

Retinal Arteriolar Diameter and Risk for Hypertension

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Background: Narrowing of the small arterioles has been hypothesized to contribute to the pathogenesis of hypertension, but prospective clinical data are lacking.

Objective: To examine the relation of retinal arteriolar narrowing to incident hypertension in healthy middle-aged persons.

Design: Prospective cohort study.

Setting: The population-based Atherosclerosis Risk in Communities Study, conducted in 4 U.S. communities.

Participants: 5628 persons 49 to 73 years of age without pre-existing hypertension.

Measurements: Diameters of retinal vessels were measured from digitized retinal photographs. A summary arteriole-to-venule ratio was computed as an indicator of generalized arteriolar narrowing; a lower ratio indicated greater narrowing. Areas of focal arteriolar narrowing were defined from photographs by using a standard protocol. Incident hypertension, defined as systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, or use of antihypertensive medication, was identified from the cohort.

Results: After 3 years of follow-up, 811 (14.4%) persons had developed hypertension. The incidence of hypertension was higher in persons with lower arteriole-to-venule ratios (incidence of 8.9%, 12.3%, 13.7%, 14.3%, and 22.3%, comparing decreasing quintiles of the ratio) and in persons with focal arteriolar narrowing than in those without focal arteriolar narrowing (25.1% vs. 13.0%). After the authors controlled for the average systolic and diastolic blood pressures over the preceding 6 years, body mass index, waist-to-hip ratio, and other risk factors, the odds of developing hypertension were approximately 60% higher in persons with lower arteriole-to-venule ratios (odds ratio, 1.62 [95% CI, 1.21 to 2.18] comparing lowest to highest quintile; $P = 0.006$ for trend) and focal arteriolar narrowing (odds ratio, 1.61 [CI, 1.27 to 2.04]; $P < 0.001$).

Conclusions: Smaller retinal arteriolar diameters are independently associated with incident hypertension, which suggests that arteriolar narrowing may be linked to the occurrence and development of hypertension.

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Hypertension affects up to 50 million people in the United States and is the single most important modifiable risk factor for stroke (1). Despite extensive research, much remains to be elucidated about the risk factors and pathogenesis of hypertension. A key characteristic of hypertension is the presence of narrowing and vasoconstriction of the small arteries and arterioles in the peripheral circulation (2–4). However, it is uncertain whether reduced arteriolar caliber, by increasing peripheral vascular resistance, contributes to the subsequent development of hypertension (5–7). Prospective clinical data demonstrating a link between smaller arteriolar caliber and risk for hypertension are unavailable, largely because the microcirculation is difficult to evaluate outside of experimental settings (5–7). As a result, the value of specific antihypertensive treatment targeted at the peripheral microcirculation remains questionable (7).

The retinal arterioles offer a unique opportunity to noninvasively investigate the relation of arteriolar characteristics to the development of cardiovascular disease (8). We recently developed a method to quantify retinal arteriolar diameters from digitized retinal photographs (9). In this study, we examine whether retinal arteriolar narrowing is related to incident hypertension in a cohort of middle-aged normotensive persons.

METHODS

Study Sample

The Atherosclerosis Risk in Communities (ARIC) study is a population-based cohort study with 4 examinations (10). The ARIC study examined 15 792 participants 45 to 64 years of age at baseline from 1987 to 1989 (10). The study sample was selected by probability sampling from 4 U.S. communities: Forsyth County, North Carolina; Jackson, Mississippi; suburbs of Minneapolis, Minnesota; and Washington County, Maryland. The Jackson sample included African-American persons only; in the other field centers, samples were representative of the populations in these communities (that is, mostly white persons in the suburbs of Minneapolis and Washington County and about 15% African-American persons in Forsyth County). Initial participation rates were 46% in Jackson and approximately 65% in the other communities. Participants were examined every 3 years; the second examination was done between 1990 and 1992 ($n = 14\,348$ [93% of 15 440 survivors]), the third examination was done between 1993 and 1995 ($n = 12\,887$ [86% of 14 944 survivors]), and the fourth examination was done between 1996 and 1998 ($n = 11\,656$ [81% of 14 485 survivors]).

