Multimarker Approach to Evaluate Correlates of Vascular Stiffness
The Framingham Heart Study

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Background—Arterial stiffness increases with age and contributes to the pathogenesis of systolic hypertension and cardiovascular disease in the elderly. Knowledge about the pathophysiological processes that determine arterial stiffness may help guide therapeutic approaches.

Methods and Results—We related 7 circulating biomarkers representing distinct biological pathways (C-reactive protein, aldosterone-to-renin ratio, N-terminal proatrial natriuretic peptide and B-type natriuretic peptide, plasminogen activator inhibitor-1, fibrinogen, and homocysteine) to 5 vascular function measures (central pulse pressure, carotid-femoral pulse-wave velocity, mean arterial pressure, forward pressure wave amplitude [all measures of conduit artery stiffness], and augmented pressure, an indicator of wave reflection) in 2000 Framingham Offspring Study participants (mean age, 61 years; 55% women). Tonometry measures were obtained on average 3 years after the biomarkers were measured. In multivariable linear regression models adjusting for covariates, the biomarker panel was significantly associated with all 5 vascular measures (P < 0.003 for all). On backward elimination, the aldosterone-to-renin ratio was positively associated with each stiffness measure (P ≤ 0.002 for all). In addition, C-reactive protein was positively related to augmented pressure (P = 0.0003), whereas plasminogen activator inhibitor-1 was positively associated with mean arterial pressure (P = 0.003), central pulse pressure (P = 0.001), and forward pressure wave (P = 0.01).

Conclusions—Our cross-sectional data on a community-based sample suggest a distinctive pattern of positive associations of biomarkers of renin-angiotensin-aldosterone system activation with pan–arterial vascular stiffness, plasminogen activator inhibitor-1 with central vascular stiffness indices, and C-reactive protein with wave reflection. These observations support the notion of differential influences of biological pathways on vascular stiffness measures.

Key Words: epidemiology ■ biomarkers ■ renin–angiotensin–aldosterone system ■ C-reactive protein ■ plasminogen activator inhibitor 1

Substantial research suggests that the steady-state and pulsatile components of arterial load have a differential impact on cardiovascular disease risk and may have various determinants. Furthermore, the concomitant increases in cen-

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trial and peripheral vascular stiffness with age are influenced by several mechanical and biological factors that result in altered vasoreactivity and arterial wall remodeling. The molecular events associated with remodeling of the large and medium to small arteries also have been well characterized and involve the combinatorial influences of adhesion molecules, integrins, metalloproteinases, the renin-angiotensin axis, and inflammation on the cellular constituents (endothelial cells, vascular smooth cells, fibroblasts, and matrix components) of the vasculature.6,7 These advances in our understanding notwithstanding, the primacy of one specific biological pathway over others in mediating the arterial remodeling process is not clearly established. The identification of key pathways implicated in vascular remodeling may offer the opportunity of reversing vascular stiffness through targeted approaches.8,9 One potential epidemiological method to identify key pathways involved in a multifactorial condition such as increased vascular stiffness is to evaluate the relations of circulating biomarkers from diverse pathways to vascular stiffness measures. In this context, previous studies (including a study from our group) have reported positive associations between circulating biomarkers and direct and indirect measures of arterial stiffness,10–13 but most studies analyzed single biomarkers or biomarkers for a single pathway; none simultaneously examined a comprehensive panel of biomarkers representing distinct physiological pathways. Accordingly, we related a panel of 7 systemic biomarkers representing inflammation, neurohormonal activation, and hemostasis to measures of arterial stiffness in a large community-based sample.

