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Original Contribution

Association of Small Artery Elasticity With Incident Cardiovascular Disease in Older Adults

The Multi-Ethnic Study of Atherosclerosis

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Functional biomarkers like large artery elasticity (LAE) and small artery elasticity (SAE) may predict cardiovascular disease (CVD) events beyond blood pressure. The authors examined the prognostic value of LAE and SAE for clinical CVD events among 6,235 Multi-Ethnic Study of Atherosclerosis participants who were initially aged 45–84 years and without symptomatic CVD. LAE and SAE were derived from diastolic pulse contour analysis. During a median 5.8 years of follow-up between 2000 and 2008, 454 adjudicated CVD events occurred, including 256 cases of coronary heart disease (CHD), 93 strokes, and 126 heart failures (multiple diagnoses were possible). After adjustment for age, race/ethnicity, sex, clinic, height, heart rate, body mass index, systolic and diastolic blood pressure, use of antihypertensive and cholesterol-lowering medications, smoking, total cholesterol, high density lipoprotein cholesterol, triglycerides, diabetes, and high-sensitivity C-reactive protein, the hazard ratio for any CVD per standard-deviation increase in SAE was 0.71 (95% confidence interval: 0.61, 0.83; $P < 0.0001$). The lowest (stiffest) SAE quartile had a hazard ratio of 2.28 (95% confidence interval: 1.55, 3.36) versus the highest (most elastic) quartile. The net reclassification index, conditional on base risk, was 0.11. SAE was significantly associated with future CHD, stroke, and heart failure. After adjustment, LAE was not significantly related to CVD. In asymptomatic participants free of overt CVD, lower SAE added prognostic information for CVD, CHD, stroke, and heart failure events.

arteries; cardiovascular diseases; elasticity; risk factors

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; LAE, large artery elasticity; MESA, Multi-Ethnic Study of Atherosclerosis; NRI, net reclassification index; SAE, small artery elasticity; SD, standard deviation; SVR, systemic vascular resistance.

Early risk identification can help prevent clinical cardiovascular disease (CVD). Persons at risk for CVD events are currently identified by screening for cholesterol, glucose, smoking, obesity, and blood pressure (1, 2). By identifying asymptomatic persons with evidence of early CVD, investigators can delineate a subpopulation that is likely to progress to clinical events, beyond prediction possible from risk factors alone (3).

Several structural markers for vascular disease, such as carotid intima-media thickness and coronary calcium score (4–7), have been studied in relation to CVD risk factors and coronary heart disease (CHD) events. In contrast, the functional vascular marker arterial stiffness probably captures an earlier phase of CVD development. Measures of arterial stiffness have been linked with CVD events (8–12). Carotid-femoral pulse wave velocity is the measure of arterial stiffness most studied in relation to CHD and stroke events. An alternative method derives small arterial elasticity (SAE) from the diastolic pulse contour analysis obtained from the radial artery waveform. In a limited retrospective study

by Grey et al. (13), an association was shown between lower SAE and self-reported CVD events. Aortic stiffness has also been associated with incident hypertension (14, 15). In the Multi-Ethnic Study of Atherosclerosis (MESA), the finding was that lower SAE was the strongest predictor of incident hypertension out of several arterial measures, including measures of large arterial stiffness and aortic distensibility (16). The small arteries, which are the primary source of the oscillatory compliance of the vascular tree, may be uniquely important in the development and initiation of hypertension (16), relative to the vascular stiffness and atherosclerotic plaque deposition of the larger vessels. Similar mechanisms may be involved in development of CVD.

We hypothesized that in MESA, which contained a large sample of persons who were free of overt CVD, SAE would predict CVD events and that large artery elasticity (LAE), following the pattern observed for incident hypertension (16), would be a more limited predictor.

MATERIALS AND METHODS

Study sample

MESA was initiated to investigate the prevalence, correlates, and progression of subclinical (asymptomatic) CVD in men and women (17). In brief, between July 2000 and August 2002, 6,814 men and women who identified themselves as white, black, Hispanic, or Chinese, were aged 45–84 years, and were free of clinically apparent CVD were recruited from portions of 6 US communities: Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; northern Manhattan and the Bronx, New York, New York; and St. Paul, Minnesota. Investigators at each clinic recruited from locally available sources, which included lists of residents, dwellings, and telephone exchanges. In the last few months of the recruitment period, supplemental sources (Centers for Medicare and Medicaid Services lists and referrals by participants) were used to ensure adequate numbers of minorities and elderly subjects. The institutional review boards at all participating centers approved the study, and all participants gave informed consent.