Retinal photographs were taken at the third examination. Of the 12 887 persons who returned for this exami-

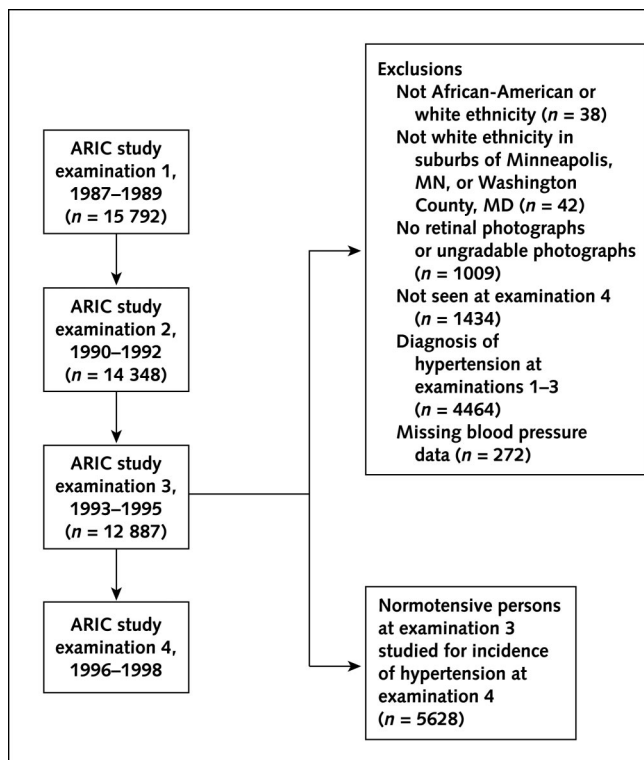
nation, we excluded 38 whose race was neither African American nor white and 42 nonwhite residents in the suburbs of Minneapolis and Washington County, 1009 with no photographs or ungradable photographs, and 1434 who did not participate in the fourth examination. We further excluded 4464 persons with prevalent hypertension diagnosed at the first, second, or third examination and 272 persons with missing hypertension data. The remaining cohort consisted of 5628 normotensive persons at the third examination (Figure 1). Excluded participants ($n = 7259$) were older and more likely to be African American; had higher systolic and diastolic blood pressures, body mass indexes, waist-to-hip ratios, and fasting glucose and triglyceride levels; had lower high-density lipoprotein cholesterol levels; and were more likely to currently smoke and drink alcohol compared with participants included in the study (data not shown).

Institutional review boards at each study site and at the Fundus Photograph Reading Center at the University of Wisconsin, Madison, Wisconsin, approved the study. Informed consent was obtained from all participants.

Measurement of Retinal Arteriolar Diameters

The retinal photography procedure has been reported in detail (9). Briefly, photographs of the retina of one randomly selected eye were taken after 5 minutes of dark adaptation. To estimate a generalized reduction in arteriolar diameters (referred to as generalized retinal arteriolar nar-

Figure 1. Study design and population.



ARIC = Atherosclerosis Risk in Communities; MD = Maryland; MN = Minnesota.

Context

Does narrowing of small arterioles lead to or result from hypertension?

Contribution

This large prospective study measured diameters of small retinal vessels using digitized photographs in people without preexisting hypertension. After 3 years, more people with narrowed arterioles at baseline had hypertension than did people without any arteriolar narrowing.

Implications

Smaller arteriolar diameters are independently associated with development of hypertension.

Cautions

Rather than leading to hypertension, reduced arteriolar diameters at baseline might have reflected elevated blood pressure in persons who did not yet meet diagnostic criteria for hypertension.

—The Editors

rowing in this paper), the photographs were digitized, and the diameters of all arterioles and venules coursing through a specified area surrounding the optic disc were measured on the computer by graders who were blinded to participant identity. The individual arteriolar and venular diameters were combined into summary measures (in μm) and combined as an arteriole-to-venule ratio on the basis of formulas described elsewhere (9). The arteriole-to-venule ratio accounts for magnification differences among photographs and is distributed normally. An arteriole-to-venule ratio of 1.0 indicates that retinal arteriolar diameters were, on average, the same as venular diameters, whereas a smaller ratio represents narrower arterioles, because venular diameters vary little (9). Figure 2 shows examples of retinas with low and high arteriole-to-venule ratios. The intra- and intergrader reliability coefficients for the arteriole-to-venule ratio were 0.84 and 0.79, respectively (9).

