The Long-term Relation among Retinal Arteriolar Narrowing, Blood Pressure, and Incident Severe Hypertension

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The authors assessed associations between retinal vascular signs and incident severe hypertension in an older population-based cohort. At baseline (1992–1994), 3,654 residents aged 49–97 years living in the Blue Mountains area west of Sydney, Australia, were examined; respectively, 2,335 (75.1%) and 1,952 (76%) survivors were re-examined 5 and 10 years later. Retinal arteriolar and venular calibers were measured, and average central retinal artery and central retinal vein equivalents for that eye were estimated. Severe hypertension was defined by previous diagnosis of hypertension plus antihypertensive medication use or by systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg at examinations. Of the 1,424 participants at risk, 618 developed severe hypertension over 10 years (cumulative incidence = 47.7%, 95% confidence interval: 44.9, 50.5). Participants who subsequently developed severe hypertension had significantly narrower mean central retinal artery equivalents than those who did not (187.0 vs. 191.9 μm, p < 0.0001). After adjusting for age, sex, body mass index, smoking, mean arterial blood pressure, and plasma glucose and triglyceride levels, baseline narrowing central retinal artery equivalent was associated with increased risk of severe hypertension (per standard deviation reduction, odds ratio = 1.1, 95% confidence interval: 1.1, 1.2; narrowest vs. widest quintile, odds ratio = 1.6, 95% confidence interval: 1.2, 2.1). These findings support structural narrowing in small arteries and arterioles antecedent to clinical onset of severe hypertension.

arteries; arterioles; Australia; cohort studies; hypertension; incidence; retinal vessels

Abbreviations: CRAE, central retinal artery equivalent; CRVE, central retinal vein equivalent; DBP, diastolic blood pressure; SBP, systolic blood pressure.
arteriolosclerosis, is associated with future increases in blood pressure levels and precedes clinically manifest hypertension (8–11). Furthermore, evidence also exists that retinal arteriolar narrowing is linked to several hypertension genes (12, 13), implicating small arterial and arteriolar narrowing in the pathogenesis of hypertension. These findings have generated new research interest to revisit the extent that small arterial and arteriolar narrowing contributes to the pathogenesis of hypertension (14–16). There have been few studies, however, with the capacity to examine the longitudinal relation of retinal small arterial and arteriolar narrowing to long-term (10-year) changes in blood pressure levels in a population-based human sample (17).

We aimed to investigate whether retinal small arterial and arteriolar caliber predicts the development of severe (World Health Organization grade 2 or grade 3 (18)) hypertension over a 10-year period in our population-based cohort of older people who were normotensive or had only mild (grade 1) hypertension at their baseline examinations.

MATERIALS AND METHODS

Study population

The Blue Mountains Eye study is a population-based cohort study of eye diseases and other health outcomes in an urban population aged 49–97 years at inception in 1992–1994. At that time, 3,654 residents (82.4 percent of those eligible) living in two postcode areas 100 km west of Sydney, Australia, participated. After 5 years, 2,335 participants (75.1 percent of survivors) returned for examinations during 1997–1999; after 10 years, 1,952 participants (76 percent of survivors) returned for examinations during 2002–2004. The study was approved by the University of Sydney and the Sydney West Area Health Service Human Research Ethics Committees, and written, informed consent was obtained from all participants (19).

Retinal photography and measurement of retinal signs

Participants attending baseline, 5-year, or 10-year follow-up examinations had stereoscopic retinal photographs (30°) taken of the macula, optic disc, and other retinal fields of both eyes with a Zeiss FF3 fundus camera (Carl Zeiss, Oberkochen, Germany) after pupil dilation. Gradable retinal photographs of both eyes were obtained from 98 percent of participants at the baseline and 5-year examinations and from 85 percent of participants at the 10-year examinations (20).

We measured the caliber of retinal arterioles and venules from the optic disc photographs at the baseline, 5-year, and 10-year examinations by using a validated computer-assisted method (21). A digitized grid was placed over the image, and all vessels passing completely through a zone between 0.5 and 1 disc diameter from the disc margin were measured. Graders identified each vessel as a venule or arteriole. The computer software program RetinalAnalysis (Department of Ophthalmology and Visual Science, University of Wisconsin, Madison, Wisconsin) was used, and five equidistant measures on each vessel and branch were measured (in μm). A density pixel histogram showing the width of the central measurement was also displayed, which could be manually adjusted with reference to the image on the screen. The validity of each measurement was judged by evaluating the consistency of the histogram and the visual image, and the correlation between the average and central widths.