Data collection and definitions of risk factors

Age, race/ethnicity, and sex were self-reported during the recruitment phase and verified at baseline. Height and weight were measured with participants wearing light clothing and no shoes. Body mass index was calculated as weight (kg) divided by height squared (m^2). Resting seated blood pressure was measured 3 times with a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, Florida). The average of the last 2 measurements was used. Hypertension was defined as systolic blood pressure $\geq$140 mm Hg, diastolic blood pressure $\geq$90 mm Hg, or current use of antihypertensive medication. Standardized questionnaires were used, and medication containers were examined. The participants were classified as current cigarette smokers, former smokers, or never smokers. Diabetes was defined as a fasting plasma glucose level $\geq$126 mg/dL ($\geq$7 mmol/L) or a history of medical treatment for diabetes; almost all persons with diabetes had type 2 diabetes.

Blood measures

A central laboratory (University of Vermont, Burlington, Vermont) measured levels of total and high density lipoprotein cholesterol, triglycerides, plasma glucose, and high-sensitivity C-reactive protein in blood samples obtained after a 12-hour fast.

LAE and SAE measurements

Arterial wave forms were recorded using the HDI/PulseWave CR-2000 (Hypertension Diagnostics, Inc., Eagan, Minnesota). Of 6,814 MESA participants, the arterial elasticity measure was unobtainable in 2.7% ($n = 184$) because of refusal ($n = 10$), physical inability ($n = 48$), equipment malfunction ($n = 41$), clinic time constraints with a failed attempt to reschedule another visit ($n = 39$), or other, unknown reasons ($n = 46$). Of the 6,630 persons in whom the procedure was carried out, LAE and SAE could not be estimated in 294 (4.4%) because of arrhythmia or participant movement. LAE and SAE were estimated in 6,336 participants, of whom 7 were found after baseline to have preexisting CVD and were excluded from these analyses. Thus, LAE and SAE were obtained in 93% of those participants in whom the procedure was attempted. After adjustment for age, race/ethnicity, and sex, no other risk factor or subclinical measure differed between the 478 persons who were not measured and the 6,336 who were measured.

A solid-state pressure transducer array (tonometer) was placed over the radial artery of the dominant arm to record the pulse contour. A 30-second analog tracing of the radial waveform, constituting continuous pressure changes during diastole, was digitized at 200 samples per second. There was an accompanying automated, oscillatory blood pressure measurement at the brachial artery of the contralateral arm.

SAE and LAE are estimated by the device (18) from the waveform modeled as a decaying exponential function plus a sinusoidal function dampened by a decaying exponential (see Web Appendix (http://aje.oxfordjournals.org/)). The quantities estimated directly from the waveform are X and Y. LAE and SAE are estimated by dividing each of X and Y by systemic vascular resistance (SVR). SVR is estimated as mean arterial blood pressure/cardiac output, and cardiac output is estimated from ejection time taken from the pulse waveform, heart rate, age, height, and weight (see Web Appendix).

The same MESA technician performed a repeat measure on the same day during the baseline clinic using the CR-2000 in 131 people (19). The mean difference was -0.13 mL/mm Hg (standard deviation [SD], 3.5) $\times$ 10 for LAE, -0.03 mL/mm Hg (SD, 1.5) $\times$ 100 for SAE, 0.01 seconds (SD, 4.6) for LAE $\times$ SVR, 0.005 seconds (SD, 1.8) $\times$ 10 for SAE $\times$ SVR, 2.8 mm Hg (SD, 8.2) for systolic blood pressure, and 1.5 mm Hg (SD, 5.0) for diastolic blood pressure. The between-measure correlation was 0.74 for LAE, 0.84 for SAE, 0.58 for LAE $\times$ SVR, 0.74 for SAE $\times$ SVR, 0.90 for systolic blood pressure, and 0.86 for diastolic blood pressure. Reproducibility findings did not differ significantly between centers.

Follow-up

We recorded new symptomatic and adjudicated cardiovascular events for a median of 5.8 years between July 2000 and August 2008 (10th, 25th, 75th, and 90th percentiles of follow-up time: 3.6, 5.6, 5.9, and 6.1 years, respectively), through the end of 7 follow-up contacts at intervals of 9–12 months. At each contact, an interviewer contacted each participant or a family member by telephone to inquire about interim hospital admissions, outpatient diagnoses of CVD, and deaths. To verify self-reported diagnoses, we requested copies of medical records for participants who had been hospitalized or had received an outpatient diagnosis of CVD. We obtained records of 98% of reported cardiovascular events associated with hospitalization. For participants who had died of cardiovascular causes outside the hospital, we conducted interviews with the next of kin and requested copies of death certificates. Physicians adjudicated the diagnoses; only symptomatic events were counted. The outcome ''CVD event'' comprised myocardial infarction, death from CHD, angina, heart failure, stroke, and peripheral vascular disease, while ''CHD event'' included myocardial infarction, death from CHD, and angina. Details are given in the Web Appendix and at www.mesa-nhlbi.org.