Trained graders who were blinded to retinal vessel measurements also evaluated photographs for the presence of localized areas of arteriolar constriction (referred to as focal retinal arteriolar narrowing) as well as other retinal microvascular characteristics (arteriovenous nicking, microaneurysms, and retinal hemorrhages) by using a standard protocol. Intra- and intergrader κ statistics ranged from 0.61 to 1.00 (9).

Definition of Incident Hypertension

Trained technicians performed a standard evaluation of blood pressure at each examination (11). Blood pressure was taken with a random-zero sphygmomanometer, and the mean of the last 2 measurements was used. Hypertension was defined as systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher,

Figure 2. Retinal photographs with arteriole-to-venule ratios.



Top. Retinal photograph showing an arteriole-to-venule ratio of 0.63. The white arrows denote arterioles, and the black arrows denote venules. Bottom. Retinal photograph showing an arteriole-to-venule ratio of 1.05. The white arrows denote arterioles, and the black arrows denote venules.

or use of antihypertensive medication during the previous 2 weeks (11). Persons without preexisting hypertension at the first, second, or third examination who met these criteria at the fourth examination were defined as having incident hypertension.

To examine the effect of “current and previous” blood pressure on these associations, we defined a person’s 6-year average systolic and diastolic blood pressures as the mean of the blood pressure measurements taken at the first, second, and third examinations. The 6-year average systolic and diastolic blood pressures were then included as covariates in the assessment of the independence of retinal arte-

riolar narrowing with incident hypertension. We categorized a person as having “normal” blood pressure for systolic values averaging less than 130 mm Hg and diastolic values averaging less than 85 mm Hg and as having “high normal” blood pressure for systolic values averaging 130 to 139 mm Hg or diastolic values of 85 to 90 mm Hg, according to the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure classification (12).

Definition of Other Variables

Height and weight were measured with participants dressed in scrub suits. Body mass index, defined as weight/height², was then computed. We calculated waist-to-hip ratio as the circumference of the waist (umbilical level) divided by the circumference of the hips (maximum circumference of the buttocks). We characterized physical activity by using a sports index; scores ranged from 1 (low) to 5 (high) (13). Diabetes mellitus was defined as a fasting glucose level of 7.0 mmol/L (126 mg/dL) or higher, a nonfasting glucose level of 11.1 mmol/L (200 mg/dL) or higher, or a history of physician-diagnosed diabetes or treatment for diabetes. Blood collection and processing for total and high-density lipoprotein cholesterol levels, triglyceride level, and fasting glucose level are described elsewhere (14). All variables were based on data from the third examination.

Statistical Analysis

For analysis of generalized retinal arteriolar narrowing, the arteriole-to-venule ratio was categorized into quintiles (with the first quintile indicating the largest arteriolar diameters and the fifth representing the smallest diameters). We also analyzed the ratio as a continuous variable (per SD reduction). Focal retinal arteriolar narrowing and other lesions were defined as binary variables. We used analysis of covariance to compare the arteriole-to-venule ratio and its components (summary measures of retinal arteriolar and venular diameters) between persons who did and did not subsequently develop hypertension. We used multiple logistic regression to calculate the odds ratio of incident hypertension by comparing a given arteriole-to-venule ratio quintile with the first quintile and the presence versus the absence of focal narrowing and other lesions. In these models, we adjusted for age, sex, race, field center, 6-year average systolic and diastolic blood pressures (mm Hg), body mass index (kg/m²), waist-to-hip ratio, sports activity index (1 to 5), diabetes (yes or no), cigarette smoking and alcohol consumption (current, former, or never), total cholesterol level, high-density lipoprotein cholesterol and triglyceride levels (mmol/L), and fasting glucose level (mmol/L). In a supplementary analysis, we stratified the cohort into 4 groups on the basis of preexisting blood pressure levels (normal and high normal) and retinal findings (presence and absence of generalized arteriolar narrowing [arteriole-to-venule ratio in the fifth quintile] and presence and ab-

Table 1. Characteristics of Study Sample in Relation to Quintiles of Retinal Arteriole-to-Venule Ratio at the Third Examination*

