

Arterial Stiffness and the Development of Hypertension

The ARIC Study

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Abstract—Decreased elasticity in large and medium-sized arteries has been postulated to be associated with cardiovascular diseases. We prospectively examined the relation between arterial elasticity and the development of hypertension over 6 years of follow-up in a cohort of 6992 normotensive men and women aged 45 to 64 years at baseline from the biracial, population-based Atherosclerosis Risk in Communities (ARIC) Study. Arterial elasticity was measured from high-resolution B-mode ultrasound examination of the left common carotid artery as adjusted arterial diameter change (in micrometers, simultaneously adjusted for diastolic blood pressure, pulse pressure, pulse pressure squared, diastolic arterial diameter, and height), Peterson's elastic modulus (in kilopascals), Young's elastic modulus (in kilopascals), and β stiffness index. Incident hypertension ($n=551$) was defined as systolic blood pressure ≥ 160 mm Hg, diastolic blood pressure ≥ 95 mm Hg, or the use of antihypertensive medication at a follow-up examination conducted every 3 years. The age-, ethnicity-, center-, gender-, education-, smoking-, heart rate-, and obesity-adjusted means (SE) of baseline adjusted arterial diameter change, Peterson's elastic modulus, Young's elastic modulus, and β stiffness index were 397 (5), 148 (2.0), 787 (12.7), and 11.43 (0.16), respectively, in persons who developed hypertension during follow-up, in contrast to 407 (1), 124 (0.6), 681 (3.7), and 10.34 (0.05), respectively, for persons who did not. The similarly adjusted cumulative incident rates of hypertension from the highest to the lowest quartiles of arterial elasticity were 6.7%, 8.0%, 7.3%, and 9.6%, respectively, when measured by adjusted arterial diameter change ($P<0.01$). One standard deviation decrease in arterial elasticity was associated with 15% greater risk of hypertension, independent of established risk factors for hypertension and the level of baseline blood pressure. These results suggest that lower arterial elasticity is related to the development of hypertension. (*Hypertension*. 1999;34:201-206.)

Key Words: distensibility ■ hypertension detection and control ■ cohort studies ■ ethnic groups

Although increased arterial stiffness (decreased arterial elasticity) had been considered intrinsic to the aging process of the arterial wall,¹ it has since been demonstrated that factors such as insulin resistance, smoking, and hypertension are important predictors of reduced arterial elasticity, independent of age.²⁻⁴ Evidence also exists to support the hypothesis that lower arterial elasticity is (directly) associated with increased risk of cardiovascular disease manifestations.^{2,3,5,6} A small number of population-based studies have been published describing the distribution and population correlates of arterial stiffness.^{2,7}

This study evaluated the prospective relation between baseline arterial elasticity and the development of hypertension in a population sample. In this report, the blood pressure (BP) adjusted arterial diameter change (AADC)^{8,9} and conventional indices⁴ (Peterson's elastic modulus [Ep], Young's elastic modulus [YEM], and β stiffness index [β index]) were used to measure elasticity.

Methods

Study Population

The sample for this study was drawn from the 15 792 individuals who participated in the baseline cohort examination of the Atherosclerosis Risk in Communities (ARIC) study. ARIC is a longitudinal study of cardiovascular and pulmonary diseases sponsored by the National Heart, Lung, and Blood Institute. It includes a community surveillance component and a cohort component. The ARIC cohort was selected as a probability sample of men and women aged 45 to 64 years at 4 study centers in the United States, 3 of which enumerated and enrolled population probability samples of the respective communities (selected Minneapolis suburbs, Minnesota; Washington County, Maryland; and Forsyth County, North Carolina). The fourth quarter of the ARIC cohort was sampled from black residents of Jackson, Miss.¹⁰ Eligible participants were interviewed and then invited to a baseline clinical examination. The baseline examination of the ARIC cohort was conducted in 1987-1989. Every 3 years after the first examination, all participants were invited to a follow-up clinical examination. The first follow-up examination was conducted in 1990-1992 and the second follow-up examination in

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TABLE 1. Baseline Characteristics by Incident Hypertension Status at Follow-Up Reexamination: The ARIC Study

