Relationships between Age, Blood Pressure, and Retinal Vessel Diameters in an Older Population

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PURPOSE. To describe the cross-sectional relationships between age, blood pressure (BP), and quantitative measures of retinal vessel diameters in an older Australian population.

METHODS. Retinal photographs from right eyes of participants (n = 3654, aged 49+ years) in the Blue Mountains Eye study taken during baseline examinations (1992–1994) were digitized. The width of all retinal vessels located 0.5 to 1.0 disc diameters from the disc margin was measured by a computer-assisted method. Summarized estimates for central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE) represent average retinal vessel diameters. The arteriole-to-venule ratio (AVR) was calculated. Associations between age and BP and CRAE, CRVE, and AVR were assessed with generalized linear models.

RESULTS. Retinal vessel diameters decreased with increasing age in both men and women. CRAE and CRVE decreased by 4.8 μm and 4.1 μm, respectively, per decade in age, after adjusting for sex and mean arterial blood pressure. Mean AVR declined by 0.01 for each increasing decade of age, until 79 years. After adjustment for age, sex, smoking, and body mass index, CRAE, CRVE and AVR were all significantly and inversely associated with BP. For every 10-mm Hg increase in mean arterial blood pressure, AVR decreased by 0.012 and CRAE and CRVE decreased by 3.5 μm and 0.96 μm, respectively.

CONCLUSIONS. Retinal arteriolar and venular diameters narrowed with increasing age, and these parameters are inversely related to BP, independent of age, gender, and smoking. The findings are consistent with those from the Atherosclerosis Risk in Communities Study suggesting that decreased retinal vessel diameters may reflect microvascular damage from elevated blood pressure. (Invest Ophthalmol Vis Sci. 2003;44: 2900–2904) DOI:10.1167/iovs.02-1114

The prevalence and incidence of retinal microvascular abnormalities and their relationships with age and blood pressure (BP) are well described. However, these reports have mainly focused on retinopathy lesions, including focal retinal arteriolar narrowing, arteriovenous nicking, microaneurysms, hemorrhages, and other retinopathy lesions. Limited data on the prevalence of generalized arteriolar narrowing and its relationship with age and BP have been reported because of the difficulties in quantifying retinal arteriolar and venular diameters objectively and accurately. Recently developed computer-assisted methods, used in several population-based studies including the Atherosclerosis Risk in Communities (ARIC) study, Cardiovascular Health Study (CHS), and Blue Mountains Eye Study (BMES), allow reliable and precise measurements of retinal vessel diameters from digitized retinal photographs.

Arteriolar narrowing is believed to be the most characteristic early sign of hypertensive retinopathy. In the CHS (n = 2405), arteriolar width equivalents were found to decrease with increasing concurrent systolic and diastolic BP in older men and women (aged 69–97 years). In the ARIC study (n = 9300, aged 50–71 years), the arteriole-to-venule ratio (AVR) was found to be monotonically and negatively associated with, not only current BP levels, but also previous BP levels measured 3 and 6 years before the retinal photographs were taken. This suggests that reduced AVR may reflect cumulative microvascular damage from hypertension over some period.

Because retinal arterioles share common anatomy (e.g., blood–brain barrier) and physiological features (e.g., autoregulation of BP) with cerebral arterioles, changes in retinal arteriolar diameter may reflect similar changes in cerebral arterioles. Generalized narrowing of retinal arterioles may be useful in predicting cerebrovascular events, if an independent predictive value from this sign is confirmed. This study, as part of the project investigating the relationship between retinal vascular signs and subsequent vascular events, describes the cross-sectional relationships between quantitative measures of retinal vessel diameters and age and BP in a general older Australian population.

METHODS

Study Participants

The BMES is a population-based cohort study of vision, common eye diseases, and other health outcomes in an urban population aged 49 years or more. Baseline participants (n = 3654) represented 82.4% of eligible potential participants living in two postal-code areas in the Blue Mountains of Australia. This study was conducted according to the recommendations of the Declaration of Helsinki and was approved by the Western Sydney Area Human Ethics Committee. Written, informed consent was obtained from all participants. At the baseline examinations (1992–1994), after pupillary dilation, 30° stereoscopic retinal photographs of the macula, optic disc, and other retinal fields of both eyes were taken, using a fundus camera (model FF3; Carl Zeiss Meditec, Oberkochen, Germany). In this study, retinal photographs of right eyes of 3555 of the 3654 participants were included, after 299
participants were excluded who had no retinal photographs taken, had photographs with a poor image that precluded the measurement, or had retinal diseases that confounded the measurement of retinal vessel width.

