Retinal Arteriolar Narrowing Is Associated With 5-Year Incident Severe Hypertension

The Blue Mountains Eye Study

Wayne Smith, Jie Jin Wang, Tien Yin Wong, Elena Rochtchina, Ronald Klein, Stephen R. Leeder, Paul Mitchell

Abstract—We assessed whether retinal arteriolar narrowing and structural abnormalities independently predicted 5-year incident severe (grade 2 or 3) hypertension in an older population-based cohort. The Blue Mountains Eye Study baseline (1992 to 1994) examined 3654 residents aged 49 and older in 2 postal code areas, west of Sydney. Of the 2335 participants (75.1% of survivors) who returned at the 5-year examinations, 1319 were normotensive or had mild (grade 1) hypertension at baseline. Baseline retinal photographs were graded for focal retinal vessel wall signs and vessel diameters were measured. Participants were classified as having normal, high-normal blood pressure [BP] (systolic BP 121 to 139 mm Hg and/or diastolic BP 81 to 89 mm Hg), mild hypertension (systolic BP 140 to 159 mm Hg and/or diastolic BP 90 to 99 mm Hg), or severe hypertension if they had a previous diagnosis of hypertension and were receiving antihypertensive medications or had systolic BP ≥160 mm Hg and/or diastolic BP ≥100 mm Hg at examination. Incident severe hypertension was defined in persons who were free of severe hypertension at baseline but classified as having severe hypertension at the 5-year examinations. Of the 1319 baseline subjects at risk, 390 (29.6%) developed severe hypertension. After adjusting for age, sex, body mass index, smoking, glucose, and total cholesterol, generalized retinal arteriolar narrowing at baseline was associated with increased risk of incident severe hypertension (odds ratio 2.6; 95% confidence interval, 1.7 to 3.9) when comparing the narrowest versus widest quintile. This association remained significant after further adjustment for baseline mean arterial BP or BP status. Our findings support the hypothesis that small vessel structural changes may precede the development of severe hypertension. (Hypertension. 2004;44:442-447.)

Key Words: arterioles ■ hypertension, detection and control

Retinal microvascular signs are frequently seen in persons with hypertension.1–11 These changes, sometimes referred to as hypertensive retinopathy, include generalized12 and focal retinal arteriolar narrowing,12,13 arteriovenous (AV) nicking,4 and retinopathy (retinal microaneurysms, hemorrhages, soft or hard exudates).3,10 However, it is unclear when these signs develop in the course of the evolution of hypertension, because a graded detrimental effect of blood pressure (BP) is found even in persons with high-normal or mild (grade 1) hypertension.14,15 It is possible that retinal vessel wall signs may occur before the clinical expression of severe hypertension, reflecting an antecedent systemic arteriolar pathology.16,17

In the Atherosclerosis Risk in Communities (ARIC) Study, normotensive persons aged 49 to 73 years with generalized or focal retinal arteriolar narrowing were 60% more likely to have incident hypertension develop within 3 years than persons without these signs, independent of vascular risk factors.18 Few other population-based data are available. In addition, it is not clear whether this association is present in older people, in whom the prevalence of severe hypertension is higher.

We aimed in this report to explore whether retinal vessel wall signs predict the development of severe (grade 2 or 3) hypertension in a population-based cohort of older normotensive or mild (grade 1) hypertensive persons aged 49 to 97 years.

Methods

The Blue Mountains Eye study is a population-based cohort study of vision, common eye diseases, and other health outcomes in an urban population aged 49 years or older. Baseline participants (1992 to

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arteriolar narrowing, focal arteriolar narrowing, and mild AV nicking were all strongly age-related. Age did not increase severe AV nicking.

Of the 1319 participants, 390 (29.6%) had severe hypertension develop over the 5 years. Baseline hypertension status was a strong predictor of progression into severe hypertension. Of those with normal BP at baseline, 23.2% (95% CI 15.3% to 32.8%) progressed to grade 1 and 6.1% (2.3% to 12.7%) progressed to grade 2 hypertension, respectively. Of those with high-normal BP at baseline, the corresponding proportions were 41.2% (37.2% to 45.3%) and 19.7% (16.5% to 23.1%), respectively. Of those with mild (grade 1) hypertension at baseline, 42.4% (38.6% to 46.5%) progressed to severe (grade 2 or 3) hypertension in 5 years.