Variable	All (n=6992)	Incident Hypertensives (n=551)	Normotensives (n=6441)
Age, y	56 (5.7)	56 (5.9)	56 (5.7)
Race, % black	15.9	22.7	15.0
Gender, % women	56.0	61.3	55.6
Current smoker, %	21.8	20.2	21.9
Former smoker, %	37.6	37.9	37.6
Never smoker, %	40.6	41.9	40.5
Education, %			
<HS	15.6	17.6	15.4
=HS	43.0	43.3	43.0
>HS	41.4	39.1	41.6
BMI, kg/m ²	26.6 (4.37)	28.4 (5.17)	26.4 (4.25)
Standing height, cm	169 (9.4)	168 (9.42)	169 (9.4)
History of CHD, %	2.8	4.25	2.64
Diabetes mellitus, %	5.9	9.7	5.6
Total cholesterol, mmol/L	5.38 (0.98)	5.51 (1.05)	5.38 (0.98)
HDL cholesterol, mmol/L	1.32 (0.44)	1.32 (0.44)	1.32 (0.44)
LDL cholesterol, mmol/L	3.41 (0.93)	3.46 (0.96)	3.41 (0.93)
Triglycerides, mmol/L	1.41 (0.86)	1.56 (0.91)	1.40 (0.85)
SBP, mm Hg	114 (12.2)	124 (10.4)	113 (12.0)
DBP, mm Hg	69 (8.4)	74 (8.5)	69 (8.2)
Follow-up, y	3.32 (0.90)	3.48 (1.07)	3.30 (0.88)
Mean ADC of left CCA, μm	410 (130)	390 (120)	410 (130)
Ep, kPa	126 (51)	155 (64)	124 (49)
YEM, kPa	690 (311)	822 (365)	679 (304)
β index	10.42 (3.86)	11.87 (4.65)	10.30 (3.76)
Heart rate, bpm	66 (10)	68 (10)	65 (9)
No. of cardiac cycles studied	5.5 (2.5)	5.5 (2.6)	5.5 (2.50)
Mean carotid IMT, μm	720 (170)	750 (190)	710 (170)

Values are mean (SD) or proportion. HS indicates high school; CHD, coronary heart disease; and CCA, common carotid artery.

1993–1995. The Institutional Review Board in each participating institution approved the ARIC Study. All participants gave informed consent before each examination.

In the ARIC cohort, arterial elasticity was assessed in 11 478 participants (73% of the entire cohort), of whom 9% were assessed during the initial cohort examination and 91% during their first follow-up examination. A total of 3780 of the 11 478 participants were excluded from this analysis because they were identified as hypertensive at the time of arterial elasticity assessment. An additional 710 individuals (9% of baseline normotensives) were excluded because of missing data on hypertension status at the follow-up examinations. Thus, a final sample of 6992 baseline normotensives was available for this analysis. The follow-up time varied from 1 to 2 cohort examination cycles (3 to 6 years) depending on the time of the arterial elasticity assessment; the average follow-up time was 3.3

years. During the follow-up, 551 individuals developed hypertension, and 6441 individuals did not.

Measurement of Arterial Stiffness

The collection and evaluation of common carotid arterial diameter and structural data in the ARIC Study have been published extensively.^{4,7–9,11–13} For this report, we used the arterial diameter data collected on the left common carotid artery (1 cm below the origin of the carotid bulb) during B-mode ultrasound examination of the carotid arteries. This method uses noninvasive ultrasonic echo-tracking methods, performed by centrally trained and certified sonographers. The data were collected after the participants had rested in a supine position for ≥ 20 minutes. In brief, with the transducer held securely by a mechanical transducer holder, transducer angulation was changed to maximize media-adventitia echoes. Electronic gates were moved to track the 2 interfaces, and the distance between them as a function of time was visualized for the consecutive cycles. These data were digitized by an analog-to-digital converter. Then the data were sent to the ARIC Ultrasound Reading Center, where the arterial diameter data were estimated as the average over as many cardiac cycles as possible (average=5.5). The reading of arterial diameter data was performed by trained and certified ultrasound readers in a central location, subject to regular quality control, retraining, and recertification. The diastolic arterial diameter (DAD) and the arterial diameter change (ADC) between systole and diastole from the left carotid artery during cardiac cycles were used for this analysis. Concurrent brachial BP was measured every 5 minutes with an automated oscillometric device (1846SX Dinamap), and the mean of 2 BP measures before the completion of ultrasound examination was used in calculating arterial stiffness indices. From these diameter and BP data, the following parameters, needed for estimating arterial elasticity indices, were assembled for the entire ARIC cohort: mean DAD, systolic arterial diameter (SAD), and ADC; carotid arterial intima-medial thickness (IMT); and diastolic and systolic blood pressure and pulse pressure (DBP, SBP, and PP, respectively) (PP=SBP–DBP).