Statistical analysis

We restricted the data to 454 CVD events in 6,235 participants who had no information missing for outcome, arterial elasticity, or covariables. We used Cox proportional hazards regression to estimate hazard ratios for a CVD event, a CHD event, and each of the specific entities (myocardial infarction or death from CHD, angina, heart failure, stroke, and peripheral vascular disease) according to SAE as a continuous variable divided by its standard deviation, and also as sex-specific quartiles. Model 1 (minimally adjusted) included the covariates age, sex, race/ethnicity, clinic, and height. Model 2 (fully adjusted) added the covariates heart rate, systolic and diastolic blood pressures, use of antihypertensive medication, body mass index, smoking (3 categories), total cholesterol, high density lipoprotein cholesterol, triglycerides, use of cholesterol-lowering medication, diabetes, and high-sensitivity C-reactive protein. Adding educational attainment to the model did not substantially alter findings (data not shown). These analyses were repeated using LAE as the predictor of interest.

C statistics (area under the receiver operating characteristic curve) were approximated by means of corresponding logistic models (odds ratios in the logistic models approximated those in the proportional hazards models). The net reclassification index (NRI), after inclusion of SAE in model 2 (base risk model without SAE), was computed as [proportion of all CVD events reclassified at higher risk – proportion reclassified at lower risk] – [proportion of all nonevents reclassified at higher risk – proportion reclassified at lower risk] (20). Unstratified NRI is confounded with base risk (in this paper, without SAE in the model) whenever the base risk function is related to actual risk, but the question we are asking is whether SAE improves classification with knowledge of base risk; therefore, in this paper we report the NRI within each quartile of this base risk. Recognizing that the weighting of NRI values over quartiles may be debated, we also present the equiweighted average of the reclassification proportions across quartiles, reflecting equal numbers of persons at risk in each base risk quartile. NRI variances were computed using an exact formula (see tabular footnote), resulting in standard errors that were 5%–22% lower than the approximation used by Pencina et al. (20). In parallel models, we replaced SAE with SAE $\times$ SVR to examine information obtained solely from the pulse waveform (SAE $\times$ SVR) separately from that estimated from physical measures (SVR). All analyses were performed with SAS software, version 9.2 (SAS Institute Inc., Cary, North Carolina). We regarded *P* values less than 0.05 as statistically significant.

RESULTS

Table 1 shows sex-specific baseline characteristics and describes LAE and SAE, as previously reported (21). The age- and sex-adjusted correlation coefficient for correlation between LAE and SAE was 0.23. Most of the baseline characteristics varied significantly by sex.

With 454 incident CVD events, compared with the highest (most elastic) SAE quartile, the hazard ratio in the lowest (stiffest) SAE quartile in the fully adjusted model (model 2) was 2.28 (95% confidence interval: 1.55, 3.36), with graded risk in the intermediate quartiles (Table 2). The decrease in risk per standard-deviation increase in elasticity was 0.71 ($P < 0.0001$). Risk was similarly significantly elevated, generally in a graded fashion, in the presence of less elastic small arteries for each CVD entity, most clearly for stroke. The area under the receiver operating characteristic curve (*c* statistic) increased only modestly by 0.005 (from 0.777 to 0.782) with the addition of SAE to the variables otherwise included in model 2 for predicting CVD events (data not shown). A more informative measure was NRI within base risk quartile; it was 0.27, 0.05, 0.09, and 0.04 for quartiles 1–4, respectively (Table 3). Each of the stratum-specific NRIs, except the one derived in base risk quartile 2, were statistically significant. The equiweighted NRI was 0.11 and was highly statistically significant. Similar computations using age, race/ethnicity, sex, and Framingham 10-year CHD risk score as the base risk yielded an average NRI of 0.15 (Web Table 1).

LAE showed prediction for several of the outcome variables in model 1 (Web Table 2) but retained statistical significance in model 2 only in prediction of heart failure ($P = 0.03$). Addition of SAE to the model for heart failure increased the *P* value for LAE to 0.06, while the corresponding *P* value for SAE ($P = 0.01$ in Table 2) increased to 0.02 (data not shown). The largest hazard ratio associated with LAE in Web Table 2 was 2.54, predicting incident stroke in the stiffest LAE quartile (quartile 1) versus the most elastic LAE quartile (quartile 4), but this hazard ratio was not significant. *C* statistics did not improve much by inclusion of LAE in the model, the largest improvement in model 2 being 0.002 for prediction of angina pectoris (data not shown).

