Original Article

Aortic Arch Pulse Wave Velocity Assessed by Magnetic Resonance Imaging as a Predictor of Incident Cardiovascular Events

The MESA (Multi-Ethnic Study of Atherosclerosis)

Yoshiaki Ohyama, Bharath Ambale-Venkatesh, Chikara Noda, Jang-Young Kim, Yutaka Tanami, Gisela Teixido-Tura, Atul R. Chugh, Alban Redheuil, Chia-Ying Liu, Colin O. Wu, W. Gregory Hundley, David A. Bluemke, Eliseo Guallar, Joao A.C. Lima

Abstract—The predictive value of aortic arch pulse wave velocity (PWV) assessed by magnetic resonance imaging for cardiovascular disease (CVD) events has not been fully established. The aim of the present study was to evaluate the association of arch PWV with incident CVD events in MESA (multi-ethnic study of atherosclerosis). Aortic arch PWV was measured using magnetic resonance imaging at baseline in 3527 MESA participants (mean age, 62±10 years at baseline; 47% men) free of overt CVD. Cox regression was used to evaluate the risk of incident CVD (coronary heart disease, stroke, transient ischemic attack, or heart failure) in relation to arch PWV adjusted for age, sex, race, and CVD risk factors. The median value of arch PWV was 7.4 m/s (interquartile range, 5.6–10.2). There was significant interaction between arch PWV and age for outcomes, so analysis was stratified by age categories (45–54 and >54 years). There were 456 CVD events during the 10-year follow-up. Forty-five to 54-year-old participants had significant association of arch PWV with incident CVD independent of CVD risk factors (hazard ratio, 1.44; 95% confidence interval, 1.07–1.95; P=0.018; per 1-SD increase for logarithmically transformed PWV), whereas >54-year group did not (P=0.93). Aortic arch PWV assessed by magnetic resonance imaging is a significant predictor of CVD events among middle-aged (45–54 years old) individuals, whereas arch PWV is not associated with CVD among an elderly in a large multiethnic population. **(*Hypertension*. 2017;70:00-00. DOI: 10.1161/HYPERTENSIONAHA.116.08749.)** ● **Online Data Supplement**

Key Words: cardiovascular diseases ■ coronary artery disease ■ heart failure ■ pulse wave analysis ■ vascular stiffness

Pulse wave velocity (PWV)—a noninvasive marker of arterial stiffness—predicts the risk of future cardiovascular disease (CVD) events and total mortality.[1–4] Arterial PWV is commonly measured using arterial applanation tonometry, an indirect method which divides the surface distance between the carotid artery and the femoral artery by the time delay of the arterial pulse between 2 sites. Carotid–femoral (cf)-PWV has been regarded as the gold standard method because of its relative ease in determination and its perceived reliability.[5] However, cf-PWV measurements by arterial tonometry may be affected by measurement error related to the surface distance of the aortic path (for instance, it does not take into account the torturous vessel routes) and related to inaccurate pulse wave detection, especially in the femoral artery.[2,6,7] Cf-PWV also has a relative blind spot for the aortic arch that normally provides nearly half of the total arterial compliance.[8]

Magnetic resonance imaging (MRI) assessment for aortic PWV is a novel method that has substantially reduced measurement error in PWV measurements by using accurate aortic length and transit times between flow waves.[9–11] MRI also allows the measurement of the aortic arch PWV that is ignored in cf-PWV assessed by tonometry. The structure of the aorta is regionally heterogeneous, so different regional PWV may have different prognostic values corresponding to differences in structural properties of the aortic wall. However, the independent association of aortic arch PWV assessed by MRI with CVD outcomes has not been established in the general population, and it is unclear whether arch PWV may improve prediction of incident CVD outcomes beyond the information provided by conventional CVD risk factors.

The aim of the present study is to assess the prospective association of aortic arch PWV from MRI with the risk of

Received November 18, 2016; first decision December 2, 2016; revision accepted June 4, 2017.

From the Department of Cardiology (Y.O., C.N., J.-Y.K., Y.T., G.T.-T., A.R.C., J.A.C.L.), Department of Radiology (B.A.-V.), and Department of Epidemiology (E.G.), Johns Hopkins University, Baltimore, MD; Imagerie Cardiovasculaire/Department of Cardiovascular Imaging DICVRI, Institut de Cardiologie, Groupe Hospitalier Pitié Salpêtrière, Paris (A.R.); Radiology and Imaging Sciences, National Institutes of Health Clinical Center, Bethesda, MD (C.-Y.L., D.A.B.); Office of Biostatistics Research, National Heart, Lung, and Blood Institute, Bethesda, MD (C.O.W.); and Department of Epidemiology and Prevention, Wake Forest School of Medicine, Winston-Salem, NC (W.G.H.).

The online-only Data Supplement is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.116.08749/-/DC1.

Correspondence to Joao A.C. Lima, Department of Cardiology, Johns Hopkins University, 600 N. Wolf St Blalock 524, Baltimore, MD 21287. E-mail jlima@jhmi.edu

incident CVD outcomes in a large multiethnic population and the predictive value of arch PWV to identify individuals who will develop CVD outcomes beyond the information provided by conventional CVD risk factors.

Method

Study Population

The MESA (multi-ethnic study of atherosclerosis) is a prospective study designed to evaluate risk factors and mechanisms that underlie the development and progression of subclinical CVDs among asymptomatic individuals across the population.[12] A total of 6814 men and women 45 to 84 years of age without clinical CVD who identified themselves as white, black, Hispanic, or Chinese from 6 US field centers (Wake Forest University, Winston-Salem, NC; Columbia University, New York, NY; Johns Hopkins Hospital, Baltimore, MD; University of Minnesota, Minneapolis, MN; Northwestern University, Chicago, IL; and University of California, Los Angeles, CA) were recruited between 2000 and 2002. Of 5098 participants who took part in the cardiac magnetic resonance (CMR) imaging examination, 3527 underwent suitable PWV measurements for analysis (173 were excluded because of poor image quality). All participants gave informed consent for the study protocol, which was approved by the institutional review boards of all MESA field centers and the CMR reading center.