The primary objective of this study was to investigate the prospective relationship between arterial elasticity and the development of hypertension. AADC was used as the primary measure of arterial stiffness, which treated ADC (strain) as the predictor of incident hypertension and other BP-related variables (DBP, PP, PP squared, height, and DAD) as covariates to be adjusted for by the following generalized linear model^{8,9}:

$$g(\mu_i) = \alpha + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \beta_5 x_5 + \beta_6 x_6 + \beta_7 x_7 + \beta_n c_n$$

where (μ_i)=E(Y_i), x_1 =ADC, x_2 =DBP, x_3 =PP, x_4 =PP squared, x_5 =DAD, x_6 =age, x_7 =height, and c_n =other potential confounders to be adjusted for. In logistic regression models, Y_i is binary, with a value of 1 indicating incident hypertension and 0 indicating without hypertension. Thus, $g(\mu) = \log[\mu/(1-\mu)]$, and $\exp(\beta_1)$ is the odds ratio associated with 1 unit increase in ADC. In linear regression models, Y_i is continuous. Thus, $g(\mu) = \mu$, and β_1 is the regression coefficient of ADC in relationship to Y , reflecting corresponding change in Y per 1 unit increase in ADC. Traditional indices of arterial stiffness (stress-strain ratio)^{7,14,15} were also used in this report for comparison with the AADC, including the following:

$$\text{Peterson's elastic modulus: } E_p = (\text{PP} \times \text{DAD}) / \text{ADC} \text{ (kPa)}$$

$$\text{Young's elastic modulus: } YEM = [E_p \times \text{DAD} / (2 \times \text{IMT})] \text{ (kPa)}$$

$$\beta \text{ stiffness index: } \beta \text{ index} = \text{Ln}(\text{SBP}/\text{DBP}) / (\text{ADC}/\text{DAD})$$

BP and Hypertension

At every examination, sitting BP was measured 3 times on each participant with a random-zero sphygmomanometer, after a 5-minute rest, by trained technicians following a standardized protocol.¹³ The systolic and fifth phase DBP measurements used in this report are the mean of the second and the third readings. Study participants were asked to bring all medications, vitamins, and supplements taken in the 2 weeks before the examination. The information on pharmaco-

logical treatment of hypertension is based on the participant's self-reported use of any medication to treat high BP and the transcription and coding of all medication names.¹³ Prevalent hypertension at the examination of arterial stiffness was defined as DBP ≥ 90 mm Hg, SBP ≥ 140 mm Hg, or use of antihypertensive medication. Incident hypertension after the arterial stiffness assessment was defined as DBP ≥ 95 mm Hg, SBP ≥ 160 mm Hg, or use of antihypertensive medication during the period.

Other Covariates

Information on age, ethnicity, gender, education levels, and cigarette smoking status was obtained by standardized questionnaires administered by trained and certified interviewers. Body mass index (BMI) was calculated as weight (kilograms)/height (meters)². Fasting serum total cholesterol, triglycerides, and HDL cholesterol were measured according to standardized procedures.¹³ LDL cholesterol was calculated in participants with triglycerides < 400 mg/dL as total cholesterol minus HDL cholesterol plus one fifth of triglycerides. Diabetes mellitus was defined as fasting (8 hours) serum glucose ≥ 140 mg/dL, glucose ≥ 200 mg/dL if fasting < 8 hours, history of physician-diagnosed diabetes, or use of an oral hypoglycemic agent or insulin.