Variable	Retinal Arteriole-to-Venule Ratio (Range)					P Value†
	1st Quintile (1.22–0.93)	2nd Quintile (0.92–0.89)	3rd Quintile (0.88–0.85)	4th Quintile (0.84–0.80)	5th Quintile (0.79–0.57)	
Participants, <i>n</i>	1060	1060	1061	1060	1060	
Mean age, <i>y</i>	58.7	58.7	58.7	58.8	59.1	>0.2
Men, %	34.4	38.5	44.3	49.3	51.8	<0.001
African American, %	8.3	10.8	11.1	12.3	14.3	0.006
Mean systolic blood pressure, <i>mm Hg</i>	110.6	112.6	114.6	116.2	119.0	<0.001
Mean diastolic blood pressure, <i>mm Hg</i>	65.6	67.3	68.4	69.4	71.4	<0.001
Mean body mass index, <i>kg/m</i> ²	26.5	26.7	27.1	27.6	28.2	<0.001
Mean waist-to-hip ratio	0.92	0.92	0.92	0.93	0.94	<0.001
Mean sports activity index	2.66	2.63	2.60	2.56	2.57	0.04
Diabetes, %	8.2	7.5	7.9	7.2	8.6	>0.2
Current cigarette smoking, %	15.9	17.1	19.2	17.5	21.6	0.009
Current alcohol drinking, %	59.0	57.6	57.3	61.8	63.1	0.01
Mean HDL cholesterol level, <i>mmol/L</i> (<i>mg/dL</i>)	1.40 (54.1)	1.40 (54.2)	1.38 (53.4)	1.39 (53.6)	1.36 (52.5)	0.11
Mean triglyceride level, <i>mmol/L</i> (<i>mg/dL</i>)	3.32 (128.0)	3.38 (130.6)	3.48 (134.2)	3.49 (134.8)	3.82 (147.6)	<0.001
Mean fasting glucose level, <i>mmol/L</i> (<i>mg/dL</i>)	5.74 (103.5)	5.71 (102.8)	5.72 (103.0)	5.70 (102.7)	5.85 (105.4)	0.18

* HDL = high-density-lipoprotein.

† P value represents difference in characteristics by arteriole-to-venule ratio quintiles, adjusted for age, sex, race, and field center except for the variables mean age (not adjusted for age), men (not adjusted for sex), and African American (not adjusted for race).

sence of focal arteriolar narrowing). We calculated the incidence of hypertension for each group and the odds ratio of hypertension of a particular group compared with the group with normal blood pressure and no generalized or focal retinal arteriolar narrowing (reference group).

Finally, to further examine whether retinal arteriolar narrowing preceded a rise in blood pressure, we analyzed the blood pressure levels over the 4 ARIC study examinations and the change in blood pressure over 2 time periods: between the first and third examinations (A), when retinal photographs were taken, and between the third and fourth examinations (B). We used a mixed-effects model; blood pressure change for each person was a piecewise linear random effect with adjustments for the variables listed earlier. We then examined the difference in the blood pressure change over the 2 time periods (from A to B) and compared persons with narrower versus wider arterioles (lower than the median vs. higher than the median arteriole-to-venule ratio). For these analyses, because persons who were taking antihypertensive medication might have blood pressure values that were influenced by treatment, we imputed a systolic blood pressure value of 148 mm Hg for these individuals if their measured systolic blood pressures were lower than 148 mm Hg (148 mm Hg was the mean systolic blood pressure of hypertensive persons not taking antihypertensive treatment). Similarly, a value of 78 mm Hg was imputed for diastolic blood pressure for hypertensive persons taking antihypertensive medication if their measured diastolic blood pressures were lower than 78 mm Hg (78 mm Hg was the mean diastolic blood pressure of hypertensive persons not taking antihypertensive treatment).

Role of the Funding Sources

The funding sources had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

RESULTS

The mean arteriole-to-venule ratio (\pm SD) in the sample was 0.858 ± 0.008 . Table 1 shows participant characteristics according to arteriole-to-venule ratio quintiles. In general, persons with lower ratios were more likely to be male and African American; to have higher systolic and diastolic blood pressures, body mass index, waist-to-hip ratio, and triglyceride levels; and to have a lower sports activity index. The arteriole-to-venule ratio was not related to age, diabetes, or fasting glucose levels.