Methods

Study Sample
Details of the design and selection criteria for the offspring cohort of the Framingham Heart Study have been described elsewhere.14 In brief, children of participants of the original Framingham cohort and the spouses of these children were enrolled (n = 5129) in 1971. Offspring cohort participants are seen in the Heart Study clinic approximately every 4 years, at which time a targeted physical examination is performed, cardiovascular risk factors are measured, and a medical history focusing on cardiovascular events since the last examination is obtained. For the present analyses, participants attending the seventh examination cycle were eligible if they had data on arterial tonometry performed at that examination and data on the 7 biomarkers evaluated (see Biomarker Measurements below). Of 3537 attendees at the index examination, 877 individuals were not eligible for tonometry because the examinations were performed at a nursing home (n = 204) or because participants attended examination cycle 7 before the tonometry measurements were implemented (n = 673).13 Of the remaining 2660 attendees, 660 were excluded from the present analysis for the following reasons: inadequate tonometry data (n = 367), missing biomarker data (n = 287), or missing data for covariates included in multivariable analyses (n = 6). After these exclusions, 2000 participants (mean age, 61 years; 55% women) remained eligible. Excluded participants had higher values (nominal P < 0.05) for systolic and diastolic blood pressures, body mass index, ratio of total to high-density lipoprotein cholesterol, fasting blood glucose, and prevalence of antihypertensive treatment, diabetes, and smoking. The higher cardiovascular risk profile in participants with inadequate noninvasive vascular function or imaging data is well established.15,16 All participants provided written informed consent, and the Institutional Review Board at the Boston University Medical Center approved the study protocol.

Biomarker Measurements

We chose a panel of biomarkers measured at the sixth examination cycle (~3 years before the seventh examination at which tonometry was performed) for the present analyses because these biomarkers represent several distinct pathophysiological pathways, as reported previously.17,18 Blood was drawn from fasting participants after they had been in a supine position for 5 to 10 minutes (typically between 7:30 and 9 AM), centrifuged immediately, and stored at −80°C until analysis such as increased vascular stiffness is to evaluate the relations of circulating biomarkers from diverse pathways to vascular stiffness measures. In this context, previous studies (including a study from our group) have reported positive associations between circulating biomarkers and direct and indirect measures of arterial stiffness,10–13 but most studies analyzed single biomarkers or biomarkers for a single pathway; none simultaneously examined a comprehensive panel of biomarkers representing distinct physiological pathways. Accordingly, we related a panel of 7 systemic biomarkers representing inflammation, neurohormonal activation, and hemostasis to measures of arterial stiffness in a large community-based sample.

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Acquisition of Arterial Waveforms With Tonometry and Analysis

With the participants in a supine position, tonometry was performed to obtain arterial waveforms from the carotid, brachial, radial, and femoral arteries (all on the right side) with a commercially available applanation tonometer (SPT-301, Millar Instruments, Houston, Tex). In parallel with the acquisition of the tonometric data, blood pressure was measured with an oscillometric device, and an ECG was recorded. The average systolic and diastolic blood pressure values were used to calibrate the pressure waveforms after they have been signal averaged with the ECG R-wave as the fiducial point. The carotid-femoral pulse-wave velocity (PWV) was calculated from the transit distances (obtained from body surface measurements and corrected for parallel transmission in the carotid) and transit times (obtained from the timing of the foot of the carotid and femoral tonometry waveforms). From the calibrated carotid pressure waveform, the following variables were derived (definitions): forward pressure wave amplitude (difference of the pressure at the foot of the waveform and the pressure at the first peak or inflection point), augmented pressure amplitude (difference between the central systolic pressure and the forward wave peak pressure), and augmentation index (percent increase in the pulse pressure relative to the systolic inflection point), which was used in secondary analyses. The calibrated carotid pressure served as a surrogate for central pressure.