Statistical Analysis

Means and SDs for major covariates were obtained from the full sample and stratified by incident hypertension. An ANCOVA was used to estimate adjusted means of arterial elasticity as measured by AADC, Ep, YEM, and β index and to test the mean differences comparing persons who developed hypertension with persons who did not during the follow-up. Logistic regression models were used to estimate the cumulative incident rate and relative odds of developing hypertension in relation to baseline arterial elasticity over 3.3 years of follow-up. SAS (SAS Institute) software was used for the statistical analyses.

Results

Of 7698 baseline normotensive participants, 91% (6992 individuals) were available for follow-up for ≥ 3 years, with an average follow-up time of 3.3 years. The characteristics of the study population at the time of arterial stiffness measurement are presented in Table 1. The mean age was 56 years, 16% were black, and 56% were women. Compared with normotensives, persons who developed hypertension during the follow-up were slightly less likely to have completed high school or higher education and more likely to have diabetes, a history of coronary heart disease, and higher levels of baseline total cholesterol, BMI, and carotid arterial IMT. They also exhibited higher baseline SBP and DBP levels, although these values were below the cutoff for hypertension (by definition). The means (SE) of AADC were 405 (3), 408 (3), 407 (3), and 403 (3) μm ($P=0.57$) from the lowest to the highest quartiles of mean arterial pressure, estimated as $(\text{PP}/3)+\text{DBP}$. In contrast, from the lowest to the highest quartiles of mean arterial pressure, the means (SE) of Ep were 105 (1), 115 (1), 128 (1), and 157 (1) kPa, respectively ($P<0.001$). These results suggest that AADC, as a measure of elasticity, is independent of BP and that conventional stress-strain ratio indices, represented here by Ep, are not.

There were 551 individuals who developed hypertension during the follow-up, defined as BP $\geq 160/95$ mm Hg or use of antihypertensive medication, with a cumulative incidence of 8%. The mean levels of arterial elasticity, as measured by AADC, Ep, YEM, and β index, are presented in Table 2. The mean level of baseline AADC was lower (indicating a stiffer

TABLE 2. Arterial Elasticity as Measured by Mean ADC of Common Carotid Artery and Other Conventional Indices, by Incident Hypertension Status at Follow-Up Reexaminations: The ARIC Study

Indices of Arterial Elasticity	Hypertension Status at Follow-Up Examinations		
	Hypertensives (n=551)	Normotensives (n=6441)	P for Mean Difference
Unadjusted			
ADC, μm	390 (5)	410 (2)	<0.001
Ep, kPa	155 (2.2)	124 (0.6)	<0.001
YEM, kPa	822 (13.3)	678 (3.9)	<0.001
β index	11.87 (0.16)	10.30 (0.05)	<0.001
Multiple variable adjusted			
ADC, μm^*	397 (5)	407 (1)	0.04
Ep, kPa \dagger	148 (2.0)	124 (0.6)	0.001
YEM, kPa \dagger	787 (12.7)	681 (3.7)	0.001
β index \dagger	11.43 (0.16)	10.34 (0.05)	0.001

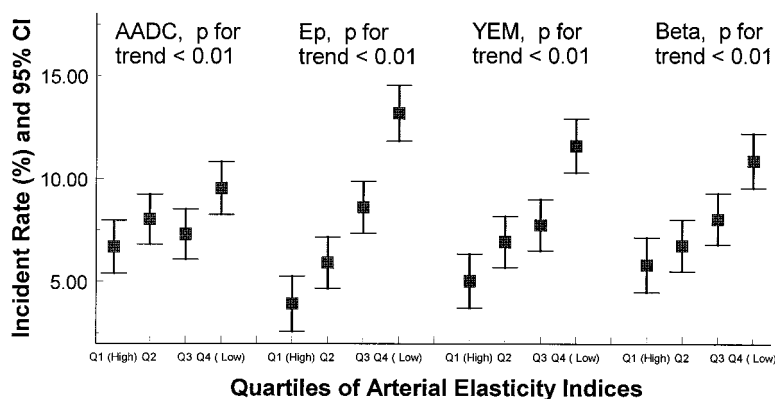
Values are mean (SE).