**Grading Methods**

Details of image digitization and grading protocols were previously described by the ARIC investigators. Grading methods involved the use of customized RetinalAnalysis software (Department of Ophthalmology Visual Science, University of Wisconsin-Madison, WI) coupled with an image library (Optimate, run-time version of Optimas 6.51; Media Cybernetics, Silver Spring, MD). A digitized grid was placed over the image, and all vessels passing completely through zone B (0.5–1 disc diameter from the disc margin) were measured. The grader identified each vessel as a venule or arteriole, using the original photograph for reference.

The RetinalAnalysis software package measures and calculates the central and average width from five equidistant measures (Fig. 1) of each vessel or branch (in micrometers). A density pixel histogram showing central width measurement was also displayed (Fig. 2), 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 grader had the option of accepting the average or the central widths (either the original measurement or the adjusted one) or of declining both and remeasuring the vessel. The branches of arterioles (regardless of their position on the grid) were measured if the trunk measured 85 μm or more. Branch measurements were excluded if either of the branches could not be measured accurately.

The magnification of the retinal photographs taken by the fundus camera has been described. Measurement from the digitized images represents the actual measurement from the retinal photographs. The Parr-Hubbard formula is used to standardize individual vessel calibers of each eye, thus enabling comparison between arterial and venous caliber of different eyes.

The formula used is

\[ W_t = (0.87W_a^2 + 1.01W_b^2 - 0.22W_aW_b - 10.73)^{1/2} \]

where \( W_t \) is calculated as the trunk arteriole caliber, and includes calibers from the smallest \( W_a \) to largest branches \( W_b \). A similar formula calculated the average venular widths of the eye, referred to as central retinal vein equivalent (CRVE). CRAE was divided by CRVE to obtain the AVR. Results reported in this study used measurements that incorporated information on the branches for the purpose of comparing with the ARIC results. Eyes were considered ungradable if one vessel, of width greater than 45 μm, could not be measured accurately. Vessels measuring less than 25 μm in width were not included.

**Intragrader and Intergrader Reliability**

The intergrader and intragrader grading reliabilities were assessed using a random subsample of 187 and 97 right eye retinal photographs, respectively. Reliability was high, with quadratic weighted \( k \) values of

\[ k = \frac{2r - 1}{2} \]

where \( r \) is the Pearson correlation coefficient between the two graders. The formulas used for calculating the central retinal artery equivalent (CRAE) and central retinal vein equivalent (CRVE) are:

CRAE: \[ W_t = (0.87W_a^2 + 1.01W_b^2 - 0.22W_aW_b - 10.73)^{1/2} \]

CRVE: \[ W_v = (0.87W_v^2 + 1.01W_v^2 - 0.22W_vW_v - 10.73)^{1/2} \]

where \( W_v \) is calculated as the trunk venule caliber, and includes calibers from the smallest \( W_v \) to largest branches \( W_v \).

\[ \text{AVR} = \frac{\text{CRAE}}{\text{CRVE}} \]

Figure 1: Digitized retinal image with grid defining the measurement area (zone B) 0.5 to 1 disc diameters from the disc margin. The five equidistant measurement markers (inset: top right) are used to calculate the average and central width of the vessel.

Figure 2: The average and central width calculated from the five equidistant measures and the pixel density histogram of the central width measurement are shown. The vessel’s edge was determined as the distance between the half-maximum pixel densities.
BP Measurements

BP was measured after participants had been comfortably seated for at least 5 minutes. A single measure of systolic (SBP) and diastolic (DBP) using a mercury sphygmomanometer was recorded from the first and fifth Korotkoff sounds. Mean arterial blood pressure (MABP) was defined as $MABP = 0.33 \times SBP + 0.67 \times DBP$. Hypertension was defined as present in participants taking antihypertensive medication(s) and/or or DBP $/H11350$ group (104.0 mm Hg) and in the group excluded ($P < 0.001$; adjusted for sex and DBP).

Statistical Methods

Statistical analysis software (SAS; SAS Institute, Cary, NC) was used for statistical analysis. Multiple regression analysis was used to examine the relationships between age, SBP, DBP, and MABP and retinal vessel measurements, adjusting for confounding variables including age, sex, and smoking (smoking was classified in three categories: never, past, or current), and body mass index (BMI). Means and standard errors were calculated. Adjusted means for the retinal vessel parameters were obtained using covariance analysis (general linear model). Significant was set at $P < 0.05$.