The Parr-Hubbard formula (22, 23) was used to summarize indices of the average retinal arteriolar and venular diameters in the eye and were referred to as the central retinal artery equivalent (CRAE) and central retinal vein equivalent (CRVE), respectively. We also computed the arteriole-to-venule ratio, representing the relative caliber size of arterioles to venules. Intra- and intergrader reliability of this method was high (21), with quadratic weighted kappa values of 0.85 (CRAE) and 0.90 (CRVE) found for intergrader reliability and between 0.80–0.93 and 0.80–0.92 for intragrader reliability of the first and second graders, respectively. Only right eye measurements were used because good correlation was found between measurements of the two eyes (24).

We assessed other focal retinal microvascular signs including focal arteriolar narrowing and arteriovenous nicking by using a light-box technique, by comparison with standard photographs, as described previously (5).

Definition of hypertension

At each visit, we measured systolic blood pressure (SBP) and diastolic blood pressure (DBP) once by using a single mercury sphygmomanometer with an appropriate adult cuff size, after participants had been seated for at least 10 minutes. We applied the 2003 World Health Organization/International Society of Hypertension guidelines (18) and definitions recommended by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) (25, 26) to classify blood pressure: grade 1 (mild) hypertension as SBP 140–159 mmHg or DBP 90–99 mmHg; and grade 2 or above (severe) hypertension in subjects previously diagnosed as hypertensive and using antihypertensive medications, or those with SBP ≥160 mmHg or DBP ≥100 mmHg, at examination. We included use of antihypertensive medication as a criterion for grade 2 hypertension since blood pressure levels are modified after use of these medications.

The World Health Organization/International Society of Hypertension guidelines, which recommended that persons with grade 1 hypertension commence using medications (18), were introduced only in 2003, after we had begun our 10-year follow-up (2002–2004). Because translation of guidelines into clinical practice takes time, we did not expect that many of our participants with grade 1 hypertension would be treated in primary care practices at that time. Instead, we assumed that older people with respective SBP and DBP levels of 140 and 90 mmHg would be more likely to have been observed rather than be prescribed antihypertensive medications either before or shortly after the new World Health Organization/International Society of Hypertension guidelines were introduced. Incident severe hypertension was defined in participants free of severe hypertension at baseline but who developed this condition either at (or before) 5-year or 10-year examinations. We calculated mean arterial blood pressure as 0.33 SBP + 0.67 DBP.
To assess longitudinal changes in blood pressure associated with retinal vessel caliber over the 10-year period, we further categorized 1,060 participants for whom data from all three examinations were available into subgroups as follows. First, in comparing mean CRAE at each examination with incident severe hypertension (figure 1), group 1 consisted of participants who were normotensive or had only mild hypertension (grade 1) over the 10-year period (both SBP and DBP <160/100 mmHg and who had not used antihypertensive medications). Group 2 comprised participants who developed severe hypertension (either or both SBP and DBP ≥160/100 mmHg or who had used antihypertensive medications). Group 3 included participants who had elevated blood pressure levels (regardless of medications used) over the three time points (BMES 1: baseline; BMES 2: 5-year follow-up examinations; BMES 3: 10-year follow-up examinations), after adjusting for age, sex, and baseline smoking status, Sydney, Australia, 1992–2004. Group 1: blood pressure level <140/90 mmHg at all examinations; group 2: blood pressure level elevated to ≥140/90 mmHg at BMES 3; group 3: blood pressure level elevated to ≥140/90 mmHg at BMES 3; group 3: blood pressure level elevated to ≥140/90 mmHg at both BMES 2 and BMES 3.

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Other risk factors

We measured baseline serum total cholesterol and glucose from fasting blood samples. Diabetes was diagnosed by either history or fasting blood glucose ≥7.0 mmol/liter. Body mass index was calculated as measured weight (kg)/measured height (m)². Smoking status was determined by interview and was classified as never, past, or current (this category included those who had stopped smoking in the past year).

