Age, Blood Pressure, and Retinal Vessel Diameter: Separate Effects and Interaction of Blood Pressure and Age

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Purpose. The association of age and blood pressure (BP) with retinal vessel change is widely reported, with inverse relationships between retinal arteriolar and venular diameter and increasing age and elevated BP. No previous studies have dissected the separate effects of age and BP on the diameter of retinal vessels.

Methods. This was a population-based, cross-sectional study comprising 3654 participants (82.4% response) aged 49+ years from the Blue Mountains region of Australia. Retinal arteriolar and venular diameters were measured from digital retinal images, using a standardized method, and were summarized as central retinal arteriolar (CRAE) and central retinal venular (CRVE) equivalents.

Results. After adjustment for venular diameter, regression plots, and regression coefficients from linear models demonstrated an inverse relationship between arteriolar diameters and mean arterial BP (MABP) in all age groups—greatest in the <60 age group and progressively diminishing thereafter. Increasing age was associated with greater arteriolar narrowing (of lesser magnitude), in each MABP category (<100, 100–109, 109–129, and >120 mm Hg) with the greatest effect in persons with MABP <100. There was evidence of interaction between age and blood pressure in their effects on arteriolar diameter ($P = 0.003$). After adjustment for arteriolar diameter, age was inversely associated with venular diameter (the effect was progressively greater for persons with progressively higher MABP), and MABP was positively associated with venular diameter in subjects aged <80 years (interaction $P = 0.05$).

Conclusions. These findings demonstrate the importance of elevated blood pressure in arteriolar narrowing, especially in those younger than 60 years and show that venules tend to widen rather than narrow with increasing blood pressure levels. (*Invest Ophthalmol Vis Sci.* 2007;48:557–561) DOI: 10.1167/iovs.06-0893

The association of age and blood pressure with narrowing of retinal arteriolar and venular diameters has been demonstrated in several population-based cohort studies. In the Blue Mountains Eye Study (BMES),[1] Beaver Dam Eye Study,[2] Atherosclerosis Risk in Communities Study,[3] Cardiovascular Health Study[4] and Rotterdam Eye Study,[5] a strong inverse relationship between retinal arteriolar diameter and both increasing age and elevated blood pressure was shown after adjustment for multiple confounders. Certain studies also demonstrated an inverse relationship between age and retinal venular diameter and a much weaker inverse relationship between blood pressure and retinal venular diameter.[2,5,6]

To our knowledge, no studies have evaluated the separate effects of age and blood pressure on retinal arteriolar or venular diameters, after considering the shared variance between arterioles and venules. In this study, we explored the separate effects of age and mean arterial blood pressure (MABP) on retinal vessel diameter, after stratifying for both MABP and age, as well as adjusting for shared variance between the two vessel diameters, in the Blue Mountains Eye Study baseline population.

Methods

The BMES is a population-based cohort study of vision, common eye diseases, and other health outcomes in an urban, predominantly white population aged 49 years or older. The baseline study, conducted during 1992 to 1994, examined 3654 eligible potential participants living in two postal code areas in the Blue Mountains, west of Sydney, Australia (82.4% response). The study was conducted in accordance with recommendations of the Declaration of Helsinki and was approved by the Western Sydney Area Health Service Human Research Ethics Committee. Written, informed consent was obtained from all participants. Details of recruitment methods have been published.[7,8]

A standardized interview and examination was performed on all participants over the period 1992 to 1994. Information on demographic variables was gathered from the questionnaire. Questions were asked regarding lifestyle factors, including smoking. Participants were asked for details of current and past smoking, including the type (manufactured or hand-rolled cigarettes, cigars, or pipe tobacco), usual amount (current and past), time of commencement, and, where applicable, time of quitting. Current smokers were defined as participants who smoked cigarettes, cigars, or a pipe regularly, and had given up smoking for less than 12 months before the examinations, whereas past smokers were defined as participants who had ever smoked cigarettes, cigars, or a pipe regularly, but had ceased smoking for at least 12 months before the examinations. A single measure of resting, seated systolic and diastolic blood pressure by mercury sphygmomanometer was recorded from the first and fifth Korotkoff sounds. MABP was defined as $0.33 \times$ systolic blood pressure $+ 0.67 \times$ diastolic blood pressure. Body-mass index was calculated as weight (in kilograms)/height (in meters).[2] Fasting blood samples were taken and processed for serum glucose. Blood samples were analyzed at the Institute of Clinical Pathology and Medical Research, Westmead Hospital.