RESULTS

Sample Characteristics

Among the 3355 persons included in our study, 1895 were women and 1460 were men. The number of women in age groups less than 60, 60 to 69, 70 to 79, and 80+ years were 556 (29%), 687 (36%), 502 (27%), and 150 (8%), respectively. The number of men in the corresponding age groups were 428 (29%), 687 (36%), 502 (27%), and 150 (8%), respectively. The average age of this study sample was 65.5 years, and the participants were largely white. Six subjects had missing data on hypertension status. From the remaining 3349 subjects, 1837 (55%) had normal BP, and 1512 (45%) had hypertension. Age- and sex-adjusted MABP were almost identical in the study group (104.0 mm Hg) and in the group excluded ($n = 299$) due to absent or ungradable photographs (104.4 mm Hg).

Relationships between Retinal Vessel Diameters and Age

For men and women, mean CRAEs were $191.2 \pm 21.3$ and $194.6 \pm 20.4$ $\mu\text{m}$, respectively, and mean CRVEs were $225.5 \pm 20.6$ and $224.6 \pm 20.8$ $\mu\text{m}$, respectively. Retinal arterioles and venules narrowed with increasing age in both men and women (Fig. 3). Mean CRAE decreased from $198.7 \pm 18.0$ $\mu\text{m}$ in persons aged less than 60 years to $181.7 \pm 17.4$ $\mu\text{m}$ in persons aged 80 years or more. Similarly, mean CRVE decreased from $228.6 \pm 19.5$ $\mu\text{m}$ in persons aged less than 60 years to $212.9 \pm 20.2$ $\mu\text{m}$ in persons aged 80 years or more. The reduction was approximately 8.5% in mean CRAE and 6.9% in mean CRVE over the age spectrum from younger than 60 years to 80 years or older. The decreasing trends of CRAE and CRVE with increasing age were similar in men and women (Fig. 3).

For each increasing decade of age, mean CRAE decreased by $4.2 \mu\text{m} (P < 0.001)$, after adjusting for gender and SBP, or by $5.7 \mu\text{m} (P < 0.001)$, when adjusting for gender and DBP. Similarly, mean CRVE decreased by $3.9 \mu\text{m} (P < 0.001)$; adjusted for sex and SBP or $4.3 \mu\text{m} (P < 0.001)$; adjusted for sex and DBP).

Mean AVR decreased with increasing age, both in men and women, up to age 70 to 79 years (Fig. 4). In women aged 80 years or older, mean AVR was unchanged but increased by 0.01 in men aged 80 years or older compared with men aged 70 to 79 years. Mean AVR was consistently higher in women than in men across the entire age spectrum of our study group (Fig. 4).
mean CRAE decreased linearly from 203 μm to 180 μm. However, when MABP further increased to more than 140 mm Hg, mean CRAE increased to 187 μm. When MABP increased from 80 mm Hg or less to 121 to 130 mm Hg, mean CRVE decreased from 228 to 220 μm. These inverse relationships remained after further adjustment for blood glucose level, in addition to age, sex, and smoking (data not shown).

After adjusting for age and smoking, for each given level of MABP, mean AVR in men was consistently lower than mean AVR in women (Fig. 6). However, the reduction trend in AVR with increasing MABP was similar between the two genders, except for very high levels of MABP (>140 mm Hg).

**DISCUSSION**

Using the same protocol and methods as the ARIC study, our findings in this general older Australian population were very similar to those from the U.S. ARIC study sample: an inverse relationship between age, BP, and retinal vessel (arteriolar or venular) diameters. Retinal vessel diameters narrowed as age BP increased. This inverse linear relationship was similar in men and women and persisted after adjusting for possible confounders, including age, sex, BP, smoking, blood sugar levels, and BMI. Possible selection bias due to the exclusion of 299 participants who either had no fundus photographs taken or had ungradable photographs was considered. Almost identical age- and sex-adjusted MABP in the excluded subgroup of 299 persons and the study group suggests that substantial bias is unlikely to have occurred by excluding these participants.