*Adjusted for concurrently measured DBP, PP and its squared term, common carotid arterial diameter, heart rate, standing height, age, ethnicity, center, gender, smoking, education, and BMI.

\dagger Adjusted for age, ethnicity, center, gender, smoking, education, BMI, and heart rate.

artery) in persons who developed hypertension. Similarly, the mean levels of Ep, YEM, and β index were higher (also indicating a stiffer artery) in this group. The 3.3-year cumulative incidence of hypertension, adjusted for age, ethnicity, gender, center, education, smoking, heart rate, and BMI, by quartiles of baseline arterial elasticity as measured by AADC, Ep, YEM, and β index, are presented in the Figure. Lower baseline arterial elasticity levels were associated with higher cumulative incidence rates of hypertension, and the association was graded (P for linear trend <0.01 for all 4 measures of arterial stiffness).

The incidence odds ratio and 95% CI of developing hypertension associated with 1 SD decrease of arterial elasticity measures estimated from multivariate logistic regression models are presented in Table 3. Lower baseline arterial elasticity was significantly associated with the development of hypertension, and the odds of developing hypertension were elevated by 17% for 1 SD (130 μm) decrease in AADC, 52% elevated per 1 SD increase in Ep (51 kPa), 35% elevated per 1 SD increase in YEM (311 kPa), and 29% elevated per 1 SD increase in β (3.86 U). After adjustment of the latter 3 indices as for AADC, all measures of arterial elasticity, except for YEM, were associated with incident hypertension of a similar magnitude: 1 SD decrease in arterial elasticity, estimated from either AADC, Ep, or β index, was associated with $\approx 15\%$ increased odds of developing hypertension (Table 4). Also presented in Table 4 are the odds ratios of incident hypertension associated with other hemodynamic factors when these factors were included in multivariable logistic regression models with each of the arterial stiffness indices. All of these hemodynamic factors, except for heart rate, were associated with the development of hypertension



Multivariable adjusted incident rates of hypertension by baseline levels of arterial elasticity indices in the ARIC Study. AADC is adjusted for DBP, PP, PP squared, DAD, height, age, ethnicity, center, gender, smoking, education, BMI, and heart rate. Ep, YEM, and β index are adjusted for age, ethnicity, center, gender, smoking, education, BMI, and heart rate.

independent of each other and of population demographic characteristics.

We also analyzed the data using lower criteria to define incident hypertension as BP $\geq 140/90$ mm Hg (or use of antihypertensive agents). By this definition, 1033 individuals were identified as having developed incident hypertension over 3.3 years of follow-up (a cumulative incidence of 15%). The relationship of arterial elasticity and incident hypertension was similar to that found by using the higher cut point definition (data not shown). The interactions between arterial stiffness and age, ethnicity, and smoking status in association with the development of hypertension were tested with the -2 log likelihood ratio test, and none was found to be statistically significant at $P < 0.15$.

Discussion

Most published studies have either used pulse wave velocity as an indirect measure of arterial stiffness or ultrasound-measured elastic modulus (stress-strain ratio and its variants) to assess arterial stiffness.^{2,7} These stress-strain ratio methods assume a fixed relationship between the change of BP during the cardiac cycle and the change of arterial diameter. Ep, YEM, and β index are typical examples of traditional stress-strain ratios.^{4,14,15} Because both the ADC and BP-related variables are included in the formulation of these conventional indices of arterial elasticity, the resulting modulus estimates are not independent of BP. The associations between these stress-strain ratios and any other end point can be attributed to the combination of BP-related measures