Stereoscopic retinal photographs (30°) of the macula and other retinal fields of both eyes with a fundus camera (model FF3; Carl Zeiss Meditec GmbH, Oberkochen, Germany), were taken at baseline. Detailed grading methods have been described previously.[1] In brief, we used a computer-assisted method, developed at the University of Wisconsin-Madison,[9] to measure the internal diameter of retinal arterioles

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Supported by Australian National Health and Medical Research Council Grants 153948 and 302068.

Submitted for publication August 1, 2006; revised September 13, 2006; accepted November 23, 2006.

Disclosure: **S. Kaushik**, None; **A. Kifley**, None; **P. Mitchell**, None; **J.J. Wang**, None

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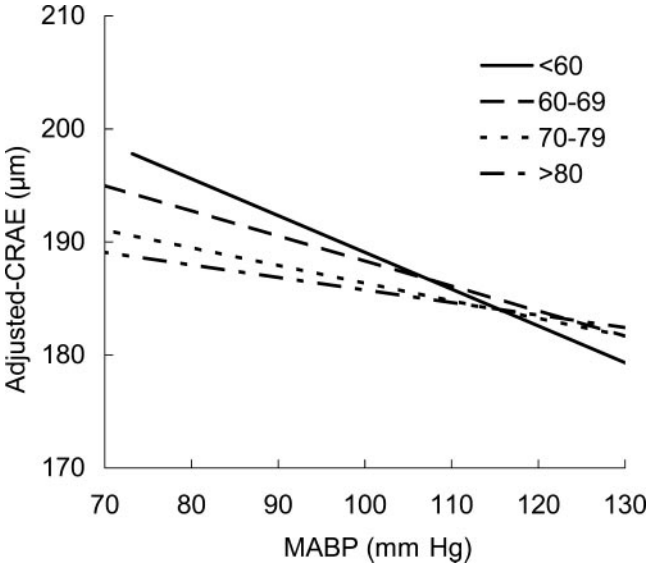

FIGURE 1. Effect of MABP on venule-adjusted retinal arteriolar diameter (CRAE) by age group.

and venules from all gradable digitized photographs, which were then summarized using formulas by Parr and Hubbard.[6,9,10] The formulas take into account branching patterns of arterioles and allow individual vessel diameters to be combined into the summary indices, central retinal arteriolar (CRAE) and central retinal venular (CRVE) equivalents, reflecting the mean arteriolar and venular diameters, respectively, of that eye.

Statistical Analysis

Statistical analyses were performed with commercial software (Statistics Analysis System ver. 8.2; SAS Institute, Cary, NC). To assess the effect of blood pressure or age on retinal arteriolar or venular diameter, independent of the fellow vessel component, we used venule-adjusted CRAE and arteriole-adjusted CRVE, calculated using the residual method initially described by Willet,[11] which controls for the shared variance between the two diameter variables. Venule adjusted arteriolar diameter was defined by using linear regression with venular diameter as the independent variable and arteriolar diameter as the dependent variable, obtaining the residuals, and adding them to an expected mean venular diameter, given the size of arterioles. Similarly, arteriole adjusted venular diameter was defined using regression of arteriolar diameter as the independent variable and venular diameter as the dependent variable, with the residuals from the regression added to the expected mean arteriolar diameter. This method has been widely used in nutritional epidemiologic research. The resultant adjusted variables, arteriole-adjusted CRVE and venule-adjusted CRAE, can be considered to represent the nonshared variance of each vessel diameter, respectively.

Regression graphs were generated that displayed the linear relationship between MABP and venule adjusted CRAE or arteriole adjusted CRVE by four age groups: <60 years, 60 to 69 years, 70 to 79 years, and ≥80 years. The slope of each line demonstrates the effect of MABP on arteriolar diameter and qualitatively the "gap" between the age group lines demonstrates the effect of age. Mean venule adjusted CRAE and arteriole adjusted CRVE were obtained using analysis of covariance (ANCOVA), stratified by age and MABP groups. Linear trends and regression coefficients for the changes in mean venule adjusted CRAE or mean arteriole adjusted CRVE (dependent variable) associated with increasing age stratified by MABP category, or the changes associated with elevated BP stratified by age group, were obtained. In these linear regression models, we included age (per decade, in models for MABP subgroups) or MABP (per 10 mm Hg, in models for age subgroups), and gender, body mass index, smoking status, and serum levels of glucose, as independent variables. Interactions between age and MABP were examined qualitatively and tested in the multiple linear regression models.