Statistical methods

Only those participants with normal blood pressure or mild hypertension at baseline were considered at risk of
severe hypertension and were included in this analysis. Cumulative incidence was calculated by using Kaplan-Meier methods (product-limit survival estimates) to incorporate incident cases from either the 5-year or 10-year examinations. Incident severe hypertension was the dependent variable. Measurements of retinal vessel caliber were independent variables and were categorized into quintiles, and they were also analyzed as continuous variables (per standard deviation change). Focal arteriolar narrowing and arteriovenous nicking were dichotomous variables (per standard deviation change). Focal arteriolar narrowing and arteriovenous nicking were dichotomous variables (per standard deviation change). Focal arteriolar narrowing and arteriovenous nicking were dichotomous variables (per standard deviation change). Focal arteriolar narrowing and arteriovenous nicking were dichotomous variables (per standard deviation change).

For potential confounding variables in discrete logistic regression models, smoking status, plasma glucose level, and triglyceride levels, higher blood pressure, and more retinal vascular abnormalities (narrower CRAE, focal arteriolar narrowing, or arteriovenous nicking). These two groups were similar with regard to sex, diabetes, and current smoking. They also had similar mean plasma glucose levels and mean CRVE (table 1).

After adjustment for baseline age, sex, body mass index, smoking status, plasma glucose level, and triglyceride level, baseline narrower CRAE, smaller arteriole-to-venule ratio, and the presence of focal arteriolar narrowing or arteriovenous nicking were all associated with an increased risk of incident severe hypertension (table 2). After further adjustment for baseline mean arterial blood pressure, the association of narrower CRAE with smaller arteriole-to-venule ratio remained significant, but the associations with focal arteriolar narrowing and arteriovenous nicking were attenuated and became nonsignificant. Each standard deviation increase of narrowing in CRAE at baseline was associated with a 10 percent increased risk of incident severe hypertension (odds ratio = 1.1, 95 percent confidence interval: 1.1, 1.2) during the 10-year period. CRAE in the narrowest quintile predicted a 60 percent greater risk of incident severe hypertension (odds ratio = 1.6, 95 percent confidence interval: 1.2, 2.1) over the period, compared with the widest quintile of CRAE. Similarly, arteriole-to-venule ratio in the lowest quintile predicted a 50 percent greater risk of incident severe hypertension (odds ratio = 1.5, 95 percent confidence interval: 1.1, 1.9).

RESULTS

When we compared baseline characteristics between participants who returned for the 10-year examinations (n = 1,952) and those who were lost to follow-up (n = 565), there were no differences in mean age (62.5 vs. 62.2 years), sex (males: 40.6 vs. 39.1 percent), mean body mass index (26.2 vs. 26.0), mean serum total cholesterol levels (both 6.0 mmol/liter), and mean high density lipoprotein cholesterol levels (1.42 vs. 1.39 mmol/liter). There was also no difference in mean CRAE (p = 0.4) and CRVE (p = 0.8) between the two groups. However, there were differences in the proportions who, at baseline, were current smokers (12.9 vs. 18.2 percent) and had diabetes (5.9 vs. 8.3 percent) and severe hypertension (39.3 vs. 48.3 percent); we also found differences in mean fasting glucose levels (5.07 vs. 5.22 mmol/liter), mean triglyceride levels (1.67 vs. 1.78 mmol/liter), and mean SBP (142.7 vs. 144.0 mmHg).

Of the 1,424 baseline participants at risk, 618 developed severe hypertension over the 10-year period. The estimated cumulative incidence, after incorporating incident cases at both the 5-year and 10-year examinations, was 47.7 percent (95 percent confidence interval: 44.9, 50.5) in this population, with no sex difference. It was 48.9 percent (95 percent confidence interval: 45.3, 52.7) in women and 46.2 percent (95 percent confidence interval: 42.1, 50.5) in men (p = 0.2) considered separately.