and/or ADC. The results of PP significantly associated with Ep and no association with AADC provide supporting evidence for these arguments. It has been demonstrated that the aforementioned assumptions for stress-strain modulus are not congruent with the association between the change of BP and the ADC during the cardiac cycle.⁸ In population samples, the relationship between stress and strain has a non-zero intercept and only modest heteroscedasticity.^{8,16} To overcome these drawbacks, we have used a non-pressure-related biased estimation of ADC in response to BP change, using component mathematical models to assess ADC, simultaneously controlling for BP and arterial diameter.^{8,9} This approach, as well as its estimate identified as BP AADC, models the ADC (strain) as an independent variable and treats BP-related variables as covariates in the model. It allows for non-zero intercepts between stress and strain and accounts more fully for the relationship between ADC and BP. It also has the ability to model the nonlinearities of stress-strain relationship, the size of the arteries, and the height of the participants.^{8,9} In this study, the AADC approach, as well as conventional Ep, YEM, and β index for comparison with AADC, were used.

Generalized narrowing in smaller arteries (arteriosclerosis) has long been recognized as the major pathophysiological change in essential hypertension.^{17,18} In contrast, the contribution of decreased elasticity in large to medium-sized arteries in the development of hypertension has not been well documented. Historically, it has been suggested that the increase in SBP with aging, accompanied by increased arterial stiffness in the large arteries, was protective in terms of maintaining sufficient flood flow to the cerebral circulation. Thus, increased SBP and loss of elasticity in large arteries in the elderly had been considered a normative aging process of the arterial wall¹ until the treatment of isolated systolic hypertension was identified as both effective and safe in reducing cardiovascular and renal disease events.^{19,20} Our finding of a graded, temporal relationship between baseline arterial elasticity and the development of hypertension during follow-up examinations provides supporting evidence that the development of hypertension is associated with lower arterial elasticity in the carotid artery. This association cannot be fully explained by age, ethnicity, gender, and other risk factors for hypertension. Although baseline level of BP is a significant predictor of incident hypertension, adjustment for baseline BP level did not diminish the arterial elasticity and

TABLE 3. Odds Ratios and 95% CIs of Developing Hypertension During Follow-Up Examinations in Relation to Increases in Arterial Elasticity Indices From Multivariable Adjusted Logistic Regression Models: the ARIC Study

Variable	Odds Ratio	95% CI
ADC (1 SD decrease [130 μ m])*	1.17	1.05, 1.31
Ep (1 SD increase [51 kPa])†	1.52	1.40, 1.65
YEM (1 SD increase [311 kPa])†	1.35	1.25, 1.46
β index (1 SD increase [3.86])†	1.29	1.19, 1.40

*Adjusted for concurrently measured DBP, PP and its squared term, common carotid arterial diameter, standing height, age, ethnicity, center, gender, smoking, education, BMI, and heart rate.

†Adjusted for age, ethnicity, gender, smoking, education, BMI, and heart rate.

TABLE 4. Odds Ratios and 95% CIs of Developing Hypertension During Follow-Up Examinations in Relation to Increases in Arterial Elasticity Indices and Other Hemodynamic Factors From Multivariable Adjusted Logistic Regression Models: The ARIC Study

Independent Variable	Model by Arterial Stiffness Indices			
	AADC (1 SD=130 μ m)	Ep (1 SD=51 kPa)	YEM (1 SD=311 kPa)	β Index (1 SD=3.86)
Arterial stiffness index (1 SD)*	1.17 (1.05, 1.31)	1.14 (1.04, 1.26)	1.04 (0.95, 1.14)	1.16 (1.05, 1.27)
DBP (1 SD=8 mm Hg)*	1.76 (1.59, 1.95)	1.78 (1.60, 1.97)	1.82 (1.64, 2.02)	1.84 (1.66, 2.04)
PP (1 SD=11 mm Hg)*	2.39 (1.34, 4.28)	2.13 (1.20, 3.81)	2.11 (1.18, 3.78)	2.12 (1.19, 3.78)
PP Squared (1 SD=121)*	0.97 (0.92, 1.03)	0.97 (0.92, 1.03)	0.98 (0.93, 1.03)	0.98 (0.92, 1.03)
SAD (1 SD=910 μ m)*	1.12 (1.00, 1.26)	1.06 (0.95, 1.18)	1.05 (0.94, 1.18)	1.06 (0.95, 1.18)
Heart rate (1 SD=10 bpm)*	1.00 (0.91, 1.11)	1.01 (0.91, 1.11)	1.03 (0.93, 1.14)	1.00 (0.91, 1.11)

All models adjusted for standing height, age, ethnicity, center, gender, smoking, education, and BMI.