Results

Of the 3654 baseline participants, photographs of the right eye of 3346 were included in analyses, after excluding 308 participants without retinal photographs, those with poor photographic quality that precluded measurement, those with retinal diseases that confounded measurement of retinal vessel width, or those who had missing or incomplete blood pressure data. The latter included 40 persons. The average age of the sample was 65.5 years. The number of persons in age groups <60, 60 to 69, 70 to 79, and ≥80 years was 984 (29.3%), 1239 (36.9%), 864 (25.8%), and 268 (8.0%), respectively. The mean MABP for corresponding age groups was 101.7, 104.0, 105.9, and 106.3 mm Hg, respectively.

Figures 1 and 2 illustrate the relationship between venule adjusted mean CRAE, arteriole adjusted mean CRVE, and MABP, stratified by four age groups. Figure 1 shows that each consecutively older age group had successively smaller mean arteriolar diameters when MABP was within the normal range (<100 mm Hg), and within each age group, there was arteriolar diameter narrowing with increasing levels of MABP. There is a greater effect of MABP on arteriolar diameter in the younger age groups, indicated by the greater slope of decline in the younger age groups than in the oldest group. This finding is supported by the data presented in Table 1, which shows mean adjusted CRAE and regression coefficients stratified by age group and the category of MABP. The regression coefficient of −2.3 per decade of age in persons with MABP < 100 represents a 2.3-μm reduction in mean venule adjusted CRAE for each decade increase in age. There is a progressive reduction in the absolute value of regression coefficients for the effect of MABP on CRAE in consecutively older age groups and smaller regression coefficients for the effect of increasing age on CRAE in the higher MABP categories than in persons whose MABP was within the normal range. The linear trends for change in arteriolar diameter associated with increasing MABP were significant in the three younger age groups, and

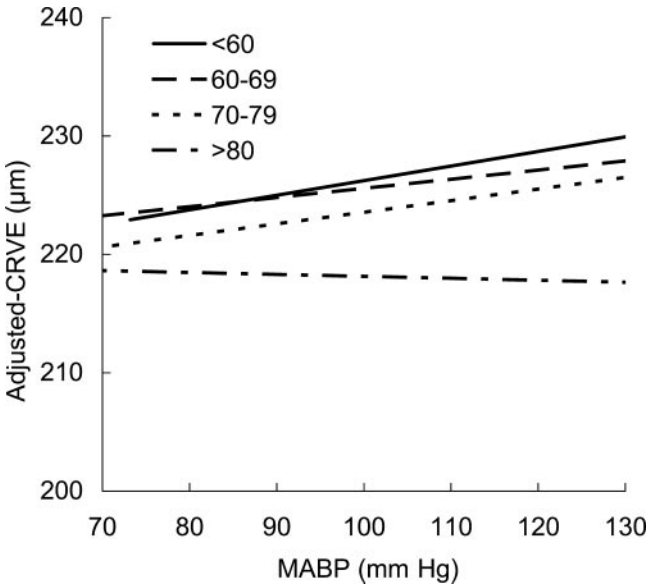

FIGURE 2. Effect of MABP on arteriole-adjusted retinal venular diameter (CRVE) by age group.

TABLE 1. Mean Venule Adjusted CRAE Stratified by Age Group and MABP

Age Group (y)	MABP (mm Hg) <100 (*n* = 1380)	100–109 (*n* = 1068)	110–119 (*n* = 597)	≥120 (*n* = 301)	*P* for Trend	β* for Trend
<60 (*n* = 981)	192.3 (473)	186.1 (327)	184.1 (120)	181.5 (61)	<0.0001	−3.3
60–69 (*n* = 1237)	190.0 (499)	187.1 (396)	184.5 (237)	183.9 (105)	<0.0001	−1.9
70–79 (*n* = 862)	187.7 (313)	185.5 (270)	183.5 (189)	182.8 (90)	0.0004	−1.6
≥80 (*n* = 266)	185.0 (95)	184.8 (75)	183.5 (51)	182.8 (45)	0.3	−0.7
P trend	<0.0001	0.5	0.6	0.8	*P* interaction	0.003
β* for trend	−2.3	−0.3	−0.4	0.3		

Data are in micrometers. Model adjusted for age (per decade, in each MABP subgroup analysis), mean arterial blood pressure (per 10 mm Hg, in each age subgroup analysis), gender, body mass index, smoking status and serum glucose. CRAE is adjusted for venular diameter using the residual method.