After excluding a further 50 subjects with missing or poor-quality (not gradable) retinal photographs, we were left with 1269 subjects who had complete data available for analyses of the association with retinal microvascular signs. These 1269 subjects included 370 with incident severe hypertension and 899 who remained either normotensive or mildly hypertensive. We compared the baseline characteristics of these 2 groups in Table 2. Participants with incident severe hypertension were significantly more likely at baseline to have higher mean BMI and higher systolic BP, generalized retinal arteriolar narrowing, or narrower mean central retinal arteriolar equivalent (CRAE) and lower arteriole-to-venule ratio (AVR).

Table 3 shows the relation between baseline retinal microvascular signs and 5-year incident hypertension. Persons with the narrowest quintile of CRAE or AVR, focal arteriolar narrowing, and moderate to severe AV nicking were more likely to have severe hypertension develop than were those with the widest quintile of CRAE or AVR and without focal arteriolar narrowing and AV nicking. After adjusting for age and sex, and after further adjusting for BMI, smoking, blood glucose, and serum total cholesterol levels (model 1), persons with generalized retinal arteriolar narrowing at baseline were more likely to have severe hypertension develop (OR, 2.6 for CRAE; OR, 2.4 for AVR). Persons with focal arteriolar narrowing (OR, 1.8) or with moderate to severe AV nicking (OR, 1.6) were also more likely to have severe hypertension develop. After additional adjustment for baseline MABP (model 2) or for baseline BP status (model 3), the associations with CRAE and AVR remained significant, but the association with focal arteriolar narrowing and AV nicking became nonsignificant.

In model 3, we adjusted simultaneously for retinal arteriolar narrowing (CRAE or AVR), baseline BP status, and other covariables, and both arteriolar narrowing and baseline BP status contributed independently and significantly to the development of severe hypertension (Table 3).

Stratification of model 1 by gender resulted in little change in the direction or magnitude of the detected associations between generalized arteriolar narrowing and incident severe hypertension (OR, 1.8; 95% CI 1.2 to 2.8 for women; OR, 2.0; 95% CI, 1.3 to 3.2 for men; adjusted for covariables in model 1).

Interaction between age and retinal vessel diameter, but not between age and AV nicking, was significant in the models.
Age stratification revealed stronger associations between generalized retinal arteriolar narrowing and incident severe hypertension among persons aged younger than 65 years (OR, 2.4; CI, 1.5 to 3.7) and a weaker association in those aged 65 years or older (OR, 1.5; CI, 1.0 to 2.4). In contrast, the adjusted association between moderate to severe AV nicking and incident hypertension among persons aged 65 years or older (OR, 2.7; CI, 1.3 to 5.6) was significant; but not among those aged younger than 65 years (OR, 0.9; CI, 0.4 to 1.9).

We repeated these analyses using 160/95 mm Hg as the dividing line above which we classified subjects as manifesting incident hypertension. This yielded very similar results to the models in which we used 160/100 as the dividing line.

**Discussion**

In this older population-based cohort, we found that generalized retinal arteriolar narrowing was significantly associated with subsequent 5-year incident severe (grade 2 or 3) hypertension, independent of other known risk factors for hypertension and baseline BP status. This association was stronger for younger (younger than 65 years) than older (65 years or older) participants. By contrast, the associations of focal arteriolar narrowing and moderate to severe AV nicking with incident severe hypertension became nonsignificant once we adjusted for baseline BP. These data support the notion that generalized structural changes in small blood vessels, visualized in the retina, may precede the development of clinical severe hypertension.

The strengths of our study include its prospective design, our use of a population-based sample with high participation rate, the objective grading of retinal photographs using a standardized protocol, and well-documented information on potential confounding variables. A fair follow-up of 75% of the original sample was seen at the 5-year examinations.