Statistical Analyses

Our primary vascular phenotypes included the following traits that reflect the different components of arterial stiffness: central pulse pressure (marker of pulsatile arterial load), mean arterial pressure (marker of steady arterial load), and carotid-femoral PWV (measure of aortic stiffness). We also analyzed the 2 main components of central pulse pressure, ie, the forward pressure wave amplitude and augmented pressure. Biomarkers were natural logarithmically transformed to normalize their distributions. PWV also was modeled as inverse PWV to improve its normality, and association results remained eligible. Excluded participants had higher values (nominal P < 0.05) for systolic and diastolic blood pressures, body mass index, ratio of total to high-density lipoprotein cholesterol, fasting blood glucose, and prevalence of antihypertensive treatment, diabetes, and smoking. The higher cardiovascular risk profile in participants with inadequate noninvasive vascular function or imaging data is well established.15,16 All participants provided written informed consent, and the Institutional Review Board at the Boston University Medical Center approved the study protocol.

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The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

## Results

The clinical and biochemical features and arterial function characteristics of our study sample are displayed in Tables 1 and 2. Our sample was middle-aged to elderly, with about a third of the participants on antihypertensive medications.

### Biomarker Panel and Measures of Vascular Stiffness

The panel of 7 biomarkers considered together was associated with each of the primary (central pulse pressure, carotid-femoral PWV, mean arterial pressure, forward pressure wave, augmented pressure) and secondary (augmentation index) arterial traits even after multivariable adjustment (Table 3). Stepwise selection identified the aldosterone-to-renin ratio (ARR) as a significant positive correlate of each vascular stiffness measure ($P<0.002$ for all).

In addition, CRP was positively associated with the augmented pressure and with carotid-femoral PWV, although the latter did not reach statistical significance after correction for multiple testing. PAI-1 was associated with central pulse pressure, but neither fibrinogen nor homocysteine was significantly associated with any of the vascular stiffness measures.

### Discussion

#### Principal Findings

We assessed the joint association of a panel of 7 biomarkers that represent distinct biological pathways with measures of arterial stiffness in a large ($n=2000$) community-based sample to elucidate the relative contribution of different pathways to aortic stiffness, wave reflection, and microvascular function. We observed an interesting pattern of association with...
vascular function measures for 3 of the biomarkers (ie, ARR, PAI-1, and CRP). ARR was positively associated with all measures of arterial function tested, including carotid-femoral PWV, forward pressure wave amplitude, and central pulse pressure (measures of conduit artery stiffness), as well as with mean arterial pressure and augmented pressure (which are measures of peripheral vascular function). These observations are consistent with a central role of the renin-angiotensin-aldosterone system (RAAS) in determining both steady-state and pulsatile components of afterload and with its influence on pan-arterial function and remodeling. In comparison, CRP and PAI-1 were differentially related to measures of central versus peripheral vascular function. CRP was associated with augmented pressure, a main correlate of peripheral vascular stiffness, whereas PAI-1 correlated mainly (and positively) with measures of conduit artery stiffness. These observations support the notion of various influences of biological pathways on central versus peripheral vascular stiffness. Overall, the biomarkers explained only a small proportion of the interindividual variability in vascular stiffness measures.

In the Context of the Current Literature

**Arterial Stiffness and the RAAS**

Clinical and experimental evidence links the RAAS to arterial stiffness. Circulating components of the RAAS have been related to measures of arterial stiffness in small to moderate-sized samples. For example, carotid-femoral PWV was noted to be higher in patients with primary aldosteronism compared with patients with essential hypertension and healthy control subjects.20 Serum aldosterone was positively associated with heart-femoral PWV in a series of patients with hypertension (n=438).11 ARR also was positively associated with PWV in 60 healthy subjects.21 These observational studies are paralleled by clinical trial data that suggest that pharmacological inhibition of the RAAS reduces arterial stiffness. For instance, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, and aldosterone antagonists have been reported to reduce PWV in small studies of heterogeneous groups of patients.8,9,22,23 Finally, genetic variants in the RAAS have been associated with measures of arterial stiffness, including aortic PWV24 and carotid distensibility.25

Substantial experimental evidence suggests that aldosterone and angiotensin II affect vascular remodeling.7 RAAS activation influences vasoreactivity and structural and functional remodeling via genomic and nongenomic mechanisms. Such activation is characterized by oxidative stress and inflammation resulting from the interactions of aldosterone and angiotensin II on the mineralocorticoid and AT1 receptors7 and upregulation of epidermal growth factor receptor expression.26 In line with these clinical and experimental data, we observed a consistent and strongly positive association of ARR with all measures of arterial function tested.