After a mean follow-up of 3.0 years (range, 0.8 to 5.5 years), 811 (14.4%) persons developed hypertension. Table 2 shows the incidence of hypertension in relation to arteriole-to-venule ratio quintiles, focal arteriolar narrowing, and other microvascular characteristics. The incidence of hypertension was higher in persons with lower arteriole-to-venule ratios (8.9%, 12.3%, 13.7%, 14.3%, or 22.3%, comparing decreasing ratio quintiles) and was higher in persons with focal arteriolar narrowing than in those without focal narrowing (25.1% vs. 13.0%). After adjustment for age, sex, race, 6-year average blood pressures, and other variables, persons with lower arteriole-to-venule ratios and focal arteriolar narrowing were significantly more likely to develop hypertension than were persons with higher arteriole-to-venule ratios and no focal narrowing, respectively.

Table 2. Incidence and Odds Ratio of Hypertension in Relation to Retinal Arteriolar Narrowing and Other Retinal Microvascular Abnormalities*

Variable	Patients at Risk, <i>n</i>	Incident Hypertension		<i>P</i> Value†
		Patients with Event, %	Multivariable-Adjusted Odds Ratio (95% CI)‡	
Generalized arteriolar narrowing§				
1st AVR quintile	1060	8.9	1.00 (reference)	
2nd AVR quintile	1060	12.3	1.21 (0.87–1.63)	
3rd AVR quintile	1061	13.7	1.29 (0.94–1.76)	
4th AVR quintile	1060	14.3	1.29 (0.95–1.75)	
5th AVR quintile	1060	22.3	1.62 (1.21–2.18)	0.006
Focal arteriolar narrowing				
Absent	4895	13.0	1.00 (reference)	
Present	565	25.1	1.61 (1.27–2.04)	<0.001
Arteriovenous nicking				
Absent	4930	14.1	1.00 (reference)	
Present	608	16.6	1.07 (0.83–1.38)	>0.2
Retinopathy (e.g., microaneurysm or retinal hemorrhages)				
Absent	5376	14.2	1.00 (reference)	
Present	251	18.3	1.33 (0.91–1.94)	0.14

* AVR = arteriole-to-venule ratio.

† *P* value represents test of trend.

‡ Odds ratio (95% CI) of incident hypertension comparing a specific arteriole-to-venule ratio quintile with the 1st quintile or the presence versus absence of focal narrowing and other retinal abnormalities, adjusted for age, sex, race, field center, 6-year average systolic and diastolic blood pressures, body mass index, waist-to-hip ratio, sports activity index, diabetes, cigarette smoking, alcohol consumption, total and high-density-lipoprotein cholesterol level, triglyceride level, and glucose level.

§ Generalized arteriolar narrowing is estimated from the retinal arteriole-to-venule ratio; the 1st quintile indicates the largest arteriolar diameters and the 5th quintile indicates the smallest diameters.

In contrast, other retinal microvascular changes were not significantly associated with the incidence of hypertension.

Because generalized and focal arteriolar narrowing may be correlated, we repeated the analysis including both variables simultaneously in the multivariable-adjusted model. The independent associations for lower arteriole-to-venule ratio (odds ratio, 1.52 [CI, 1.13 to 2.05] comparing the fifth to first arteriole-to-venule ratio quintile) and focal narrowing (odds ratio, 1.60 [CI, 1.25 to 2.03]) persisted.

In a separate analysis, the arteriole-to-venule ratio was included as a continuous variable. After multivariable adjustment, each SD reduction in the arteriole-to-venule ratio (0.08) was associated with a 12% higher odds of hypertension (odds ratio, 1.12 [CI, 1.03 to 1.21]).

Table 3 shows the associations of arteriole-to-venule ratio and focal arteriolar narrowing with incident hypertension in people with high normal and normal blood pressure. After multivariable adjustment, persons with high normal blood pressure levels and arteriole-to-venule ratios in the fifth quintile of the sample had 2.31 times the odds of developing hypertension than did people with normal blood pressure levels and arteriole-to-venule ratios in the first to fourth quintiles. Similarly, the odds of hypertension in persons with high normal blood pressure and focal arteriolar narrowing were 3.05 times higher than in persons with normal blood pressure without focal narrowing.