The study also has several limitations. Those who did not return were older and had a slightly higher prevalence of retinal microvascular signs, attributes that define an increased risk of mortality. Our findings thus could have underestimated the association between retinal arteriolar narrowing and incident hypertension. The use of single measures of blood pressure, which exhibited significant terminal digit preference, may have meant that we misclassified some subjects as having hypertension when they did not and that we missed some who did. This nondifferential misclassification is likely to bias our observed association.

**Table 1. Retinal Vessel Wall Signs and Blood Pressure by Age Among Normotensive or Mild Hypertensive Baseline Participants Who Returned for the 5-Year Examinations**

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>All Ages</th>
<th>&lt;60</th>
<th>60–69</th>
<th>70–79</th>
<th>80+</th>
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<tbody>
<tr>
<td>Central retinal arteriolar equivalent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>200.9 (19.4)</td>
<td>196.2 (19.5)</td>
<td>190.7 (21.7)</td>
<td>182.2 (18.5)</td>
<td></td>
</tr>
<tr>
<td>Quintile</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Widest</td>
<td>23.7</td>
<td>19.5</td>
<td>15.1</td>
<td>5.7</td>
<td></td>
</tr>
<tr>
<td>Fourth</td>
<td>23.9</td>
<td>20.2</td>
<td>13.3</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td>Third</td>
<td>22.1</td>
<td>19.7</td>
<td>16.5</td>
<td>17.1</td>
<td></td>
</tr>
<tr>
<td>Second</td>
<td>17.3</td>
<td>20.0</td>
<td>25.2</td>
<td>25.7</td>
<td></td>
</tr>
<tr>
<td>Narrowest</td>
<td>12.9</td>
<td>20.6</td>
<td>29.8</td>
<td>48.6</td>
<td></td>
</tr>
<tr>
<td>Arteriole-to-venule ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.88 (0.08)</td>
<td>0.87 (0.08)</td>
<td>0.86 (0.08)</td>
<td>0.85 (0.09)</td>
<td></td>
</tr>
<tr>
<td>Quintile</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Widest</td>
<td>21.7</td>
<td>19.9</td>
<td>16.5</td>
<td>20.0</td>
<td></td>
</tr>
<tr>
<td>Fourth</td>
<td>21.9</td>
<td>19.3</td>
<td>18.8</td>
<td>11.4</td>
<td></td>
</tr>
<tr>
<td>Third</td>
<td>21.3</td>
<td>20.4</td>
<td>17.0</td>
<td>14.3</td>
<td></td>
</tr>
<tr>
<td>Second</td>
<td>17.7</td>
<td>21.4</td>
<td>21.6</td>
<td>22.9</td>
<td></td>
</tr>
<tr>
<td>Narrowest</td>
<td>17.3</td>
<td>19.1</td>
<td>26.2</td>
<td>31.4</td>
<td></td>
</tr>
<tr>
<td>Focal retinal arteriolar narrowing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>61 (4.7)</td>
<td>1.6</td>
<td>3.8</td>
<td>10.4</td>
<td>21.4</td>
</tr>
<tr>
<td>AV nicking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>488 (37.3)</td>
<td>30.2</td>
<td>41.4</td>
<td>40.4</td>
<td>53.4</td>
</tr>
<tr>
<td>Moderate to severe</td>
<td>83 (6.3)</td>
<td>4.4</td>
<td>7.7</td>
<td>7.8</td>
<td>4.8</td>
</tr>
<tr>
<td>BP, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean arteriolar BP</td>
<td>97.7 (97.0–98.5)</td>
<td>98.2 (97.5–98.9)</td>
<td>99.0 (98.0–100.0)</td>
<td>97.8 (95.7–100.0)</td>
<td></td>
</tr>
<tr>
<td>Mean systolic BP</td>
<td>131.7 (130.6–132.8)</td>
<td>135.9 (134.8–137.0)</td>
<td>139.3 (137.8–140.8)</td>
<td>137.8 (134.3–142.4)</td>
<td></td>
</tr>
<tr>
<td>Mean diastolic BP</td>
<td>81.0 (80.4–81.7)</td>
<td>79.7 (79.0–80.3)</td>
<td>79.2 (78.1–80.2)</td>
<td>78.2 (76.0–80.4)</td>
<td></td>
</tr>
</tbody>
</table>
between retinal vascular disease and incident hypertension toward the null. Our findings thus would be an underestimate of the true association between retinal vascular disease and hypertension. By way of sensitivity analysis, we repeated the principal analyses using diastolic BP ≥110 mm Hg, ≥105 mm Hg, and ≥110 mm Hg at examination instead of ≥100 mm Hg; and using systolic BP ≥155 mm Hg, ≥165 mm Hg, and ≥170 mm Hg at examination instead of ≥160 mm Hg, and found essentially the same results (data not shown).