We examined prediction of CVD events with the pulse waveform component of SAE, that is, SAE $\times$ SVR, which is

Table 1. Characteristics of Participants by Sex, Multi-Ethnic Study of Atherosclerosis, 2000–2002

	Women (n = 3,265)		Men (n = 2,970)		P for Difference
	%	Mean (SD)	%	Mean (SD)	
Age, years		61.9 (10.2)		62.1 (10.2)	0.46
Race/ethnicity					0.23[a]
White	38		39		
Chinese	12		12		
Black	28		26		
Hispanic	22		23		
Height, cm		159.9 (7.1)		173.5 (7.6)	<0.0001
Heart rate, beats/minute		65.1 (9.9)		62.2 (10.4)	<0.0001
Hypertension[b]	46.4		42.9		0.005
Blood pressure, mm Hg					
Systolic pressure		126.8 (23.2)		126.0 (19.2)	0.14
Diastolic pressure		69.1 (10.2)		75.1 (9.4)	<0.0001
Use of antihypertensive medication	35		31		<0.0001
Body mass index[c]		28.7 (6.2)		27.8 (4.4)	<0.0001
Cigarette smoking					
Ever smoker	40		59		<0.0001
Current smoker	12		14		0.003
Cholesterol, mg/dL					
Total cholesterol		199.6 (35.5)		188.2 (34.9)	<0.0001
High density lipoprotein cholesterol		56.1 (15.1)		45.1 (11.7)	<0.0001
Triglycerides, mg/dL		128.8 (78.6)		135.3 (95.5)	0.003
Use of cholesterol-lowering medication	17		15		0.17
Diabetes mellitus[d]	11		14		0.002
High-sensitivity C-reactive protein, mg/L		4.5 (6.0)		2.8 (5.4)	<0.0001
LAE, mL/mm Hg × 10		11.8 (5.1)		15.1 (5.7)	<0.0001
SAE, mL/mm Hg × 100		3.8 (2.3)		5.2 (3.1)	<0.0001
SVR, dyne × seconds/cm^5		1,684 (435)		1,608 (344)	<0.0001
LAE × SVR, seconds		1.40 (0.54)		1.75 (0.57)	<0.0001
SAE × SVR, seconds × 10		0.44 (0.22)		0.58 (0.29)	<0.0001

Abbreviations: LAE, large artery elasticity; SAE, small artery elasticity; SD, standard deviation; SVR, systemic vascular resistance.

[a] The P value for race/ethnicity tested for any difference in this variable between men and women.

[b] Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or current use of antihypertensive medication.

[c] Weight (kg)/height (m)^2.

[d] Diabetes was defined as a fasting plasma glucose level ≥126 mg/dL (≥7 mmol/L) or a history of medical treatment for diabetes.

a measure that indexes the amount and timing of oscillations in the diastolic waveform and does not include any physical measures in its estimation. The directionality and statistical significance of the findings (Web Table 3) were the same as in Table 2 (Web Table 4), except that the P value for heart failure in model 2 was 0.06 and the findings for SAE × SVR were weaker than those for SAE in prediction of stroke.

In sensitivity analyses, the sex interaction in prediction of CVD events from SAE was not statistically significant ($P = 0.57$). In separate models for women and men, among 170 CVD events in 3,265 women, the hazard ratio per standard-deviation increase in SAE was 0.72 (95% confidence interval: 0.52, 1.00), while in 2,970 men with 284 events, the corresponding hazard ratio was 0.70 (95% confidence interval: 0.58, 0.84).

DISCUSSION

This prospective analysis of the MESA cohort, whose participants were initially free of symptomatic CVD, showed that SAE provided incremental predictive information for any CVD event and for each of its different components: myocardial infarction and CHD death, angina, heart failure, stroke, and peripheral vascular disease. This predictive value

Table 2. Hazard Ratio for Cardiovascular Endpoints by Quartile of Small Artery Elasticity ($n = 6,235$), Multi-Ethnic Study of Atherosclerosis, 2000–2008