After we excluded subjects whose retinal vessel measurements were missing, 1,369 baseline participants at risk of severe hypertension were included in our study. Of those, 590 (43.1 percent) developed incident severe hypertension over the 10-year period. Compared with those who did not develop incident severe hypertension, these participants were older and had higher body mass index, higher triglyceride levels, higher blood pressure, and more retinal vascular abnormalities (narrower CRAE, focal arteriolar narrowing, or arteriovenous nicking). These two groups were similar with regard to sex, diabetes, and current smoking. They also had similar mean plasma glucose levels and mean CRVE (table 1).

FIGURE 3. Longitudinal change in mean retinal arterial and arteriolar caliber (mean central retinal artery equivalent, CRAE) and blood pressure level (regardless of antihypertensive medication use) over three Blue Mountains Eye Study (BMES) examinations among 287 participants who had hypertension grade 1 (blood pressure ≥140/90 mmHg but <160/100 mmHg) at baseline, by subgroups with and without blood pressure levels reversed to <140/90 mmHg at different time points (BMES 1: baseline; BMES 2: 5-year follow-up examinations; BMES 3: 10-year follow-up examinations), after adjusting for age, sex, and baseline smoking status, Sydney, Australia, 1992–2004. Group 1: blood pressure ≥140/90 mmHg but <160/100 mmHg at BMES 1, decreased to <140/90 mmHg at BMES 2 and BMES 3; group 2: blood pressure ≥140/90 mmHg but <160/100 mmHg at BMES 1 and BMES 2, decreased to <140/90 mmHg at BMES 3; group 3: blood pressure ≥140/90 mmHg but <160/100 mmHg at all examinations.
interval: 1.2, 2.0) than the highest quintile of arteriole-to-venule ratio (table 2). CRVE at baseline, however, was not associated with incident severe hypertension (table 2).

Temporal associations between blood pressure or hypertension and mean CRAE over the 10-year period are shown in figures 1–3, after adjustment for age, sex, and baseline smoking status. Figure 1 shows the change in mean CRAE over the three Blue Mountains Eye Study examinations among participants with and without severe hypertension at baseline, by hypertension category at the three different time points. Of the 1,060 participants for whom blood pressure and retinal vessel caliber data were available from all three examinations (after excluding those with incomplete data from both follow-up times), participants in group 1 (normotensive or mild hypertension grade 1 throughout the entire 10-year period) had the widest mean CRAE compared with the other three groups. Participants in group 2, who developed severe hypertension only at the 10-year examination, had narrower mean CRAE than group 1 but wider mean CRAE than groups 3 or 4. Participants in group 3, who developed severe hypertension at the first 5-year follow-up time, had a mean CRAE at baseline similar to that of participants in group 4, who had already developed severe hypertension by that time.

Figure 2 shows mean CRAE over the three Blue Mountains Eye Study examinations among 380 participants whose SBP and DBP were both <140/90 mmHg at baseline, stratified by blood pressure levels at different time points,

<table>
<thead>
<tr>
<th>TABLE 1. Comparison of baseline characteristics of participants with and without incident severe hypertension over 10 years in the Blue Mountains Eye Study, Sydney, Australia, 1992–2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline characteristics</td>
</tr>
<tr>
<td>Demographics and risk factors</td>
</tr>
<tr>
<td>Mean age (years)</td>
</tr>
<tr>
<td>Sex: women (%)</td>
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<tr>
<td>Mean body mass index (kg/m²)</td>
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<tr>
<td>Mean total cholesterol (mmol/liter)</td>
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<tr>
<td>Mean triglycerides (mmol/liter)</td>
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<tr>
<td>Mean high density lipoprotein cholesterol (mmol/liter)</td>
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<tr>
<td>Mean glucose (mmol/liter)</td>
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<tr>
<td>Diabetes (%)</td>
</tr>
<tr>
<td>Current smoker (%)</td>
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<tr>
<td>Retinal vessel wall signs</td>
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<tr>
<td>Generalized retinal arteriolar narrowing defined as central retinal artery equivalent in the narrowest quintile (%)</td>
</tr>
<tr>
<td>Generalized retinal arteriolar narrowing defined by arteriole-to-venule ratio in the narrowest quintile (%)</td>
</tr>
<tr>
<td>Mean central retinal artery equivalent (µm)</td>
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<tr>
<td>Mean central retinal vein equivalent (µm)</td>
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<tr>
<td>Mean arteriole-to-venule ratio</td>
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<tr>
<td>Focal retinal arteriolar narrowing (%)</td>
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<tr>
<td>Arteriovenous nicking (%)</td>
</tr>
<tr>
<td>Mild</td>
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<tr>
<td>Moderate to severe</td>
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<tr>
<td>Blood pressure (mmHg)</td>
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<tr>
<td>Mean arterial†</td>
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<tr>
<td>Mean systolic</td>
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<tr>
<td>Mean diastolic</td>
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</tbody>
</table>

