaver Dam data, we estimate that there are 1.2 million people aged 43 to 86 years in the United States with retinal emboli in at least 1 eye, about 450,000 of whom are aged 75 to 86 years.

After adjustments were made for systemic factors, a fatal stroke was about 3 times as likely to develop in persons with retinal emboli in Beaver Dam during an 8-year period as in those without retinal emboli. These findings are consistent with findings of higher mortality in previous case-series studies of persons with retinal emboli.

The association of cardiovascular disease and its risk factors with retinal emboli is consistent with data from previous studies. One of the strongest independent relations found in our study with the prevalence and incidence of retinal emboli is that of smoking. In addition, we found a strong association of hypertension and diabetes mellitus with the presence of retinal emboli at baseline. In the cross-sectional Blue Mountains Eye Study, after age and sex were controlled for, hypertension was associated with an OR of 2.2 of having retinal emboli, smoking with an OR of 2.6, and diabetes mellitus with an OR of 0.7. In a case-control study of 70 men with asymptomatic retinal cholesterol emboli and 21 control subjects, Bruno and colleagues found a higher prevalence of smoking (56% vs 28%; P < .001) and hypertension (78% vs 33%; P < .001) in patients than in control subjects. Whereas a strong association was found in the prevalence data, the relationship of hypertension to the incidence of retinal emboli in Beaver Dam was no longer statistically signifi-
cant. This is probably due, in part, to the low incidence of retinal emboli.

What should an ophthalmologist who discovers a retinal embolus in an asymptomatic patient do? In a case series,13 18% of those with retinal emboli who were asymptomatic had internal or common carotid artery stenosis of greater than 75%. In the studies done by Bruno and colleagues,8,9 those with retinal emboli had a higher frequency of carotid artery stenosis of 50% or more on either side (20% vs 0%; P = .06), a higher rate of heterogenous or echoluent carotid artery plaque on either side (95% vs 60%; P = .001), and a higher frequency of ischemic heart disease (38% vs 33%; P = .08) than did control subjects. Follow-up of these patients showed a higher incidence of stroke (8.3% vs 0.8% per year; P = .002) but not of myocardial infarction (5.7% vs 4.1% per year; P = .65) compared with that in controls. These findings suggest the need for a referral for medical intervention to control hypertension, dyslipidemia, and diabetes mellitus, if present. The use of aspirin therapy along with the cessation of smoking may provide an optimal approach for preventing stroke and other cardiovascular disease morbidity and mortality in asymptomatic people in whom a retinal embolus is discovered on routine examination.34 Because of the morbidity and mortality associated with carotid endarterectomy in asymptomatic patients, the decision to do this procedure in patients with retinal emboli will depend on a number of factors, including the severity of carotid stenosis, age, the severity and extent of comorbidities and other risk factors, and the experience and skill of the surgeons doing the procedure.35-39

Conclusions regarding estimates of the prevalence and incidence of retinal emboli and associations described herein must be made with caution. These emboli may be of short duration and recurrent and thus may be easily missed, resulting in an underestimate of their incidence.1,15 In addition, it is possible that persons with some risk factors such as cigarette smoking or hypertension in whom retinal emboli developed were more likely to die before follow-up, possibly underestimating the association.

In conclusion, the presence of retinal emboli at baseline was associated with a significant increase in the risk of stroke mortality in the cohort.

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