Endpoint	Small Artery Elasticity, mL/mm Hg × 100								Trend per Standard-Deviation Increase		*P* for Trend
	Quartile 4[a]		Quartile 3		Quartile 2		Quartile 1[b]		HR	95% CI	
	Median	Range	Median	Range	Median	Range	Median	Range			
Women	6.390	4.793–17.821	3.846	3.187–4.792	2.593	2.109–3.186	1.701	0.69–2.108			
Men	9.118	6.969–22.304	5.538	4.500–6.967	3.597	2.788–4.498	2.097	0.696–2.787			
	Quartile 4[a] ($n = 1,558$)		Quartile 3 ($n = 1,557$)		Quartile 2 ($n = 1,552$)		Quartile 1[b] ($n = 1,568$)				
	% of Events	No. of Cases	% of Events	No. of Cases	% of Events	No. of Cases	% of Events	No. of Cases			
CVD event ($n = 454$)	2.6	41	5.4	83	9.4	147	11.8	183			
CHD event ($n = 256$)	1.5	23	3.0	46	5.7	89	6.3	98			
MI/CHD death ($n = 145$)	0.6	9	1.6	25	3.0	48	4.0	63			
Angina ($n = 183$)	1.5	23	2.1	32	4.6	71	3.7	57			
Heart failure ($n = 126$)	0.7	11	1.6	25	2.4	38	3.3	52			
Stroke ($n = 93$)	0.3	4	0.7	11	2.2	34	2.8	44			
PVD ($n = 46$)	0.3	5	0.4	6	0.6	10	1.6	25			
	Quartile 4[a]		Quartile 3		Quartile 2		Quartile 1[b]				
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI			
CVD event											
Model 1[c]	1	Referent	1.70	1.16, 2.48	2.55	1.77, 3.67	2.94	2.03, 4.26	0.64	0.55, 0.74	<0.0001
Model 2[d]	1	Referent	1.43	0.98, 2.09	2.03	1.40, 2.94	2.28	1.55, 3.36	0.71	0.61, 0.83	<0.0001
CHD event											
Model 1	1	Referent	1.71	1.03, 2.84	2.82	1.74, 4.57	2.85	1.74, 4.69	0.66	0.55, 0.80	<0.0001
Model 2	1	Referent	1.52	0.91, 2.54	2.46	1.50, 4.02	2.45	1.46, 4.11	0.71	0.58, 0.86	0.0006
MI/CHD death											
Model 1	1	Referent	2.28	1.06, 4.93	3.62	1.73, 7.59	4.32	2.04, 9.14	0.61	0.47, 0.80	0.0004
Model 2	1	Referent	2.02	0.93, 4.38	3.01	1.42, 6.37	3.40	1.56, 7.38	0.68	0.51, 0.90	0.01
Angina											
Model 1	1	Referent	1.24	0.72, 2.14	2.41	1.46, 3.97	1.77	1.03, 3.03	0.72	0.58, 0.89	0.002
Model 2	1	Referent	1.12	0.65, 1.94	2.21	1.32, 3.70	1.64	0.93, 2.89	0.74	0.59, 0.92	0.01
Heart failure											
Model 1	1	Referent	1.74	0.85, 3.58	2.05	1.02, 4.13	2.47	1.22, 4.99	0.66	0.50, 0.88	0.005
Model 2	1	Referent	1.51	0.73, 3.11	1.81	0.89, 3.70	2.36	1.12, 4.94	0.67	0.49, 0.91	0.01
Stroke											
Model 1	1	Referent	2.21	0.70, 7.00	5.63	1.94, 16.31	6.53	2.23, 19.12	0.45	0.30, 0.69	0.0002
Model 2	1	Referent	1.75	0.55, 5.57	3.97	1.35, 11.64	4.08	1.35, 12.33	0.58	0.38, 0.90	0.01
PVD											
Model 1	1	Referent	1.18	0.35, 3.92	1.91	0.61, 5.96	4.82	1.63, 14.26	0.43	0.25, 0.73	0.002
Model 2	1	Referent	0.91	0.27, 3.09	1.28	0.39, 4.16	2.83	0.87, 9.19	0.56	0.32, 0.97	0.04

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MI, myocardial infarction; PVD, peripheral vascular disease.

[a] Most elastic.

[b] Stiffest.

[c] Model 1 covariates: age, race/ethnicity, sex, clinic, and height. Height was included in the minimal model to control for participant's size as a proxy for bore of artery.

[d] Model 2 covariates: above variables plus heart rate, systolic blood pressure, diastolic blood pressure, use of blood pressure medication, body mass index, ever smoking, current smoking, total cholesterol, high density lipoprotein cholesterol, triglycerides, use of cholesterol-lowering medication, diabetes, and C-reactive protein.

Table 3. Net Reclassification Index for Predicted Incident Cardiovascular Disease Events With Inclusion of Small Artery Elasticity in the Prediction Model Versus Without Inclusion (454 Cases Among 6,235 Persons at Risk), Multi-Ethnic Study of Atherosclerosis, 2000–2008[a]

Risk Category Before Addition of SAE to the Model	Risk Category After Addition of SAE to the Model								No. Reclassified		Total No. of Participants	Proportion Reclassified Downward	Proportion Reclassified Upward	Proportion Reclassified (Upward – Downward)	Stratified and Unstratified NRI (Standard Error)	*P* for Nonzero NRI
	Q1		Q2		Q3		Q4									
	No.	Row %	No.	Row %	No.	Row %	No.	Row %	Lower Risk Predicted by Including SAE	Greater Risk Predicted by Including SAE						
Noncases																
Q1	1,337	87	206	13	0		0		0	206	1,543	0	0.13	0.13		
Q2	197	13	1,133	75	184	12	0		197	184	1,514	0.13	0.12	−0.01		
Q3	11	1	166	12	1,141	79	122	8	177	122	1,440	0.12	0.08	−0.04		
Q4	0		5	0	115	9	1,164	91	120	0	1,284	0.09	0	−0.09		
Cases																
Q1	9	60	6	40	0		0		0	6	15	0	0.40	0.40	0.27 (0.137)[b]	0.04
Q2	3	7	37	82	5	11	0		3	5	45	0.07	0.11	0.04	0.05 (0.058)	0.36
Q3	1	1	6	5	99	83	13	11	7	13	119	0.06	0.11	0.05	0.09 (0.036)	0.013
Q4	0		0		15	5	260	95	15	0	275	0.05	0	−0.05	0.04 (0.016)	0.014
Average stratified NRI															0.11 (0.015)	<0.0001
Total for noncases	1,545		1,510		1,440		1,286		494	512	5,781	0.13	0.15	0.02		
Total for cases	13		49		119		273		25	24	454	0.07	0.11	0.04		
Unstratified NRI															−0.01 (0.016)	0.72

Abbreviations: CI, confidence interval; NRI, net reclassification index; Q, quartile; SAE, small artery elasticity.