* Severe hypertension was defined as grade II or above.
† Arteriole-to-venule ratio was calculated as the ratio of central retinal artery equivalent to central retinal venular equivalent.
‡ Mean arterial blood pressure was calculated as 0.33 systolic blood pressure + 0.67 diastolic blood pressure.
regardless of whether they used antihypertensive medications. Compared with persons whose SBP remained <140 and whose DBP remained <90 mmHg throughout the entire 10-year period (group 1), those whose SBP was elevated to ≥140 and/or whose DBP was elevated to ≥90 mmHg at the 10-year visit (group 2) had narrower mean CRAE than group 1 but wider mean CRAE than group 3, whose SBP was elevated to ≥140 and/or whose DBP was elevated to ≥90 mmHg, some 5 years earlier than participants in group 2.

Figure 3 shows mean CRAE over the three Blue Mountains Eye Study examinations among 287 participants with SBP ≥140 but <160 mmHg and/or DBP ≥90 but <100 mmHg (stage 1 hypertension) at baseline, stratified by the adequacy of blood pressure control at different time points, regardless of whether they used antihypertensive medications. Group 1, whose SBP and DBP levels were both under control (<140/90 mmHg) during the next 5 years, had slightly wider mean CRAE than groups 2 and 3, whose

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TABLE 2. Associations of baseline retinal vessel signs with 10-year incident severe hypertension in participants of the Blue Mountains Eye Study, Sydney, Australia, 1992–2004

