Aortic Stiffness, Blood Pressure Progression, and Incident Hypertension

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Vascular stiffness increases with advancing age and is a major risk factor for age-related morbidity and mortality. A compliant aorta provides an important buffer for each ventricular contraction that maintains pulse pressure at low levels. Stiffening of the aortic wall and improper matching between aortic diameter and flow are associated with unfavorable alterations in pulsatile hemodynamics, including an increase in forward arterial pressure wave amplitude, which increases pulse pressure. Stiffening of the aortic wall also is associated with elevated pulse wave velocity (PWV) and premature wave reflection. The resulting increase in pulsatile hemodynamic load increases cardiac afterload, reduces diastolic coronary flow, and damages microcirculation, particularly in high-flow organs such as the kidneys and brain. Cross-sectional studies have shown a strong association of aortic stiffness with advancing age and is a major risk factor for age-related morbidity and mortality. Vascular stiffness and blood pressure pulsatility are related; however, temporal relationships between vascular stiffening and blood pressure elevation have not been fully delineated.

Objective To examine temporal relationships among vascular stiffness, central hemodynamics, microvascular function, and blood pressure progression.

Design, Setting, and Participants Longitudinal community-based cohort study conducted in Framingham, Massachusetts. The present investigation is based on the 2 latest examination cycles (cycle 7: 1998-2001; cycle 8: 2005-2008 [last visit: January 25, 2008]) of the Framingham Offspring study (recruited: 1971-1975). Temporal relationships among blood pressure and 3 measures of vascular stiffness and pressure pulsatility derived from arterial tonometry (carotid-femoral pulse wave velocity [CFPWV], forward wave amplitude [FWA], and augmentation index) were examined over a 7-year period in 1759 participants (mean [SD] age: 60 [9] years; 974 women).

Main Outcome Measures The primary outcomes were blood pressure and incident hypertension during examination cycle 8. The secondary outcomes were CFPWV, FWA, and augmentation index during examination cycle 8.

Results In a multivariable-adjusted regression model, higher FWA (β, 1.3 [95% CI, 0.5-2.1] mm Hg per 1 SD; P=.002) and higher CFPWV (β, 1.5 [95% CI, 0.5-2.6] mm Hg per 1 SD; P=.006) during examination cycle 7 were jointly associated with systolic blood pressure during examination cycle 8. Similarly, in a model that included systolic and diastolic blood pressure and additional risk factors during examination cycle 7, higher FWA (odds ratio [OR], 1.6 [95% CI, 1.3-2.0] per 1 SD; P<.001), augmentation index (OR, 1.7 [95% CI, 1.4-2.0] per 1 SD; P<.001), and CFPWV (OR, 1.3 [95% CI, 1.0-1.6] per 1 SD; P=.04) were associated with incident hypertension during examination cycle 8 (338 cases [32%] in 1048 participants without hypertension during examination cycle 7). Conversely, blood pressure during examination cycle 7 was not associated with CFPWV during examination cycle 8. Higher resting brachial artery flow (OR, 1.23 [95% CI, 1.04-1.46]) and lower flow-mediated dilation (OR, 0.80 [95% CI, 0.67-0.96]) during examination cycle 7 were associated with incident hypertension (in models that included blood pressure and tonometry measures collected during examination cycle 7).

Conclusion In this cohort, higher aortic stiffness, FWA, and augmentation index were associated with higher risk of incident hypertension; however, initial blood pressure was not independently associated with risk of progressive aortic stiffening.

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stiffness not only with age, but also with other cardiovascular risk factors such as hypertension, obesity, impaired glucose tolerance, and dyslipidemia.\textsuperscript{3,4} The European Society of Cardiology considers elevated PWV a negative prognostic factor to be considered in the management of patients with hypertension.\textsuperscript{5} The association between vascular stiffening and blood pressure is particularly interesting because the functional relationship is likely bidirectional. Elevated blood pressure may cause vascular damage and accelerated conduit artery stiffening.\textsuperscript{6} Conversely, aortic stiffening increases pressure pulsatility and therefore affects systolic blood pressure. However, temporal relationships between vascular stiffness and blood pressure remain incompletely elucidated. In particular, whether vascular stiffness antedates hypertension or vice versa is unclear.

To examine temporal relationships between vascular stiffening and blood pressure, we evaluated vascular stiffness, central hemodynamics, peripheral blood pressure, and incident hypertension longitudinally in the Framingham Heart Study Offspring cohort. Because both macrovascular stiffness and microvascular properties affect blood pressure, we also assessed whether sonographic measures of endothelial and microvascular function are related to future blood pressure, vascular stiffness, and central hemodynamics.