Decreasing AVR was found with increasing age or BP, because arteriolar diameters decreased to a greater extent than venular diameters. In the CHS, ARIC study, and our study, the inverse BP association was weaker with CRVE than with CRAE.11,16 This could suggest that the impact of BP on arterioles is more prominent than on venules. Retinal veins are thought to have relatively constant caliber unless there is a complicating condition such as raised intracranial pressure associated with papilledema, ischemia associated with diabetic retinopathy or central or local retinal venous obstruction.15

Mean AVR was higher in men aged than 80 years or more compared with men aged 70 to 79 years. This may be explained by random variation due to the smaller number of subjects in the older age group. Men aged 80 years or more represented only 8% of the whole male sample in this study. Survival bias could also explain this finding. Men with small AVR may have died earlier, and those who continued to live to more than 80 years of age could have been more likely to have large AVR. No comparison can be made with the ARIC study in this aspect, because their participants were younger (50 to 71 years) than our sample.

In the ARIC study (average age was 59.1 years for women and 59.9 years for men), after controlling for age, race, medication use, current cigarette smoking status, and body height, the mean AVR decreased by 0.021 in women and 0.019 in men for every 10-mm Hg increase in MABP. In our study group (average age, 65.5 years), a smaller decrease in AVR was found, but this was relatively similar in women and men (age-adjusted decrease in AVR of 0.010 and 0.013, respectively). The smaller reduction in AVR with increasing MABP in our study group compared with that in the ARIC study sample may reflect more prominent effects from elevated BP in younger than in older persons. In the older group, the rigidity of the arteriolar wall caused by age-related involutionsclerosis of retinal arterioles may prevent the same degree of narrowing that is seen in younger persons.22 Also, older persons are likely to have more significant arteriosclerosis, which may cause focal arteriolar narrowing (possibly from vasospastic influences) in nonsclerotic segments, with either no diameter change in fixed sclerotic segments or poststenotic dilatation, resulting in less prominent generalized arteriolar narrowing.25

Mean AVR was lower in men than in women (0.83 vs. 0.85) in the ARIC study.11 Similarly, our study found smaller AVR in men than in women across all age groups and across the whole spectrum of MABP. Rodriguez et al.24 measured cerebral blood flow in age-matched and normotenstive men and women (age, 18–72 years) using the 133-xenon inhalation method. From a small sample (38 men and 38 women), they found 11% higher global cerebral blood flow level in women than in men of all ages. A possible explanation of such gender difference is the vasodilating effect of estrogen. Estrogen, through a receptor-mediated pathway, may upregulate endothelial expression of the nitric oxide synthase gene, leading to increased nitric oxide production and resultant arteriolar dilatation.25 Estradiol was also shown to promote vasodilation of small-diameter cerebral arteries. Further investigation of the relationships between retinal vessel diameters and hormonal parameters in older women in the BMES is now underway.

Mean CRAE decreased linearly with increasing MABP from 80 mm Hg or less to 131 to 140 mm Hg. When MABP increased from 131 to 140 mm Hg to more than 140 mm Hg, mean CRAE increased from 180 to 187 μm but CRVE varied to a lesser extent (222–225 μm). We do not have an explanation for the wider mean CRAE when MABP was more than 140 mm Hg. Mean AVR in women was significantly higher when MABP was more than 140 mm Hg, compared with MABP of 131 to 140 mm Hg (0.85 vs. 0.82), whereas mean AVR in men remained relatively unchanged (0.793 vs. 0.794; Fig. 4). This may also
suggest that the vasodilating effects of estrogen are greater at high BP levels.

There are several potential limitations in evaluating retinal vessel calibers by using our study methods. First, on color photographs, the column of blood cells was surrounded by a transparent sleeve of plasma; therefore, it was the column of formed blood cells rather than the actual internal diameters of the vessel lumen that was measured. However, generalized arteriolar narrowing as part of arteriosclerosis may reduce the width of the blood cell column. Therefore, measurements of retinal vessel width from fundus photographs, at least to some extent, may reflect arteriosclerosis. Second, only a single BP measurement was obtained from each participant in our study, compared with three measurements over a 6-year period in the ARIC study. Finally, BP taken at one particular time may not represent the average BP of a person over a long period.

In conclusion, using a computer-assisted method to measure retinal vessel width, we found that the diameters of retinal arterioles and venules narrowed with increasing age and were inversely and monotonically related to BP level, independent of age. Such inverse linear relationships were similar in men and women in our study group and persisted after adjustment for possible confounders. CRVE had a weaker inverse association with MABP than did CRAE. Women had a larger AVR than men, indicating that possible effects of estrogen on arterioles are worth further investigation. Our findings are in keeping with those reported from the ARIC study that generalized retinal arteriolar narrowing is inversely related to current BP and to BP levels measured 3 and 6 years earlier. Findings from both these studies suggest that retinal arteriolar narrowing may be the result of long-term microvascular damage caused by elevated BP.

References