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Mean (SD*)</th>
<th>% affected</th>
<th>Age and sex adjusted</th>
<th>Multivariate adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR* 95% CI</td>
<td>OR 95% CI</td>
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<tr>
<td></td>
<td></td>
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<td>Model 1</td>
<td>Model 2</td>
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<tr>
<td>Central retinal artery equivalent (µm)</td>
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<td></td>
</tr>
<tr>
<td>Per SD decrease</td>
<td>1.2</td>
<td>1.1, 1.3</td>
<td>1.2</td>
<td>1.1, 1.3</td>
</tr>
<tr>
<td>Quintile</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Widest</td>
<td>213.9 (9.2)</td>
<td>34.7</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Fourth</td>
<td>198.9 (2.8)</td>
<td>38.3</td>
<td>1.1</td>
<td>0.8, 1.5</td>
</tr>
<tr>
<td>Third</td>
<td>190.3 (2.4)</td>
<td>43.4</td>
<td>1.3</td>
<td>1.0, 1.7</td>
</tr>
<tr>
<td>Second</td>
<td>181.0 (3.0)</td>
<td>44.9</td>
<td>1.4</td>
<td>1.1, 1.8</td>
</tr>
<tr>
<td>Narrowest</td>
<td>164.8 (10.3)</td>
<td>54.2</td>
<td>1.7</td>
<td>1.3, 2.2</td>
</tr>
<tr>
<td>p for trend</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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<tr>
<td>Central retinal vein equivalent (µm)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per SD increase</td>
<td>1.0</td>
<td>0.9, 1.1</td>
<td>1.0</td>
<td>0.9, 1.0</td>
</tr>
<tr>
<td>Quintile</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Widest</td>
<td>255.2 (10.9)</td>
<td>45.6</td>
<td>1.0</td>
<td>0.8, 1.3</td>
</tr>
<tr>
<td>Fourth</td>
<td>235.6 (3.4)</td>
<td>35.0</td>
<td>0.7</td>
<td>0.6, 1.0</td>
</tr>
<tr>
<td>Third</td>
<td>225.9 (2.6)</td>
<td>40.9</td>
<td>0.9</td>
<td>0.7, 1.1</td>
</tr>
<tr>
<td>Second</td>
<td>216.8 (3.1)</td>
<td>46.4</td>
<td>1.0</td>
<td>0.8, 1.3</td>
</tr>
<tr>
<td>Narrowest</td>
<td>199.7 (9.2)</td>
<td>47.3</td>
<td>1.0</td>
<td>0.9</td>
</tr>
<tr>
<td>p for trend</td>
<td></td>
<td></td>
<td>0.4</td>
<td>0.2</td>
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<tr>
<td>Arteriole-to-venule ratio</td>
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</tr>
<tr>
<td>Per SD decrease</td>
<td>1.2</td>
<td>1.1, 1.3</td>
<td>1.2</td>
<td>1.1, 1.3</td>
</tr>
<tr>
<td>Quintile</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Widest</td>
<td>0.94 (0.03)</td>
<td>35.4</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Fourth</td>
<td>0.87 (0.01)</td>
<td>40.9</td>
<td>1.2</td>
<td>0.9, 1.6</td>
</tr>
<tr>
<td>Third</td>
<td>0.84 (0.01)</td>
<td>39.8</td>
<td>1.2</td>
<td>0.9, 1.5</td>
</tr>
<tr>
<td>Second</td>
<td>0.80 (0.01)</td>
<td>43.8</td>
<td>1.3</td>
<td>1.0, 1.7</td>
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<tr>
<td>Narrowest</td>
<td>0.74 (0.03)</td>
<td>55.7</td>
<td>1.8</td>
<td>1.4, 2.3</td>
</tr>
<tr>
<td>p for trend</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Focal retinal arteriolar narrowing</td>
<td></td>
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</tr>
<tr>
<td>Absent (n = 1,305)</td>
<td>42.2</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Present (n = 64)</td>
<td>60.9</td>
<td>1.4</td>
<td>1.0, 2.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Arteriovenous nicking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent/questionable/mild (n = 1,282)</td>
<td>42.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Moderate to severe (n = 87)</td>
<td>58.6</td>
<td>1.4</td>
<td>1.0, 1.9</td>
<td>1.3</td>
</tr>
</tbody>
</table>

* SD, standard deviation; OR, odds ratio; CI, confidence interval.
† Adjusted for age, sex, body mass index, smoking, plasma glucose, and triglycerides.
‡ Further adjusted for baseline mean arterial blood pressure.

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SBP and/or DBP were poorly controlled (either or both ≥140/90 mmHg) for at least 5 years.

**DISCUSSION**

In this population-based sample of older Australians, we showed that retinal arteriolar narrowing antedates the future development and clinical diagnosis of severe hypertension and blood pressure elevation. Persons with relatively small arteries and arterioles in the retina had the greatest risk of developing severe hypertension during the next 10 years. We also showed that persons who developed severe hypertension within 5 years already had a baseline mean arterial and arteriolar caliber similar to those with severe hypertension at baseline. As with other studies, we found no longitudinal association between retinal venular caliber and incident hypertension or changes in blood pressure level.

On the basis of evidence showing higher risk of cardiovascular complications associated with blood pressure levels previously considered normal (26), the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines suggested that the traditional SBP/DBP diagnostic cutpoint of 140/90 mmHg for hypertension does not identify all high-risk people and so introduced a "prehypertension" stage. Our study provides further evidence that blood pressure-related microvascular structural damage may occur from blood pressure levels previously considered normal, possibly reflecting differences in susceptibility to blood pressure among individuals (28). Population-based data suggest the absence of a blood pressure threshold in terms of its relation to the narrowing of small arteries and arterioles. The same continuous, inverse linear association between blood pressure level and CRAE has been consistently documented in the many population-based studies to investigate this association (1–11). This association is evident before the onset of clinical or severe hypertension, as demonstrated by our study and in previous reports (8–11). These findings support a potential role for retinal arterial and arteriolar narrowing as an intermediate phenotype (29) that could be used as a marker for future hypertension risk.