**METHODS**

The study sample consisted of individuals who were participants of the Framingham Offspring cohort and the details and design have been described.\textsuperscript{7} Offspring (and their spouses) of the Framingham Original cohort were recruited beginning in 1971. Participants have undergone follow-up examinations at the Heart Study clinic approximately every 4 to 6 years, including standardized questionnaires, a physical examination, and assessment of standard cardiovascular risk factors. The examining physician measured the blood pressure of seated participants using a mercury column sphygmomanometer, an appropriately sized cuff, and a standardized protocol.\textsuperscript{8} The average of 2 blood pressure readings taken by a physician served as the examination blood pressure, the primary exposure, and end point for subsequent analyses. Pulse pressure was calculated as systolic blood pressure minus diastolic blood pressure. Mean arterial pressure was calculated as diastolic blood pressure plus pulse pressure divided by 3. Presence of hypertension was defined as a systolic blood pressure of 140 mm Hg or greater, diastolic blood pressure of 90 mm Hg or greater, or the use of antihypertensive medication.

The present investigation is based on examination cycles 7 (1998-2001) and 8 (2005-2008), with examination cycle 7 representing the first cycle to include tonometry measurements. The study protocol was approved by the Boston University Medical Center institutional review board; written informed consent was obtained from all participants.

**Arterial Tonometry**

We evaluated 3 measures of arterial stiffness and pressure pulsatility derived from arterial tonometry, namely carotid-femoral pulse wave velocity (CFPWV), central forward pressure wave amplitude (FWA), and augmentation index. The CFPWV is the criterion standard for assessing aortic stiffness.\textsuperscript{9} The FWA depends on peak systolic blood flow and characteristic impedance of the aorta, which is the resistance of the aorta to the pulsatile component of blood flow.

The FWA and CFPWV are both dependent on aortic wall stiffness and luminal diameter. However, compared with CFPWV, FWA has a markedly (5-fold) greater dependence on aortic diameter and can be conceptualized as a measure of matching between peak systolic blood flow and diameter of the aorta. Because the central pressure wave propagates distally, it is partly reflected at the interface with muscular arteries due to impedance mismatch, creating a backward traveling reflected wave. Augmentation index is defined as the proportion of central pulse pressure that is attributable to a late systolic increase in pressure due to overlap between the forward and reflected pressure wave, and hence is a measure of peripheral wave reflection.

Arterial tonometry measures were acquired as previously described.\textsuperscript{10,11} After more than 5 minutes of rest, supine brachial systolic and diastolic blood pressures were obtained. For tonometry calibration only, we used an oscillometric blood pressure device for examination cycle 7 and an auscultatory device for examination cycle 8.\textsuperscript{10,11} Arterial tonometry with a simultaneously acquired electrocardiogram was obtained for the brachial, radial, femoral, and carotid arteries.\textsuperscript{10,11} All recordings were performed on the right side of the body. Transit distances were assessed by body surface measurements from the suprasternal notch to the pulse recording site. Details of signal analyses and data processing have been published elsewhere and are summarized in eFigure 1 and eFigure 2 at http://www.jama.com.\textsuperscript{10,11}

**Brachial Artery Flow and Flow-Mediated Dilation**

Brachial artery flow velocity and flow-mediated dilation (FMD) measurements were performed using a Toshiba SSH-140A ultrasound system as previously described in detail.\textsuperscript{12} In brief, after acquiring baseline brachial artery flow velocity and brachial artery diameter, a cuff was inflated on the right forearm to at least 50 mm Hg above the participant’s systolic blood pressure, interrupting blood flow for 5 minutes. Brachial artery flow was measured again during the first 15 seconds after deflating the cuff and brachial artery diameter was reassessed 60 seconds after cuff release. Flow-mediated dilation was defined as the percentage change in brachial diameter between baseline and hyperemia.
Statistical Analyses

Carotid-femoral PWV was inverse-transformed to reduce heteroscedasticity and was then multiplied by −1000 to restore directionality and convert the units to milliseconds per meter. Correlates of blood pressure and tonometry traits were explored using multivariable regression analysis. The primary outcomes (dependent variables) assessed were continuous systolic blood pressure, diastolic blood pressure, mean arterial pressure, and pulse pressure during examination cycle 8 as well as incident hypertension in those participants free of hypertension during examination cycle 7. The secondary outcomes were CFPWV, FWA, and augmentation index measured during examination cycle 8.