**Arterial Stiffness and Inflammation**

Biomarkers of inflammation like CRP, interleukin-6, and tumor necrosis factor-α have been associated positively with...
both indirect (e.g., brachial artery pulse pressure\textsuperscript{20}) and direct measures of arterial stiffness in previous studies in apparently healthy individuals,\textsuperscript{27} in specific patient groups (e.g., patients with hypertension\textsuperscript{28}), and in community-based samples.\textsuperscript{13,29} Most of these studies had modest sample sizes.\textsuperscript{27,29} In a recent report focusing on inflammatory biomarkers from our group, we demonstrated a positive association between CRP (measured at the same examination cycle as the tonometry) and the augmented pressure amplitude.\textsuperscript{30} We replicated that finding in the present investigation. It is conceivable that inflammatory processes within the vessel wall (as part of vascular remodeling) manifest in both increased reflected wave amplitude and higher systemic levels of CRP. Alternatively, excessive wave reflection may contribute to vascular inflammation and remodeling because of associated abnormalities in pressure and flow in the larger arteries. Longitudinal and interventional studies may be required to establish the directionality of these relations.

**Arterial Stiffness and Natriuretic Peptides and Homocysteine**

Previous studies reported associations of natriuretic peptide levels and homocysteine with different measures of arterial stiffness, including carotid-femoral and carotid-radial PWV.\textsuperscript{13,31,32} In the present investigation, using a multimarker approach, we observed weaker positive associations of BNP with central pulse pressure that did not reach statistical significance on correction for multiple testing. Homocysteine levels were not associated with vascular stiffness measures when modeled with other biomarkers. It is important to note that our observations (based on a statistical procedure to select from among a panel of biomarkers) do not exclude an important role for the natriuretic peptides or homocysteine in vascular remodeling. Many of the biomarkers tested are correlated, and the fact that certain markers drop out of the model during the backward elimination process (likely because other markers are more closely related to arterial function as a result of additional direct or indirect effects) does not rule out an important role for these biomarkers in arterial physiology.

**Arterial Stiffness and Hemostasis**

PAI-1 has been associated positively with PWV\textsuperscript{33} and aortic stiffness in previous studies.\textsuperscript{34} In our analyses, PAI-1 was positively related to measures of conduit artery stiffness, ie, mean arterial pressure, central pulse pressure, and forward pressure wave amplitude, even after multivariable adjustment. Epidemiological evidence further supports that PAI-1 modulates vascular remodeling. In the Atherosclerosis Risk in Communities (ARIC) cohort, PAI-1 levels were positively associated with intima-media thickness.\textsuperscript{35}

Experimental data suggest that PAI-1 inhibits the activity of the fibrin-degrading enzyme plasmin and has direct effects on the vessel wall.\textsuperscript{36} PAI-1 is bound to vitronectin in the extracellular matrix, where it inhibits migration of vascular smooth muscle cells.\textsuperscript{37} Thus, clinical and experimental data suggest that higher PAI-1 levels may contribute to stiffening of the aorta over the life course, which might explain its association with forward pressure wave and blood pressure traits like central pulse pressure and mean arterial pressure.

Fibrinogen was related to carotid-femoral PWV in hypertensives (n=229)\textsuperscript{38} and to pulse pressure/stroke index in a large sample of American Indians.\textsuperscript{39} However, no association was observed between fibrinogen and PWV in patients with end-stage renal disease\textsuperscript{40} and in apparently healthy middle-aged women.\textsuperscript{41} Our results are consistent with the last 2 studies. Fibrinogen was weakly associated with central pulse pressure, but this association was no longer significant after consideration of the multiple comparisons performed. All other measures of arterial function were not related to fibrinogen in this multimarker approach.