We tested these associations for interactions with sex, race, and hypertension risk factors (diabetes, body mass

index, waist-to-hip ratio, and physical activity index) by stratification and by inclusion of cross-product terms in the logistic regression models. We did not find significant interactions ($P > 0.2$ for any cross-product terms) (data not shown).

Finally, we examined the blood pressure trend of this cohort over the 4 study examinations (Figure 3) and the change in blood pressure between the first and third examinations and between the third and fourth examinations (Table 4) in relation to retinal arteriolar diameters. Narrower arterioles were associated with higher mean systolic and diastolic blood pressures at each examination (Figure 3). Persons with both narrower and wider arterioles had a greater increase in blood pressure between the third and fourth examinations than between the first and third examinations. The magnitude of this difference was smaller for people with narrower arterioles (for example, 1.73 mm Hg for systolic blood pressure) than for those with wider arterioles (for example, 1.87 mm Hg for systolic blood pressure), although the difference was not statistically significant.

DISCUSSION

In this prospective, population-based study of normotensive middle-aged persons, both generalized and focal narrowing of the retinal arterioles were independently associated with incidence of hypertension developing over a

3-year period. After we controlled for age, sex, race, current and previous blood pressure averaged over 6 years, body mass index, waist-to-hip ratio, and other risk factors, persons with retinal arteriolar diameters (as reflected by the arteriole-to-venule ratio) in the lowest quintile of the sample were approximately 60% more likely to develop hypertension than were those with arteriolar diameters in the highest quintile. Independently, persons with focal areas of narrowing in their retinal arterioles were also more likely to develop hypertension than were those without focal narrowing. These associations remained significant in subgroups with high normal and normal blood pressure.

Histopathologically, generalized narrowing reflects intimal thickening, medial hyperplasia and hyalinization, and sclerosis of the retinal arterioles, whereas focal narrowing represents areas of localized vasoconstriction (8). In the ARIC study, we previously reported that generalized retinal arteriolar narrowing was related to concurrent blood pressure values and independently to previous blood pressure values and markers of inflammation (15, 16). Focal narrowing was related to concurrent but not previous blood pressure values (15). Because similar arteriolar changes in association with hypertension are documented elsewhere in the body (17, 18), studying the retinal arterioles may provide insights regarding structural changes of the peripheral microcirculation in health and disease.

Our findings provide additional insights to an important hypothesis in the pathogenesis of hypertension. Existing data, which are largely based on animal models (2, 3) or on cross-sectional studies in highly selected human patients (4), have suggested that arteriolar constriction and narrowing may play a critical role in the earliest stages of the disease. Our study now provides prospective evidence

suggesting that reduced retinal arteriolar diameters are independently associated with the occurrence and risk for hypertension in the general population at large. Our study is supported by similar findings from the Beaver Dam Eye Study in which, after the authors controlled for preexisting blood pressure values and other risk factors, participants with retinal arteriolar narrowing were significantly more likely to develop hypertension over a 10-year interval (multivariable-adjusted relative risk, 1.59 [CI, 1.27 to 1.98], comparing the lowest to highest quartiles of arteriole-to-venule ratio quartile) (Wong TY. Unpublished data). However, neither study differentiated whether the narrowing of the retinal arterioles, as measured from photographs, was “functional” in nature or a “structural” change with irreversible pathologic damage to the vessel walls. Experimental studies will be required to elucidate more precisely the meaning of reduced retinal arteriolar diameters.

Alternative explanations should also be discussed. It is possible that reduced retinal arteriolar diameters may simply be a marker of elevated blood pressure in persons not yet meeting the diagnostic criteria for hypertension (5). However, other markers of retinal vascular damage (for example, microaneurysms and retinal hemorrhages) and arteriolar sclerosis (for example, arteriovenous nicking) were not related to incident hypertension in this study, suggesting that arteriolar narrowing is the specific microvascular characteristic related to the development of hypertension. Another plausible explanation is that arteriolar narrowing results from and contributes to the development of hypertension (5–7). An increase in blood pressure might cause arteriolar vasoconstriction and greater peripheral vascular resistance, leading to further elevation of blood pressure and the development of a dynamic “vicious cycle” in which

Table 3. Effect of Current and Previous Blood Pressure on the Association of Retinal Arteriolar Narrowing and Risk for Hypertension*