Our study suggests that generalized structural abnormalities in retinal blood vessels are prospectively associated with subsequent risk of severe hypertension in a representative general population. These findings add support to a longstanding hypothesis about the pathogenesis of hypertension. Others have found from animal studies and cross-sectional studies in highly selected human subjects that arteriolar constriction and narrowing may play a critical role in the earliest stages of hypertension development. In addition to their association with hypertension, the retinal vessel wall signs evaluated here have been associated with systemic markers of inflammation. This is consistent with recent studies that suggest inflammation may also play a role in the development of hypertension.

Our data are comparable to those from the ARIC study. The 2 studies used identical methods to define retinal arteriolar narrowing from digitized photographs. The magnitude of the association of generalized retinal arteriolar narrowing and incident hypertension in this study was similar to the ARIC study, although the latter was conducted in a younger population (49 to 73 years versus 49 to 97 years) with a shorter follow-up (3 years versus 5.1 years) and examined incident mild (grade 1) hypertension. Taken in totality, the close concordance of the findings in these 2 populations provides consistent evidence that microvascular narrowing may contribute to the development of clinical hypertension.

Two additional observations deserve further comments. First, when we controlled for baseline MABP (model 2) or baseline BP status (model 3), the associations between retinal arteriolar wall signs and incident hypertension attenuated for generalized narrowing and were no longer significant for AV nicking and focal arteriolar narrowing. However, because of the close association of long-term BP levels and retinal vessel wall signs, controlling for baseline BP may have resulted in overadjustment. By including baseline BP in the model, we demonstrated that the contribution from retinal vessel signs to the outcome (incident severe hypertension) could add incrementally to the contribution from baseline BP.

Second, we found somewhat stronger associations between generalized retinal arteriolar narrowing and weaker associations between AV nicking with incident severe hypertension in younger than in older persons. This may reflect the
complex associations of small vessel wall signs with several factors other than BP (e.g., hormonal status, obesity, insulin resistance, inflammatory marker status) that change as people age. Alternatively, there may be a survivor cohort effect. For example, if there is a differential early cardiovascular mortality among those with retinal arteriolar narrowing, the association between retinal arteriolar narrowing and incident severe hypertension will be less evident among older people who survive.

Although findings from our study and the ARIC study suggest that retinal microvascular signs may identify individuals at greater risk for clinically severe hypertension developing, the variability in the measurements of arteriolar caliber currently limits their applicability to predicting hypertension in individuals seen in clinical practice. The development of automated methods to quantify retinal vessel wall signs may well improve the clinical usefulness of these findings.

### TABLE 3. Retinal Arteriolar Narrowing and Vascular Signs at Baseline and 5-Year Incident Severe Hypertension in the Blue Mountains Eye Study Population Aged 49 Years and Older