[a] Based on shift in risk assessment across quartiles of risk in model 2 of Table 2 (base risk without SAE).

[b] The variance of NRI is computed as $(p_{down}q_{down} + p_{up}q_{up} - 2p_{down}p_{up})_{events}/N_{events} + (p_{down}q_{down} + p_{up}q_{up} - 2p_{down}p_{up})_{nonevents}/N_{nonevents}$, where $q = 1 - p$, p_{down} is the proportion reclassified downward, p_{up} is the proportion reclassified upward, and N is the number contributing to the given category. Base risk category subscripts are suppressed. Cumulative cardiovascular disease event rates were as follows: base risk Q1, 0.96% (95% CI: 0.48, 1.45); base risk Q2, 2.89% (95% CI: 2.06, 3.72); base risk Q3, 7.63% (95% CI: 6.32, 8.95); and base risk Q4, 17.64% (95% CI: 15.75, 19.53).

was significant not only after adjustment for demographic and anthropometric characteristics but also with further adjustment for CVD risk factors. In contrast to SAE, LAE was also predictive of CVD events in models adjusted for demographic factors, but in the fully adjusted model (model 2) it retained statistical significance only for heart failure. The NRI, conditional on base risk, was 0.11. SAE and the part of SAE that is derived solely from the waveform, SAE × SVR, were similarly predictive of total CVD events.

Several noninvasive methods exist for assessing arterial stiffness/elasticity. The largest amount of evidence regarding arterial stiffness as an additive predictor beyond traditional risk factors for CVD events has been derived from carotid-femoral pulse wave velocity. Initial studies were mainly focused on subjects at high risk (end-stage renal disease, diabetes, hypertension) (22). Among the few studies of asymptomatic people, in the Rotterdam Study, a Dutch study of apparently healthy persons aged ≥55 years, aortic pulse wave velocity was associated with CHD and stroke (10). In a small group of 141 elderly persons (age range, 70–100 years), aortic pulse wave velocity was associated with cardiovascular death (11). In the Health ABC Study, which included people aged 70–79 years, aortic pulse wave velocity was associated with higher CVD mortality, CHD, and stroke, although the association was not as strong as might have been expected in the highest quartile of pulse wave velocity, and no association was found in predicting heart failure (8). In an asymptomatic Danish population aged 40–70 years, aortic pulse wave velocity showed a trend toward prediction of CHD after controlling for traditional risk factors (9). A smaller study of Japanese Americans living in Hawaii showed that aortic pulse wave velocity was associated with CVD death (12). In the Framingham Offspring Study (151 incident CVD events in 2,232 persons; average age = 63 years), the relative hazard was 1.48 per standard-deviation increase in aortic pulse wave velocity but was not significant for augmentation index (23). The above findings, plus findings in diseased persons, were summarized in a meta-analysis (24). A second meta-analysis (25) from the same group of investigators considered measures of central hemodynamics. The augmentation index was positively associated with CVD outcome and all-cause mortality in studies of diseased persons.

Interpretation of the 2 measures, LAE and SAE, as pertaining to elasticity of the large and small arteries is based on a literal interpretation of the windkessel (''air chamber'') model (18). An accessible heuristic description of the windkessel model is rapid drainage of the blood into a large sink (the larger arteries), with subsequent evacuation from the sink into a smaller container (the smaller arteries). There has been some skepticism in the literature regarding LAE and SAE (26). LAE and SAE are derived from an algebraic decomposition of the diastolic waveform into one part that is primarily declining between aortic closure and aortic opening (decaying exponential function) and a second part that is largely flat but may be oscillating (sinusoidal function dampened by a decaying exponential function) (18). An alternative to the windkessel model is to interpret SAE by considering the possible sources of the oscillations during diastole (second part of the algebraic decomposition), when the left ventricle is considered to be ''still.'' The oscillations could be the result of a variety of activities of the arterial system during diastole, including left ventricular filling and untwisting, accommodation of reflection waves, spontaneous contraction of the vascular smooth muscle cells, and slow dissipation of the blood over the precapillary sphincters.