*β, regression coefficient.

the trend for change in arteriolar diameter associated with increasing age was significant only in those who were normotensive (MABP < 100 mm Hg). The qualitative impression of interaction between age and MABP on arteriolar diameter taken from Figure 1 and Table 1 was verified statistically ($P = 0.003$).

Figure 2 demonstrates that the younger age groups had wider venular diameters than did the older age groups. Conversely, within each age group except the oldest, there was a linear trend for venular widening associated with increasing MABP. Table 2, which shows mean arteriole adjusted CRVE and regression coefficients, stratified by age group and MABP categories, demonstrates progressively larger negative regression coefficients for change in venular diameter associated with increasing age in consecutively higher MABP categories and smaller positive regression coefficients for change in venular diameter with increasing MABP in the two middle age groups compared with the youngest one. In the oldest age group, the regression coefficient for changes in CRVE associated with MABP was negative. The linear trends for reduction in venular diameter with increasing age were significant in the three higher MABP categories (Table 2). Interaction between age and MABP on venular diameter was of borderline statistical significance ($P = 0.05$).

Tables 3 and 4 show the unadjusted (crude) CRAE and CRVE, stratified by age group and MABP. In the consecutively older age groups, there was successively smaller arteriolar diameter, which declined with increasing MABP (Table 3). In the case of venular diameter, both increasing BP and age were negatively associated with a decrease in venular diameter, and there was a greater decline associated with increasing age than that associated with increasing MABP (Table 4). The findings for unadjusted CRVE and BP (Table 4) are opposite to the positive association between arteriole adjusted CRVE and BP (Table 2). Finally, results were essentially unchanged when systolic blood pressure was used instead of MABP.

DISCUSSION

In this study, we attempted to investigate the separate effects of age and blood pressure on retinal arteriolar and venular diameter while controlling for influence from the correlated fellow component. We found the following: (1) The effect of blood pressure on arteriolar diameter narrowing interacts with age and is more prominent in younger persons (<60 years), and the effect of blood pressure on arteriolar diameter narrowing diminishes with increasing age; (2) the effect of age on arteriolar diameter narrowing also depends on blood pressure level and is greatest in persons within the normal blood pressure range than in persons within higher MABP categories; (3) elevated blood pressure is positively associated with retinal venular diameter after adjustment for shared variance with arterioles (i.e., the higher the blood pressure, the wider the mean venular diameter, in subjects up to age 80 years; and (4) the effect of age on venular diameter narrowing is progressively greater in persons within progressively higher levels of MABP. Given that older persons and those with elevated blood pressure have initially narrower arterioles, further arteriolar narrowing (at a slope similar to that seen in younger or normotensive persons) is conceivably less likely to occur. Previous studies have suggested that this may be due to arteriosclerosis causing stiffening of arteries in older persons, thus limiting the degree of vasoconstriction that can occur.[2]

To our knowledge, previous studies have not accounted for the shared variance between arteriolar and venular diameters,

TABLE 2. Mean Arteriole Adjusted CRVE Stratified by Age Group and Mean Arterial Blood Pressure

Age Group (y)	MABP (mm Hg) <100 (*n* = 1380)	100–109 (*n* = 1068)	110–119 (*n* = 597)	≥120 (*n* = 301)	*P* for Trend	β* for Trend
<60 (*n* = 981)	224.7 (473)	227.4 (327)	229.0 (120)	228.0 (61)	0.06	0.9
60–69 (*n* = 1237)	225.0 (499)	225.9 (396)	227.5 (237)	225.2 (105)	0.2	0.6
70–79 (*n* = 862)	223.0 (313)	224.5 (270)	224.6 (189)	225.4 (90)	0.2	0.7
≥80 (*n* = 266)	219.4 (95)	218.8 (75)	217.0 (51)	216.7 (45)	0.4	−0.7
P trend	0.4	0.01	0.004	0.01	*P* interaction	0.05
β* for trend	−0.4	−1.6	−2.5	−3.1		

Data are in micrometers. Model adjusted for age (per decade, in each MABP subgroup analysis), MABP (per 10 mm Hg, in each age subgroup analysis), gender, body mass index, smoking status and serum glucose. CRVE adjusted for arteriolar diameter using the residual method.