**Study Limitations**

Our cohort consists of middle-aged to elderly Americans of European descent, which limits the generalizability of our findings. A time lag of \(\approx\)3 years occurred between the tonometry and biomarker measurements, which might have diminished our ability to detect associations between some biomarkers and the tonometry traits. However, we have shown in previous studies in our cohort that biomarkers (measured at the sixth examination cycle) were powerful correlates of endothelial function (measured at the seventh examination cycle) even if the traits are not measured contemporaneously.\textsuperscript{42} Furthermore, a significant proportion of attendees had to be excluded because of missing or inadequate tonometry and biomarker data. This is a well-known but unavoidable limitation of large epidemiological cohort studies that may bias toward the null hypothesis because of loss of cases that presumably had more extreme values for the analyzed variables.\textsuperscript{15,16} An additional limitation specific to the homocysteine concentrations was the fact that folic acid fortification of enriched cereal grain products was introduced during the course of the sixth examination cycle. Consequently, the homocysteine concentrations related to the measures of arterial stiffness may reflect recently reduced levels for many of the participants, not their usual homocysteine exposure before fortification. Finally, we cannot infer causality from these observational data.

**Conclusions**

We have observed both specific and generalized relations between various biomarkers of distinct biological pathways and a comprehensive but concise group of vascular function measures. We observed a consistent positive association of the ARR with various measures of arterial stiffness, wave reflection, and microvascular function. This convincing association is consistent with the notion that pharmacological inhibition of the RAAS may revert or reduce the progression of arterial stiffness and associated abnormalities in wave reflection and mean arterial pressure. In addition, the pleiotropic effects of the RAAS pathway on various physiologically and anatomically distinct vascular measures may contribute to the observed interplay between large- and small-artery function.\textsuperscript{19} CRP and PAI were significantly associated with certain arterial stiffness measures, indicating that inflammation and hemostasis also modulate (or are modulated by) peripheral and central arterial stiffness, respectively. Our findings suggest pathways that should be studied further to elucidate the pathophysiology of large-artery stiffening. Such studies offer
the potential to identify much needed interventions that specifically limit or reverse stiffening of the large arteries.

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Disclosures
Dr Mitchell is owner of Cardiovascular Engineering Inc, a company that designs and manufactures devices that measure vascular stiffness. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Arterial stiffness increases with age and contributes significantly to cardiovascular morbidity and mortality in the elderly. A better understanding of the pathophysiology of vascular ageing and the biochemical pathways involved might help in the development of appropriate therapeutic strategies. In 2000 Framingham Offspring Study participants, we related 7 biomarkers (C-reactive protein, aldosterone-to-renin ratio, N-terminal proatrial natriuretic peptide and B-type natriuretic peptide, plasminogen activator inhibitor-1, fibrinogen, and homocysteine), representing inflammation, neurohormonal activation, and hemostasis, to a panel of tonometric measures, which reflect the different components of arterial stiffness (ie, central pulse pressure [marker of pulsatile arterial load], mean arterial pressure [marker of steady arterial load], and carotid-femoral pulse-wave velocity [measure of aortic stiffness]). In addition, we analyzed the 2 main components of central pulse pressure: the forward pressure wave amplitude and augmented pressure. We first related the multibiomarker panel as a whole to each vascular function measure and then applied a backward elimination procedure to identify a parsimonious set of markers that displayed the strongest associations with each arterial stiffness measure. We identified the aldosterone-to-renin ratio as a key correlate of pan–arterial stiffness; it was associated with all 5 tonometric measures ($P \leq 0.002$). In addition, plasminogen activator inhibitor-1 displayed an association with central vascular stiffness indices, and CRP showed an association with wave reflection. These observations support the notion that distinct biological pathways may selectively influence the different components of vascular stiffness.
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