*All hemodynamic factors were included in the statistical models with each of the arterial stiffness indices.

hypertension association, except for YEM, which was no longer statistically associated with incident hypertension after adjustment for baseline BP. This departure of YEM from other indices may be due to competing for the variance between IMT (in the YEM formulation) and other BP-related variables in the full model. In these data, the association between elasticity and hypertension is consistent across age, ethnicity, and gender groups (data not shown). Thus, the results from this longitudinal study suggest that impaired elasticity of larger arteries is an antecedent factor in the natural history of BP elevation at the population level.

The development of hypertension in relation to arterial elasticity was seemingly stronger in this population when conventional stress-strain ratios as indices of elasticity were used in comparison to the new mathematical model approach (Table 3). However, this was largely due to the BP-related bias intrinsic to several of the conventional stress-strain measures. After statistical adjustment for BP-related covariates, the associations were of similar magnitude for all 4 indices, as presented in Table 4. To our knowledge, this is the first study to empirically compare the new mathematical modeling approach with the conventional stress-strain ratio approaches in a population sample.

The mechanisms linking large arterial stiffness to the development of hypertension are not clear at present. Although our results were not confounded statistically by other hemodynamic factors, our data suggest that the hemodynamic factors presented in Table 4 are associated with the development of hypertension in this population. It can be hypothesized that greater arterial stiffness (loss of elasticity) in large and medium-sized arteries represents a cumulative adverse impact of conventional risk factors on the arterial wall, and that arterial stiffness, together with its adverse impact on other target organs such as the kidneys, contributes to the development of hypertension. It should be noted that the association between arterial elasticity and the development of hypertension reported here is estimated from observational, population-based empirical testing. The interrelationship between elasticity, structural properties of the large arteries, and the development of hypertension can only be thoroughly investigated by the use of other research methods and techniques.

It is also worth noting that the BP used to estimate arterial stiffness was assessed at the brachial artery, which often overestimates central PP (a key variable in the noninvasive estimation of arterial stiffness in this study).^{21,22} This study is based on a short follow-up (3.3 years). In addition, we excluded 710 (9% of all baseline normotensives) from this analysis because of loss to follow-up, although their baseline cardiovascular characteristics were similar to those included in this report. Consequently, the generalizability of our findings to the long-term natural history of BP elevation is probably limited. Stiffening of the larger arteries is most likely to be reflected in a fall in DBP, a feature that should be considered in the interpretation of our findings related to incident hypertension. Thus, we anticipate that a stiffening of larger arteries is associated predominately with a sustained elevation of SBP and a corresponding increase in the development of "systolic hypertension." Despite the large sample sizes in this study, our ability to empirically test this expectation is greatly limited by the high proportion of diagnosed and treated hypertension (>75% of incident hypertensives were treated medically in this population). Although the high levels of hypertension detection and treatment are certainly desirable, this result of the efforts by clinical practitioners and public health-oriented campaigns limits the study of the natural history of BP elevation in populations.

As another caveat, we compared the strength of associations between different measures of arterial stiffness and the development of hypertension by using a 1 SD change benchmark (standardized odds ratios, as presented in Tables 3 and 4). This strategy may not be valid in comparing different populations, especially when the independent variables under study are not distributed similarly between populations. Nevertheless, this study represents the first population-based, prospective study to identify lower elasticity (high stiffness) in the common carotid artery as an antecedent factor of hypertension. Additional long-term, population-based follow-up studies are needed to confirm our findings, and studies of a different design are required before it can be concluded that reduced elasticity in large and medium-sized arteries plays a causal role in the development of hypertension.