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Mean (SD)</th>
<th>% Affected</th>
<th>Age- and Sex-Adjusted</th>
<th>Model 1*</th>
<th>Model 2†</th>
<th>Model 3‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinal Width (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Widest (n=254)</td>
<td>224.4 (9.7)</td>
<td>21.3</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Fourth (n=254)</td>
<td>207.5 (3.1)</td>
<td>23.6</td>
<td>1.2 (0.8–1.7)</td>
<td>1.3 (0.8–2.0)</td>
<td>1.2 (0.8–1.9)</td>
<td>1.3 (0.8–2.0)</td>
</tr>
<tr>
<td>Third (n=254)</td>
<td>196.7 (2.9)</td>
<td>28.4</td>
<td>1.4 (1.0–2.2)</td>
<td>1.5 (1.0–2.3)</td>
<td>1.3 (0.8–2.0)</td>
<td>1.4 (0.9–2.1)</td>
</tr>
<tr>
<td>Second (n=254)</td>
<td>186.3 (3.3)</td>
<td>32.3</td>
<td>1.7 (1.2–2.6)</td>
<td>1.8 (1.2–2.8)</td>
<td>1.5 (0.9–2.3)</td>
<td>1.6 (1.0–2.5)</td>
</tr>
<tr>
<td>Narrowest (n=253)</td>
<td>168.5 (12.0)</td>
<td>40.3</td>
<td>2.4 (1.6–3.5)</td>
<td>2.6 (1.7–3.9)</td>
<td>1.9 (1.2–2.9)</td>
<td>2.1 (1.4–3.3)</td>
</tr>
</tbody>
</table>

*P for trend*  
<0.0001 <0.0001 <0.0001 0.0037 0.0005

Narrowest quintile vs others  
1.8 (1.3–2.4) 1.9 (1.4–2.5) 1.5 (1.1–2.1) 1.6 (1.2–2.2)

Baseline BP status  
Normal 1.0
High-normal BP 3.1 (1.3–7.4)
Grade 1 hypertension 8.9 (3.8–21.0)

Arteriole-to-venule ratio  
Widest (n=254) 0.98 (0.04) 22.8 1.0 1.0 1.0 1.0
Fourth (n=254) 0.91 (0.01) 23.6 1.0 (0.7–1.6) 1.2 (0.7–1.8) 1.1 (0.7–1.7) 1.1 (0.7–1.8)
Third (n=254) 0.87 (0.01) 26.4 1.2 (0.8–1.8) 1.3 (0.8–2.0) 1.1 (0.7–1.8) 1.2 (0.8–1.9)
Second (n=254) 0.83 (0.01) 31.9 1.5 (1.0–2.3) 1.6 (1.0–2.4) 1.2 (0.8–1.9) 1.4 (0.9–2.2)
Narrowest (n=253) 0.76 (0.04) 41.1 2.4 (1.6–3.5) 2.4 (1.6–3.6) 1.7 (1.1–2.6) 2.0 (1.3–3.0)

*P for trend*  
<0.0001 <0.0001 <0.0001 0.0095 0.0011

Narrowest quintile vs others  
2.0 (1.5–2.7) 1.9 (1.4–2.6) 1.5 (1.1–2.1) 1.6 (1.2–2.3)

Baseline BP status  
Normal 1.0
High-normal BP 3.1 (1.3–7.2)
Grade 1 hypertension 8.8 (3.7–20.6)

Focal retinal arteriolar narrowing  
Absent (n=1248) 28.7 1.0 1.0 1.0 1.0
Present (n=61) 44.3 1.7 (1.0–2.9) 1.8 (1.0–2.3) 1.3 (0.7–2.5) 1.6 (0.9–2.9)

AV nicking  
Absent/questionable (n=738) 27.5 1.0 1.0 1.0 1.0
Mild (n=488) 30.3 1.1 (0.8–1.4) 1.0 (0.8–1.3) 1.0 (0.7–1.3) 1.0 (0.7–1.3)
Moderate to severe (n=83) 41.0 1.7 (1.1–2.7) 1.6 (1.0–2.6) 1.3 (0.8–2.2) 1.3 (0.8–2.2)

*Adjusted for age, sex, BMI, smoking, glucose, and serum cholesterol (continuous variables).
†Additionally adjusted for baseline MABP.
‡Additionally adjusted for baseline BP status (normal, high-normal, and grade 1 hypertension).
In conclusion, this prospective study found that retinal arteriolar wall signs predicted 5-year incident severe hypertension, independent of known vascular risk factors and baseline BP. These data support the hypothesis that structural micro-arteriolar damage, visible in the retina, precedes the development and progression of severe hypertension.

References
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