In a first modeling stage, we investigated clinical and biochemical variables during examination cycle 7 (not including blood pressure, tonometry measures, and brachial ultrasound traits) that were associated (P < .05) with at least 1 of the assessed continuous outcomes in a multivariable model. The following independent variables were eligible for entry into the model: age, sex, body mass index (calculated as weight in kilograms divided by height in meters squared), height, heart rate, diabetes, total cholesterol, high-density lipoprotein cholesterol, triglycerides, lipid-lowering treatment, fasting glucose, prevalent cardiovascular disease, current smoking, and time between examination cycles 7 and 8. All variables except lipid-lowering treatment and prevalent cardiovascular disease were identified as correlates of future blood pressure or tonometry traits and were included in later linear regression models. Models with tonometry traits as the dependent variable were additionally adjusted for antihypertensive treatment.

In a second stage, we used a stepwise procedure to identify blood pressure and tonometry measures collected during examination cycle 7 (systolic blood pressure, diastolic blood pressure, mean arterial pressure, pulse pressure, CFPWV, FWA, and augmentation index) that were associated with the assessed continuous outcome in multivariable models. To avoid collinearity effects among blood pressure components, models for systolic and diastolic blood pressure during examination cycle 8 considered only systolic and diastolic blood pressure during examination cycle 7, whereas models for pulse pressure and mean arterial pressure during examination cycle 8 considered only pulse pressure and mean arterial pressure during examination cycle 7; tonometry measures were included in all models. In a third step, we explored whether brachial flow or FMD, which were available in a subset of participants, further improved the regression models.

Correlates of incident hypertension were assessed in an analogous 3-stage design using multivariable logistic regression modeling. From the list of potential clinical covariates described above, modeling stage 1 identified only age, sex, body mass index, height, and triglycerides as significant correlates of incident hypertension in our study sample. Hence, for reasons of model parsimony, no other covariates were used in stages 2 and 3 of the logistic regression modeling for incident hypertension.

In all analyses, a 2-sided P value of less than .05 was regarded as significant. All analyses were performed using SAS software version 9.2 (SAS Institute Inc).

RESULTS

Of the 3539 participants who attended examination cycle 7, 1263 (36%) were excluded because they either underwent an off-site examination (n = 205), did not have tonometry measures (n = 1041), which were added after the cycle started, or had a missing covariate (n = 17). Of the 2276 participants who met criteria during examination cycle 7, 1263 (56%) of incident hypertension during examination cycle 8 were older (66 vs 60 years), included more men (47% vs 45%), and included more smokers (16% vs 12%) and those with prevalent cardiovascular disease (23% vs 10%) and diabetes (17% vs 8%). For the analysis of incident hypertension, we excluded 711 participants (40%) with prevalent hypertension during examination cycle 7, resulting in 1048 participants who experienced 338 cases (33%) of incident hypertension during examination cycle 8. Brachial artery measures were available in 1606 of the participants from the full sample and 957 of the participants free of hypertension during examination cycle 7.

Clinical and biochemical characteristics of the study sample during examination cycle 7 appear in Table 1. Blood pressure, tonometry, and brachial artery ultrasound measurements during examination cycles 7 and 8 appear in Table 2. The pairwise correla-
tions for all assessed blood pressure, tonometry, and brachial artery variables during examination cycle 7 appear in the eTable at http://www.jama.com.

**Correlates of Blood Pressure and Incident Hypertension During Examination Cycle 8**

In a multivariable-adjusted regression model, higher FWA and higher CFPWV during examination cycle 7 were associated jointly with higher systolic blood pressure during examination cycle 8. In addition, lower baseline (β, −0.8 [95% CI, −1.2 to 0.3] mm Hg/1 SD; *P* = .002) and higher hyperemic (β, 0.6 [95% CI, 0.1 to 1.1] mm Hg/1 SD; *P* = .02) forearm blood flow during examination cycle 7 were associated with higher diastolic blood pressure during examination cycle 8. Higher FWA, CFPWV, and augmentation index and lower mean arterial pressure during examination cycle 7 were associated with higher pulse pressure during examination cycle 8 (Table 3).

Relationships among tonometry measures or blood pressure during examination cycle 7 and incident hypertension during examination cycle 8 appear in eFigure 3 and Table 4. We observed that systolic blood pressure, diastolic blood pressure, FWA, augmentation index, and CFPWV considered together in a single multivariable model were associated with incident hypertension during examination cycle 8 (Table 4). Higher baseline brachial artery flow and lower FMD considered together in a single multivariable model that included blood pressure and tonometry traits during examination cycle 7 were associated with incident hypertension during examination cycle 8 (Table 4).