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References

- O'Rourke MF. The arterial pulse in health and disease. *Am Heart J*. 1971; 82:687-702.
- Arnett DK, Evans GW, Riley WA. Arterial stiffness: a new cardiovascular risk factor? *Am J Epidemiol*. 1994;140:669-682.
- Hodes RJ, Lakatta EG, McNeil CT. Another modifiable risk factor for cardiovascular disease? Some evidence points to arterial stiffness. *J Am Geriatr Soc*. 1995;43:581-582.
- Salomaa V, Riley W, Kark JD, Nardo C, Folsom AR. Non-insulin-dependent diabetes mellitus and fasting glucose and insulin concentrations are associated with arterial stiffness indexes: the ARIC Study. *Circulation*. 1995;91:1432-1443.
- Benetos A, Safar ME. Aortic collagen, aortic stiffness, and AT1 receptors in experimental and human hypertension. *Can J Physiol Pharmacol*. 1996;74:862-866.
- Dzau VJ. Cell biology and genetics of angiotensin in cardiovascular disease. *J Hypertens Suppl*. 1994;12:S3-S10.
- Riley WA, Barnes RW, Evans GW, Burke GL. Ultrasonic measurement of the elastic modulus of the common carotid artery: the Atherosclerosis Risk in Communities (ARIC) Study. *Stroke*. 1992;23:952-956.
- Riley WA, Barnes RW, Evans GW, Smith SO, Heiss G. Measurement of arterial distensibility in the Atherosclerosis Risk in Communities (ARIC) cohort. In: Borgatti F, ed. *Follow-Up and Prevention of Atherosclerotic Plaque*. Torino, Italy: Centro Scientifico Editore; 1992:45-54.
- Riley WA, Evans GW, Sharrett AR, Burke LB, Barnes RW. Variation of common carotid artery elasticity with intimal-medial thickness: the ARIC Study. *Ultrasound Med Biol*. 1997;23:157-164.
- ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. *Am J Epidemiol*. 1989;129:687-702.
- Bond MG, Barnes RW, Riley WA, Wilmoth SK, Chambless LE, Howard G, Owens B. High resolution B-mode ultrasound scanning methods in the Atherosclerosis Risk in Communities (ARIC) Study. *J Neuroimag*. 1991; 1:68-73.
- Howard G, Sharrett AR, Heiss G, Evans GW, Chambless LE, Riley WA, Burke GL. Carotid artery intimal-medial thickness distribution in general populations as evaluated by B-mode ultrasound. *Stroke*. 1993;24: 1297-1304.
- National Heart, Lung, and Blood Institute. *The ARIC Manuals of Operation*. Chapel Hill: University of North Carolina; 1987.
- Riley WA, Barnes RW, Schey HM. An approach to the noninvasive periodic assessment of arterial elasticity in the young. *Prev Med*. 1984; 13:169-184.
- Hirai T, Sasyama S, Kawasaki T, Yagi S-J. Stiffness of systemic arteries in patients with myocardial infarction: a noninvasive method to predict severity of coronary atherosclerosis. *Circulation*. 1989;80:78-86.
- Evans WG, Riley WA, Arnett DK, Barnes RW, Burke GL. Analysis of ratios: a case study based on arterial distensibility. *Control Clin Trials*. 1993;14:447. Abstract.
- Frohlich ED. Pathophysiology of systemic arterial hypertension. In: Schlant RC, Alexander RW, O'Rourke RA, Robert R, Sonnenblick EH, eds. *Hurst's The Heart*. 8th ed. New York, NY: McGraw-Hill Publishing Co; 1993:1391-1401.
- Scheme HG. Evaluation of ophthalmoscopic changes of hypertension and arteriolar sclerosis. *Arch Ophthalmol*. 1953;49:117-138.
- SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA*. 1991;265:3255-3264.
- Amery A, Birkerhanger W, Brixko R, Bulpitt C, Clement D, Deruyttere M, De Schaepdryver A, Dollery C, Fagard R, Roette F. Mortality and mobility results from the European Working Party on High Blood Pressure in the Elderly trial. *Lancet*. 1985;1:1349-1354.
- O'Rourke M. Arterial stiffness, systolic blood pressure, and logical treatment of arterial hypertension. *Hypertension*. 1990;15:339-347.
- Safar ME. Pulse pressure in essential hypertension: clinical and therapeutic implications. *J Hypertens*. 1989;7:769-776.