Current and Previous Blood Pressure†	Retinal Arterioles	Patients at Risk, n	Incident Hypertension		P Value‡	
			Patients with Event, %	Multivariable-Adjusted Odds Ratio (95% CI)§		
Generalized narrowing 						
Normal blood pressure	1st to 4th AVR quintile	3831	9.1	1.00 (reference)	<0.001	
	5th AVR quintile	878	16.5	1.35 (1.07–1.69)		
High normal blood pressure	1st to 4th AVR quintile	410	41.7	1.67 (1.27–2.17)		
	5th AVR quintile	182	50.0	2.31 (1.62–3.30)		
Focal narrowing						
Normal blood pressure	Absent	4390	9.9	1.00 (reference)		
	Present	456	17.5	1.44 (1.08–1.91)		
High normal blood pressure	Absent	505	39.8	1.41 (1.10–1.80)		
	Present	109	56.9	3.05 (1.98–4.70)		

* AVR = arteriole-to-venule ratio.

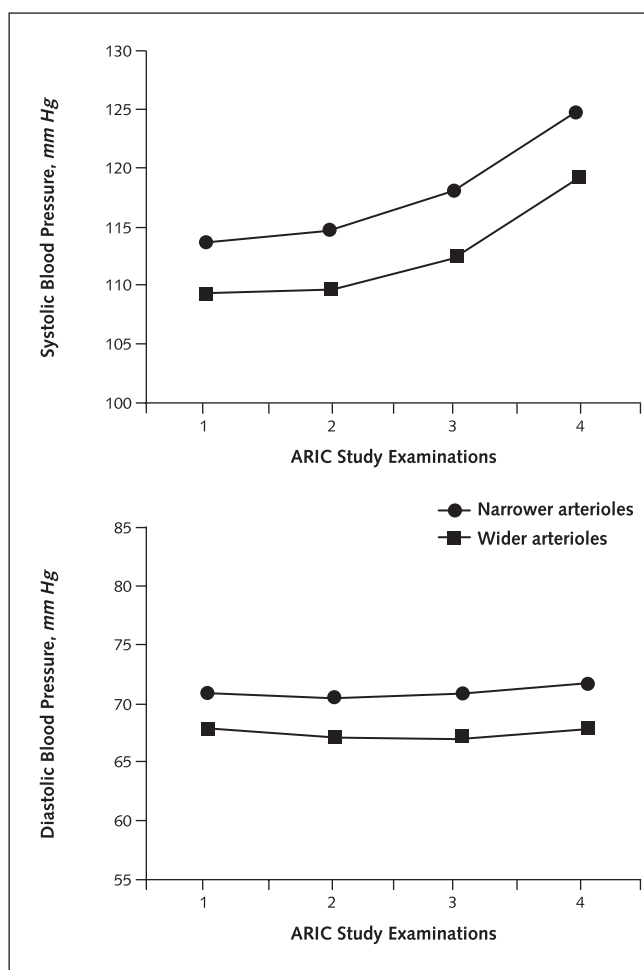
† Current and previous blood pressure reflected by the average of the blood pressure measurements taken at the first, second, and third examinations. “Normal” blood pressure is defined as systolic values of less than 130 mm Hg and diastolic values of less than 85 mm Hg, and “high normal” blood pressure is defined as systolic values of 130 to 139 mm Hg and/or diastolic values of 85 to 90 mm Hg.

‡ P value represents test of trend.

§ Multivariable-adjusted odds ratio (95% CI) of hypertension comparing a specific category versus the reference, adjusted for age, sex, race, field center, 6-year average systolic and diastolic blood pressures, body mass index, waist-to-hip ratio, sports activity index, diabetes, cigarette smoking, alcohol consumption, total cholesterol level, high-density lipoprotein cholesterol level, triglyceride level, and glucose level.

|| Generalized arteriolar narrowing is estimated from the retinal arteriole-to-venule ratio; the 1st quintile indicates the largest arteriolar diameters and the 5th quintile indicates the smallest diameters.

Figure 3. Mean systolic and diastolic blood pressures over Atherosclerosis Risk in Communities (ARIC) Study examinations 1 to 4 in relationship to retinal arteriolar diameters.