Of particular interest, we found that elevated blood pressure at baseline that, over time, reverted to normal at follow-up examinations was associated with relatively larger arteries and arterioles throughout the entire follow-up period (figure 3). These findings can be interpreted in two ways. Participants whose blood pressure is consistently elevated may have more persistent damage to their microvascular structure. Alternately, persons with relatively larger arteries and arterioles may achieve blood pressure control more easily because their peripheral resistance is lower than in those with relatively smaller arteries and arterioles. This interpretation, if proven, would have clinical implications for future hypertension prevention strategies in targeting a reduction in total peripheral resistance.

The hypothesis that peripheral resistance was implicated in initial increases in blood pressure in the pathogenesis of essential hypertension originated more than 50 years ago (30). Later observations in the 1960s, however, focused on the alternative mechanism of increased cardiac output as the initiating trigger (30). In exercise-induced blood pressure elevation and in rats with renal hypertension, it is now widely accepted that an initial increase in cardiac output leads to an increase in blood flow, and, in response, the peripheral vascular system autoregulates small arterioles to maintain blood supply to end organs (30, 31). It is highly likely that both or even more mechanisms operate (32), with a differing relative contribution for specific cases, depending on patient characteristics, including genetic susceptibility and exposure to environmental triggers (15, 28, 30).

Strengths of our study include its population-based cohort and longitudinal follow-up over 10 years, with documentation by retinal photographs taken at each visit of retinal vessel caliber changes over time. Because of the development of age-related lens opacities in this study sample, measurement of retinal arteriolar caliber could have been more difficult at this age than in samples from younger individuals. We compared the CRAE–blood pressure associations between subjects with and without cataract and found no significant difference (adjusted beta coefficient for quintile reduction in CRAE = 1.7 for subjects with cataract; corresponding adjusted beta coefficient = 1.6 for subjects without cataract). There was no significant effect modification of cataract on the CRAE–blood pressure association (p = 0.9). Therefore, we consider that this potential, nondifferential measurement error, if it occurred, would be unlikely to have a major influence on our findings. Furthermore, venular caliber would be subject to similar measurement error from lens opacities, and our finding of no association between retinal venular caliber and incident hypertension provides further reassurance.

Our study also has several limitations. Those study participants who did not return for the 10-year examinations were more likely to have been current smokers at baseline, to have had diabetes and severe hypertension, and to have a slightly higher mean SBP. However, there were no differences in mean baseline age, DBP, CRAE, and CRVE between the two groups. The use of single blood pressure measurements could have resulted in some misclassification of hypertension. This nondifferential misclassification would be likely to bias our observed association toward the null; that is, our findings would be an underestimate of the true association between narrowing arterial and arteriolar caliber and incident severe hypertension. In our previous report of 5-year follow-up data (10), we conducted sensitivity analyses by using a range of different cutpoints of SBP and DBP at examination as alternative diagnostic criteria for hypertension, and we found essentially the same results.

We also noticed, as evident in figures 1–3, that by the time the Blue Mountains Eye Study 10-year examinations were conducted, all groups, regardless of blood pressure level, had developed substantial narrowing of their mean CRAE. This pattern could suggest either 1) other age-related factors that begin to influence arteries and arterioles when persons reach a certain age, for example, age 65 or 70 years; or 2) a systematic measurement difference between the latest and the two previous Blue Mountains Eye Study examinations. We therefore plotted CRVE in a way similar to that shown in these three figures, and we found that change in CRVE over
time displayed a declining linear pattern that was much
smoother than the declining pattern of CRAE. We thus feel
that the possibility of a systematic measurement difference
over the three examinations is highly unlikely. We con-
ducted further analysis to assess the effect of age on CRAE
by using Blue Mountains Eye Study I cross-sectional data,
and we found a significant difference between younger (<65
years) and older (≥65 years) age groups in the slope of the
linear associations of age with CRAE. Mean CRAE de-
creased by 0.18 μm and 0.52 μm per-year increase in age
in the younger and older age groups, respectively. Other
age-related factors could explain this difference in the mag-
nitude of age effect on arteries and arterioles, so further
investigations are warranted (33).

In conclusion, our 10-year follow-up data from an older
population-based cohort further support a consistent associ-
ation between the narrowing of small retinal arteries and
arterioles and subsequent increased risk of developing se-
vere hypertension.

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