*β, regression coefficient.

TABLE 3. Mean Unadjusted CRAE Stratified by Age Group and MABP

Age Group (y)	MABP (mm Hg) <100 (n = 1380)	100–109 (n = 1068)	110–119 (n = 597)	≥120 (n = 301)	P for Trend	β^* for Trend
<60 (n = 981)	203.9 (473)	195.5 (327)	191.7 (120)	185.9 (61)	<0.0001	−5.3
60–69 (n = 1237)	198.9 (499)	193.6 (396)	189.8 (237)	185.9 (105)	<0.0001	−3.5
70–79 (n = 862)	192.3 (313)	188.8 (270)	185.9 (189)	182.0 (90)	<0.0001	−3.0
≥80 (n = 266)	183.8 (95)	180.5 (75)	179.2 (51)	174.7 (45)	0.006	−2.6
P for trend	<0.0001	<0.0001	0.0006	0.004	P interaction	0.05
β^* for trend	−5.5	−3.8	−3.5	−3.6		

Data are in micrometers. Model adjusted for age (per decade, in each MABP subgroup analysis), MABP (per 10 mm Hg, in each age subgroup analysis), gender, body mass index, smoking status and serum glucose.

* β, regression coefficient.

when evaluating the association between either arteriolar or venular diameter and age or blood pressure. Biologically, persons with smaller arterioles are naturally more likely to have smaller venules, which may be explained by body size or a commonality of genetic determinants between venules and arterioles within the same individual. This explains the considerable correlation between arteriolar diameter, CRAE, and venular diameter, CRVE (correlation coefficient, $r = 0.59$). The arteriolar-to-venular ratio (AVR) was initially used to account for this correlation, but was misinterpreted as representing changes in arteriolar diameter[5,9] by assuming stable venular diameter. When including the correlated fellow vessel component in multivariate models (CRVE when CRAE is the dependent variable, and vice versa), the variation of CRAE explained by the resultant model is more than doubled, from <20% to >40%. Using the residual method to adjust for the fellow vessel component, we are able to eliminate the shared variance and thus assess associations with each vessel type independently. The potential confounding effect from the correlated fellow vessel component has been documented previously.[12,13] The adjusted vessel diameter variables would permit an assessment of the effects of age and blood pressure on vessel diameter changes that was independent of the effect from the fellow component, while accounting for factors shared by the two retinal vessel diameter components, including the effects of body size and genetic determination.

However, there are some concerns about using this method and interpreting the adjusted variables. The adjusted vessel diameter variables should not be considered equivalent to the unadjusted diameter variables. We may have overadjusted for the shared factors, or there may be the possibility of masking or exaggerating the associations assessed. For example, it may be possible that the observed widening of arteriole adjusted venular diameter with increasing blood pressure represents the relative difference from arterioles, which narrow with increasing blood pressure, rather than an absolute change in venular diameter itself. Although there are biologically plausible links between widening venular diameter and elevated BP, as outlined in the next paragraph, the interpretation of these findings should be undertaken with these possibilities borne in mind.

In this study, analyses using unadjusted arteriolar diameter showed that age and blood pressure had a similar magnitude and direction of effect on arteriolar diameter narrowing, whereas after adjustment for venular diameter, blood pressure had a greater effect on arteriolar diameter than did age, though the direction of the effect remained the same. In contrast, analyses using unadjusted venular diameter showed that higher blood pressure was negatively associated with venular narrowing, whereas after adjustment for arteriolar diameter, blood pressure was positively associated with venular widening. This finding contrasts with previously reported cross-sectional analytic results[2,6] of increasing blood pressure associated with narrower venular diameters and a longitudinal association between venular narrowing and incident hypertension.[12] Nevertheless, we believe that our study findings with analyses that coadjusted for vessel diameters avoid the potential confounding effect from the fellow vessel component[13,14] and are consistent with existing evidence. In the case of arteriolar diameter, it is consistent with existing knowledge, and the interaction found between blood pressure and age is biologically plausible. In the case of venular diameter, it replicates our recently reported data on the association between venular widening and incident hypertension.[13] Such an association is also biologically plausible, as inflammatory processes and/or damage to vascular endothelium are likely contributors to the pathogenetic link between wider venular diameter and ele-