**Correlates of Tonometry Traits During Examination Cycle 8**

In multivariable models, CFPWV but not blood pressure or other tonometry measures during examination cycle 7 was associated with CFPWV during examination cycle 8 (Table 5). Higher CFPWV, lower diastolic blood pressure, and higher pulse pressure during examination cycle 7 were associated with a higher FWA measure during examination cycle 8 (Table 5). Lower CFPWV and higher systolic blood pressure during examination cycle 7 were associated with a higher augmentation index measure during examination cycle 8 (Table 5). In models considering tonometry and blood pressure traits during examination cycle 7, brachial ultrasound measures during examination cycle 7 were not associated with tonometry measures during examination cycle 8.

**COMMENT**

**Principal Findings**

We investigated longitudinal relationships among aortic stiffness, central hemodynamics, microvascular properties, and peripheral blood pressure. We observed that 3 key tonometry measures were jointly related to future blood pressure levels (particularly sys-
Aortic stiffness, blood pressure progression, and incident hypertension

Several studies have established important relationships among tonometry measures (particularly CFPWV) and clinical cardiovascular events. Fewer studies have investigated whether measures of vascular stiffness are related to future blood pressure or incident hypertension and were limited by size or a less comprehensive assessment of aortic stiffness and central pulsatile hemodynamics. A study by Dernellis and Panaretou found that higher proximal dynamics were limited by size or peripheral wave reflection, large artery endothelial function, and microvascular function jointly antedate and potentially contribute to the development of clinical hypertension. Arterial stiffness and function may therefore be important potential targets for interventions aimed at preventing incident hypertension.

**Correlates of Future Vascular Stiffness and Central Hemodynamics**

Longitudinal studies investigating correlates of vascular stiffness are sparse and not conclusive. In a case-control study, Benetos et al reported that the presence of hypertension was associated with steeper progression of CFPWV, whereas systolic blood pressure within groups (normotensive and hypertensive) was not. Li et al reported that childhood or lifetime burden of systolic blood pressure was associated with adult brachial-ankle PWV; however, these analyses were not adjusted for baseline PWV because childhood measurements were not performed.

Similarly, McEniery et al showed that midlife blood pressure was associated with CFPWV 20 years later, but again these analyses were not adjusted for baseline vascular stiffness. Our investigation indicates that future FWA (which partially and inversely depends on aortic diameter) is associated with initial aortic stiffness, pulse pressure, and diastolic blood pressure.

### Table 4. Correlates of Incident Hypertension During Examination Cycle 8

<table>
<thead>
<tr>
<th>Predictor Variables During Examination Cycle 8</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tonometry model</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>3.2 (2.3-4.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>1.5 (1.1-1.9)</td>
<td>.004</td>
</tr>
<tr>
<td>Forward wave amplitude</td>
<td>1.6 (1.3-2.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Augmentation index</td>
<td>1.7 (1.4-2.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CFPWV</td>
<td>1.3 (1.0-1.6)</td>
<td>.04</td>
</tr>
<tr>
<td>Brachial artery model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flow-mediated dilation</td>
<td>0.80 (0.67-0.96)</td>
<td>.01</td>
</tr>
<tr>
<td>Baseline brachial artery flow</td>
<td>1.23 (1.04-1.46)</td>
<td>.01</td>
</tr>
</tbody>
</table>

Abbreviation: CFPWV, carotid-femoral pulse wave velocity.

### Table 5. Correlates of Tonometry Measures During Examination Cycle 8 (N = 1759)

<table>
<thead>
<tr>
<th>Dependent Variable During Examination Cycle 8</th>
<th>Predictor Variables During Examination Cycle 7</th>
<th>Estimated Regression Coefficient (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFPWV</td>
<td>CFPWV</td>
<td>17.5 (16.2 to 18.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Forward wave amplitude</td>
<td>Pulse pressure</td>
<td>4.3 (3.4 to 5.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Forward wave amplitude</td>
<td>3.5 (2.7 to 4.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>CFPWV</td>
<td>2.8 (1.8 to 3.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Diastolic blood pressure</td>
<td>−0.9 (−1.6 to −0.2)</td>
<td>.01</td>
</tr>
<tr>
<td>Augmentation index</td>
<td>Augmentation index</td>
<td>4.6 (4.0 to 5.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Systolic blood pressure</td>
<td>1.1 (0.4 to 1.8)</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>CFPWV</td>
<td>−1.1 (−1.9 to −0.2)</td>
<td>.01</td>
</tr>
</tbody>
</table>

Abbreviation: CFPWV, carotid-femoral pulse wave velocity.