For patients who were taking antihypertensive medication at examination 4, a systolic blood pressure of 148 mm Hg was imputed if the measured blood pressure was lower than 148 mm Hg, and a diastolic blood pressure of 78 mm Hg was imputed if measured blood pressure was lower than 78 mm Hg.

the microcirculation maintains and amplifies an initial increase in blood pressure (19). An analogous complex relationship between blood pressure and left ventricular hypertrophy has been hypothesized (20). To examine this hypothesis, we conducted an analysis of the longitudinal change in blood pressure over the 4 study examinations (Figure 3 and Table 4). While people with both narrower and wider arterioles had a larger increase in blood pressure between the third and fourth examinations than between the first and third examinations, the magnitude of this increase was not significantly greater in people with narrower compared with wider arterioles. This is compatible with the hypothesis that arteriolar narrowing may also accompany, rather than simply precede, the development of hypertension. However, these longitudinal analyses of blood pressure trend should be interpreted with caution because blood pressure values were imputed for persons who were taking antihypertensive medication.

Our study may also have clinical implications. First, these data support recent research that highlights the potential value of specifically targeting the microcirculation in the treatment of hypertension (7). For example, some evidence shows that diuretics and β -blockers, the 2 longest-established classes of antihypertensive agents, have little beneficial effects on the microcirculation, whereas angiotensin-converting enzyme inhibitors seem to have direct effects on microvessel structure and may have therapeutic value in preventing cardiovascular morbidity beyond that of lowering blood pressure (21). However, much future work is needed to determine whether these antihypertensive medications have any special role in persons with retinal evidence of early arteriolar changes.

Strengths of our study include its population-based nature, the quantitative and masked evaluation of retinal arteriolar diameters, and the standardized measurement of blood pressure. Our study also has limitations. First, because we did not have multiple blood pressure measurements for each person, hypertension status may have been misclassified, although this bias is probably not systematic.

Table 4. Change in Systolic and Diastolic Blood Pressures over Atherosclerosis Risk in Communities Study Examinations 1 to 4, in Relation to Retinal Arteriolar Diameters*

Variable	Change in Blood Pressure, mm Hg†			P Value Comparing Low vs. High AVR
	Examinations 1 to 3 (A)	Examinations 3 to 4 (B)‡	Difference (B) – (A)	
Systolic blood pressure				
Narrower arterioles (low AVR)	0.70	2.42	1.72	>0.2
Wider arterioles (high AVR)	0.51	2.37	1.86	
Diastolic blood pressure				
Narrower arterioles (low AVR)	–0.03	0.31	0.34	0.11
Wider arterioles (high AVR)	–0.12	0.36	0.48	

* Retinal arteriolar diameters are estimated from the retinal AVR and are classified as narrower arterioles (AVR lower than the median) and wider arterioles (AVR higher than the median). AVR = arteriole-to-venule ratio.

† Adjusted for age, sex, race, field center, body mass index, waist-to-hip ratio, sports activity index, diabetes, cigarette smoking, alcohol consumption, total cholesterol level, high-density lipoprotein cholesterol level, triglyceride level, and glucose level.

‡ For patients who were taking antihypertensive medication at examination 4, a systolic blood pressure of 148 mm Hg was imputed if measured blood pressure was less than 148 mm Hg, and a diastolic blood pressure of 78 mm Hg was imputed if measured blood pressure was less than 78 mm Hg.

Second, selection bias may have masked some associations or accentuated others. Many participants were excluded, and retinal photographs were taken only at the third ARIC examination. If persons with reduced arteriolar diameters at risk for hypertension were more likely to die before being photographed, these associations could be falsely attenuated. Finally, physiologic differences between systemic and retinal arterioles are not assessed here. For example, raised intraocular pressure may affect retinal arteriolar caliber (22). The ARIC study did not include an assessment of intraocular pressure. However, in an analysis of the Beaver Dam Eye Study, retinal vessel diameters, measured by using a similar computer-assisted technique, were not associated with glaucoma or intraocular pressure (Klein R. Personal communication).

In conclusion, our population-based study suggests that arteriolar narrowing is associated with the occurrence and development of hypertension. This finding highlights the important role of the small vessels in the pathogenesis of hypertension and provides additional support to recent research on the potential value of specifically targeting the microcirculation to reduce peripheral arteriolar resistance in the prevention of hypertension.

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