The pulse wave velocity (derived from behavior of the large arteries), augmentation index (derived from the systolic waveform), LAE, and SAE (derived from the oscillatory component of the diastolic waveform) appear to impart some common information, given that they were correlated in several studies (27–31). Observed correlations between SAE and augmentation index included −0.36 (27), −0.59 (28), and −0.71 (29), while correlations of LAE with augmentation index were −0.36 (28) and −0.41 (30). The correlation between aortic pulse wave velocity and augmentation index was 0.56 (30); that between SAE and femoral-popliteal pulse wave velocity was −0.52 in healthy subjects and −0.34 in older subjects with diabetes, while corresponding correlations with LAE were −0.32 and −0.46 (31). Concordance among pulse wave velocity, augmentation index, and SAE was further elucidated in the experimental study by Gilani et al. (32). They blocked nitric oxide release by N^G-nitro-L-arginine methyl ester in 10 healthy persons; this blockade resulted in an increase in aortic pulse wave velocity (8.25–8.98 m/second; $P = 0.04$), an increase in augmentation index (48.3%–64.6%; $P < 0.05$), and a decrease in SAE (9.9–6.9 mL/mm Hg × 100; $P < 0.001$). LAE, in contrast, did not change significantly (32). However, there are also differences among these measures. This was illustrated in the Anglo-Cardiff Collaborative Trial, where a different age course was seen for augmentation index (increased rapidly during middle age and slowly in the elderly) than for pulse wave velocity (changed slowly during middle age and rapidly in the elderly) (30). Morbidity and mortality studies comparing and contrasting these 3 measures and other measures would be useful.

In a theory of a temporal sequence of events, vascular disease originates in endothelial dysfunction, which has a profound influence on the microvasculature. In this view, evaluation of the smaller arteries and other microvasculature would be helpful in predicting early clinical events, consistent with our study. Stiffening of the small arteries, whether as a consequence of endothelial dysfunction, vasoconstriction, or structural changes due to remodeling, alters the magnitude and timing of reflected waves. Loss of arterial elasticity strengthens the early reflected pressure wave; the consequent increased afterload may eventually result in heart failure, as we observed in this study. In line with this temporal sequence hypothesis, the relatively weak predictive ability of LAE may reflect several features of the MESA sample, including the absence of people with clinical heart disease, their relatively low blood pressure, and the lack of extended follow-up. We speculate that abnormalities in large arteries, such as those reflected in low LAE, will gain predictive power as some MESA participants develop clinical CVD.

The current study was strengthened by the large sample size, the community-based setting, the multiethnic sample, and standardized subclinical atherosclerosis assessments and risk factor measurements. Other strengths were the prospective

design and the reliance on adjudicated symptomatic endpoints, which avoids detection bias related to less thoroughly investigated CVD events or to cross-sectional evaluation of subjects with known subclinical atherosclerosis. This report fills a need, called for in a consensus document on arterial stiffness, to obtain ''evidence, in a longitudinal study, that systemic arterial stiffness or systemic arterial compliance has independent predictive value for CV events'' (33, p. 2594). Limitations include the relatively small number of peripheral vascular disease events to date. Results could be different for long-term CVD prediction, especially as this population ages and specific clinical manifestations of CVD emerge. Caution should be exercised in interpreting *P* values in light of the multiple comparisons made; the statistical tests were correlated because a participant may have had more than 1 of the outcome diagnoses. In addition, the exact value of NRI is sensitive to categorization and cutpoints selected to represent the base and augmented risk functions.

In conclusion, the present observation in a population sample without clinically overt CVD or a history of CVD demonstrated that standardized and quality-controlled noninvasive measurement of the radial artery pulse contour over a few heart cycles was significantly associated with future CVD events above and beyond classic risk factors.