**Note:** Models were adjusted for age, sex, body mass index (calculated as weight in kilograms divided by height in meters squared), height, heart rate, total cholesterol, high-density lipoprotein cholesterol, triglycerides, fasting glucose, diabetes, antihypertensive treatment, current smoking, and time between examination cycles 7 and 8.

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AORTIC STIFFNESS, BLOOD PRESSURE PROGRESSION, AND INCIDENT HYPERTENSION

In the present work, we have shown that initial blood pressure was not independently associated with future CFPWV when analyses were adjusted for initial CFPWV and cardiovascular risk factors added to growing evidence that, in contrast to a widelyheld belief, arterial stiffness precedes the development of hypertension rather than vice versa.

Endothelial Function and Microvascular Resistance

Prior work from Framingham cohorts has shown that aortic stiffness is correlated with higher baseline and hyperemmic forearm vascular resistance, supporting the hypothesis that excessive aortic stiffness and pressure pulsatility may impair function of or damage microcirculation. A strong negative relationship between FMD and systolic blood pressure in cross-sectional studies also has been reported together with speculation that impaired endothelial function may be a precursor of hypertension.

In the present work, we have shown that initial measures of endothelial and microvascular function are associated prospectively with incident hypertension even after considering the potential confounding effects of initial blood pressure as well as aortic stiffness and excessive pressure pulsatility. Higher FMD is a favorable indicator of endothelial function and hence a protective association was observed as expected. The association of higher baseline brachial artery flow with higher risk of hypertension may be related to the observation that higher baseline brachial artery flow is associated with components of the metabolic syndrome. Our present longitudinal findings support the hypothesis that subclinical alterations in aortic stiffness, pressure pulsatility, and brachial artery ultrasound measures of microvascular resistance and endothelial function are jointly associated with incident hypertension, suggesting both conjoint and independent effects of these various measures of vascular function on the pathogenesis of hypertension.

Limitations

Several limitations of our study deserve consideration. Our study is observational and therefore does not allow for causal inferences. A proportion of our study sample was receiving antihypertensive treatment during examination cycle 7 or may have received new or higher doses of antihypertensive medication between examination cycles, which may have caused us to underestimate the relationships among blood pressure progression and tonometry measures. We used oscillometric blood pressure during examination cycle 7 and auscultatory blood pressure during examination cycle 8 to calibrate FWA. Hence, we may have misclassified FWA during examination cycle 7 and change in FWA. Of note, other tonometry measures (CFPWV, augmentation index) are not affected by calibration method.

We did not correct for multiple statistical testing, leading to an inflated type 1 error. However, because our traits are correlated, classic correction (eg, Bonferroni method) would be overly conservative. Nevertheless, we acknowledge that borderline significant findings should be interpreted with caution. Generally, our approach of multivariable adjustment has potential limitations. It is likely that some of the cardiovascular risk factors (such as age, heart rate, or lipid profile) for which we adjusted our analyses exert their effects on blood pressure through vascular stiffening, endothelial function, or microvascular alterations. Therefore, our models may be overadjusted and hence we may have underestimated the relationships among tonometry and brachial artery ultrasound measures and blood pressure progression and incident hypertension. Our participants were middle-aged to older adults of European ancestry; our findings may not be generalizable to younger individuals or ethnic/racial minorities.

CONCLUSIONS

In a longitudinal assessment of the temporal relationships among peripheral blood pressure, vascular stiffness, central hemodynamics, wave reflection, and microvascular function, we demonstrate that aortic stiffness, central FWA, and wave reflection are jointly associated with future systolic blood pressure, pulse pressure, and incident hypertension. Initial blood pressure traits were associated with future FWA and augmentation index but not with aortic stiffness assessed by CFPWV. Our findings support the notion that vascular stiffness is a precursor rather than the result of hypertension.
ship with Cardiovascular Engineering Inc or any other conflicts of interest.

Funding/Support: This work was supported through contracts NO1-HC25195, HL076784, AG028321, HL070100, HL060040, HL080124, HL071039, HL077447, and HL107385 with the National Institutes of Health, National Heart, Lung, and Blood Institute, and a grant from the Donald W. Reynolds Foundation.

Role of the Sponsor: The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Online-Only Material: eFigures 1-3, eTable, and the Author Video Interview are available at http://www.jama.com.

REFERENCES