TABLE 4. Mean Unadjusted CRVE Stratified by Age Group and MABP

Age Group (y)	MABP (mm Hg) <100 (n = 1380)	100–109 (n = 1068)	110–119 (n = 597)	≥120 (n = 301)	P Trend	β^* for Trend
<60 (n = 981)	229.8 (473)	227.7 (327)	228.1 (120)	224.0 (61)	0.003	−1.8
60–69 (n = 1237)	227.9 (499)	226.3 (396)	226.2 (237)	222.2 (105)	0.04	−1.1
70–79 (n = 862)	222.7 (313)	222.7 (270)	220.9 (189)	221.4 (90)	0.4	−0.5
≥80 (n = 266)	214.5 (95)	213.4 (75)	209.5 (51)	208.3 (45)	0.06	−1.8
P trend	<0.0001	0.0003	<0.0001	0.0008	P interaction	0.8
β^* for trend	−2.9	−2.7	−4.2	−4.4		

Data are in micrometers. Model adjusted for age (per decade, in each MABP subgroup analysis), MABP (per 10 mm Hg, in each age subgroup analysis), gender, body mass index, smoking status and serum glucose.

* β, regression coefficient.

vated blood pressure. Wider venular diameter has been shown to be associated with inflammatory factors such as C-reactive protein, interleukin-6, amyloid-A levels, and markers of endothelial dysfunction,[15] and accumulated evidence also points to an inflammatory pathogenesis for hypertension.[16]

We have shown that higher blood pressure is associated with greater retinal arteriolar diameter decline compared with age across all age groups, albeit with a decreasing magnitude in older persons. This finding underscores the importance of regulating elevated blood pressure in all age groups. In addition, the implication of effect of increasing age on arteriolar diameter in persons who are normotensive deserves discussion. Current research is focused on identifying the differences between changes due to "normal" aging and those due to pathologic processes associated with age, as well as identifying biomarkers that distinguish between age-dependent diseases and "normal" aging. In terms of cardiovascular disease, age has traditionally been considered a dominant, nonmodifiable risk factor. A review by Najjar et al.[17] showed that normal ageing is accompanied by a number of structural and functional changes in the cardiovascular system. Luminal dilatation of elastic arteries, increased arterial wall thickening and endothelial dysfunction are some of the changes described. The authors suggest that these changes observed in subjects with cardiovascular disease are similar to aging changes but occur at earlier ages. Our results showing a greater effect of aging on arteriolar diameter among normotensive subjects and a greater effect of elevated blood pressure in younger persons compared with older persons, suggest that hypertension accelerates aging-related arteriolar changes.

The current analyses demonstrated statistically significant narrowing of venules associated with age, independent of retinal arteriolar diameter. Though this has been reported in previous studies,[2,6] the reason for this finding has not been explained. A pathologic study has described age-related anatomic changes in the human renal veins.[18] It found that though the muscle fiber bundles atrophied with age, the elastic fiber bundles hypertrophied. Hypertrophy of elastic fibers may be a mechanism for the venular narrowing with age, found in our study. Conversely, age-related narrowing of retinal vessels, including arterioles and venules, demonstrated in our findings, may be a vascular phenomenon or due to loss of retinal neurons associated with older age. Previous experimental studies have shown age-dependent reductions in ocular (both choroidal and retinal) blood flow.[19,20] Other studies have also shown that there is a loss of ganglion cells and their axons, photoreceptors, and retinal pigment epithelial cells in the retina associated with age.[21–23] Such depletion of nerve fiber numbers could reduce ocular perfusion requirements, thus leading to the vessel narrowing observed. We are unable, however, to explain our findings of a stronger effect of age on venular diameter narrowing as blood pressure increases.

In summary, we used a novel method that accounts for correlation between arterioles and venules and also for variation in vessel diameter associated with body size or genetic factors, to explore the relationship between retinal arterioles, venules, and age or blood pressure. Our findings demonstrate an interaction between age and blood pressure on these small vessel diameters, and emphasize the importance of elevated blood pressure to arteriolar narrowing, especially in those younger than 60 years. We have also shown that venules widen rather than narrow with increased blood pressure. The effect of age on vessel diameter could be considered to be related not only to biological aging but also to age-related conditions other than elevated blood pressure. These findings, if confirmed in future studies, may have clinical implications in cardiovascular disease prevention and in studies of healthy aging.

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