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REFERENCES

1. Greenland P, Lloyd-Jones D. Defining a rational approach to screening for cardiovascular risk in asymptomatic patients. *J Am Coll Cardiol*. 2008;52(5):330–332.
2. Mozaffarian D, Wilson PW, Kannel WB. Beyond established and novel risk factors: lifestyle risk factors for cardiovascular disease. *Circulation*. 2008;117(23):3031–3038.
3. Cohn JN, Duprez DA. Time to foster a rational approach to preventing cardiovascular morbid events. *J Am Coll Cardiol*. 2008;52(5):327–329.
4. Cao JJ, Arnold AM, Manolio TA, et al. Association of carotid artery intima-media thickness, plaques, and C-reactive protein with future cardiovascular disease and all-cause mortality: the Cardiovascular Health Study. *Circulation*. 2007;116(1):32–38.
5. O'Leary DH, Polak JF, Kronmal RA, et al. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. *N Engl J Med*. 1999; 340(1):14–22.
6. Budoff MJ, Shaw LJ, Liu ST, et al. Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. *J Am Coll Cardiol*. 2007;49(18): 1860–1870.
7. Folsom AR, Kronmal RA, Detrano RC, et al. Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-Ethnic Study of Atherosclerosis (MESA). *Arch Intern Med*. 2008;168(12):1333–1339.
8. Sutton-Tyrrell K, Najjar SS, Boudreau RM, et al. Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. Health ABC Study. *Circulation*. 2005;111(25):3384–3390.
9. Willum-Hansen T, Staessen JA, Torp-Pedersen C, et al. Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. *Circulation*. 2006;113(5): 664–670.
10. Mattace-Raso FU, van der Cammen TJ, Hofman A, et al. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. *Circulation*. 2006;113(5):657–663.
11. Meaume S, Benetos A, Henry OF, et al. Aortic pulse wave velocity predicts cardiovascular mortality in subjects >70 years of age. *Arterioscler Thromb Vasc Biol.* 2001;21(12): 2046–2050.
12. Shokawa T, Imazu M, Yamamoto H, et al. Pulse wave velocity predicts cardiovascular mortality: findings from the Hawaii-Los Angeles-Hiroshima study. *Circ J*. 2005;69(3):259–264.
13. Grey E, Bratteli C, Glasser SP, et al. Reduced small artery but not large artery elasticity is an independent risk marker for cardiovascular events. *Am J Hypertens*. 2003;16(4):265–269.
14. Dernellis J, Panaretou M. Aortic stiffness is an independent predictor of progression to hypertension in nonhypertensive subjects. *Hypertension*. 2005;45(3):426–431.
15. Najjar SS, Scuteri A, Shetty V, et al. Pulse wave velocity is an independent predictor of the longitudinal increase in systolic blood pressure and of incident hypertension in the Baltimore Longitudinal Study of Aging. *J Am Coll Cardiol*. 2008;51(14): 1377–1383.
16. Peralta CA, Adeney KL, Shlipak MG, et al. Structural and functional vascular alterations and incident hypertension in normotensive adults: the Multi-Ethnic Study of Atherosclerosis. *Am J Epidemiol*. 2010;171(1):63–71.
17. Bild DE, Bluemke DA, Burke GL, et al. Multi-Ethnic Study of Atherosclerosis: objectives and design. *Am J Epidemiol*. 2002;156(9):871–881.

18. Finkelstein SM, Cohn JN. First- and third-order models for determining arterial compliance. *J Hypertens Suppl*. 1992; 10(6):S11–S14.
19. Brumback LC, Jacobs DR Jr, Dermond N, et al. Reproducibility of arterial elasticity parameters derived from radial artery diastolic pulse contour analysis: the Multi-Ethnic Study of Atherosclerosis. *Blood Press Monit.* 2010;15(6):312–315.
20. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, et al. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;27(2):157–172.
21. Duprez DA, Jacobs DR Jr, Lutsey PL, et al. Race/ethnic and sex differences in large and small artery elasticity—results of the Multi-Ethnic Study of Atherosclerosis (MESA). *Ethn Dis*. 2009;19(3):243–250.
22. Duprez DA, Cohn JN. Arterial stiffness as a risk factor for coronary atherosclerosis. *Curr Atheroscler Rep*. 2007;9(2):139–144.
23. Mitchell GF, Hwang SJ, Vasan RS, et al. Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation*. 2010;121(4):505–511.
24. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;55(13):1318–1327.
25. Vlachopoulos C, Aznaouridis K, O'Rourke MF, et al. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. *Eur Heart J*. 2010;31(15):1865–1871.
26. Manning TS, Shykoff BE, Izzo JL Jr. Validity and reliability of diastolic pulse contour analysis (windkessel model) in humans. *Hypertension*. 2002;39(5):963–968.
27. Segers P, Qasem A, De Backer T, et al. Peripheral ''oscillatory'' compliance is associated with aortic augmentation index. *Hypertension*. 2001;37(6):1434–1439.
28. Duprez DA, Kaiser DR, Whitwam W, et al. Determinants of radial artery pulse wave analysis in asymptomatic individuals. *Am J Hypertens*. 2004;17(8):647–653.
29. Rietzschel ER, Boeykens E, De Buyzere ML, et al. A comparison between systolic and diastolic pulse contour analysis in the evaluation of arterial stiffness. *Hypertension*. 2001; 37(6):E15–E22.
30. McEniery CM, Yasmin Hall IR, et al. Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). ACCT Investigators. *J Am Coll Cardiol*. 2005;46(9):1753–1760.
31. Wilson AM, O'Neal D, Nelson CL, et al. Comparison of arterial assessments in low and high vascular disease risk groups. *Am J Hypertens*. 2004;17(4):285–291.
32. Gilani M, Kaiser DR, Bratteli CW, et al. Role of nitric oxide deficiency and its detection as a risk factor in pre-hypertension. *J Am Soc Hypertens*. 2007;1(1):45–55.
33. Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. European Network for Non-Invasive Investigation of Large Arteries. *Eur Heart J*. 2006;27(21): 2588–2605.