MRI Imaging

MRI images were acquired with 1.5T whole-body scanners.[13] Gradient echo phase-contrast cine MRI with electrocardiographic gating was performed to evaluate aortic flow and aortic area. Images of the ascending and descending aorta were obtained in the transverse plane perpendicular to the aortic lumen at the level of the right pulmonary artery. Imaging parameters were as follows: repetition time, 10 ms; echo time, 1.9 ms; flip angle, 20 degree; field of view, 340 mm; slice thickness, 8 mm; matrix, 256×256; number of images, 20 for 1 cardiac cycle; encoding velocity, 150 cm/s; and bandwidth, 245 Hz/pixel.

By providing an automated segmentation of the modulus and velocity images acquired by phase-contrast cine MRI, ARTFUN software (INSERM U678) allowed us to obtain the flow wave transit time between the ascending to descending aorta.[14,15] The transit time was calculated as the average time difference using the least squares estimate between all data points on the systolic upslope of the ascending and descending aortic flow curves after peak flow normalization. Using oblique sagittal images with a bright-blood sequence through the thoracic aorta, the distance between ascending and descending aorta were measured at precise locations where the through-plane velocities were measured (Figure 1). Aortic arch PWV was then calculated as follows:

PWV (meters per second)=distance (millimeter)/transit time between ascending to descending (ms).

Ascending and descending aortic area at diastole were measured using the modulus images of phase-contrast cine MRI.

CMR imaging was also performed with measures of left ventricular (LV) mass as previously described.[16]

CVD Risk Factors and Measures of Subclinical Atherosclerosis

During baseline examination, all participants completed standardized questionnaires to provide information about demographic variables, smoking history, and medication use. Resting systolic (SBP) and diastolic blood pressures (DBP) were measured in the seated position using an automated oscillometric sphygmomanometer. Pulse pressure was calculated as SBP−DBP. Glucose and lipids were measured after a 12-hour fast. Diabetes mellitus was defined as fasting glucose ≥126 mg/dL or use of insulin or oral hypoglycemic medication. Hypertension was defined as SBP ≥140 mm Hg, DBP ≥90 mm Hg, or current use of antihypertensive medications. The ankle–brachial index was calculated by dividing SBP at the ankle by brachial SBP. Carotid artery intima-media thickness (IMT) was measured on near and far walls of the common and internal carotid artery using B-mode

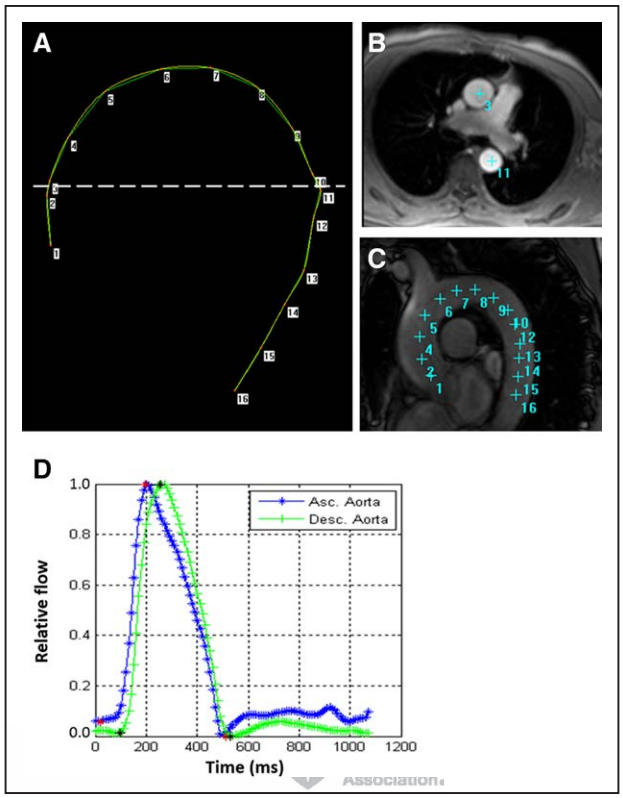

Figure 1. Measurement for aortic arch pulse wave velocity (PWV). **A**, Phase-contrast cine transverse view. **B**, Aortic arch view with steady-state free precession sequence. **C**, Measurement of the transit distance in the aortic arch. Numbers correspond to those in **A** and **B**. Arch length is measured as the distance from 3 to 11 in this case. **D**, Flow wave curves of ascending and descending aorta after peak flow normalization. Transit time is measured as the average time difference using the least squares estimate between all data points on the systolic upslope of the ascending and descending aortic flow curves. PWV is calculated as transit distance divided by transit time.

echocardiography. A composite *Z* score for overall maximal IMT was calculated by summing the 2 carotid IMT sites after normalization by the SD of each measure and divided by the SD of the sum.[17] Coronary artery calcium (CAC) score was measured by computed tomography as previously described.[17] The sex-specific global CVD Framingham 10-year risk score was calculated on the basis of the following risk factors: SBP, antihypertensive medication, total cholesterol, high-density lipoprotein cholesterol, smoking, and diabetes mellitus.[18]

Outcomes

Participants were followed for an average 10.3 years from their baseline examinations. In addition to MESA follow-up examinations every 2 years, a telephone interviewer contacted each participant (or representative) every 6 to 9 months to inquire about all interim hospital admissions, cardiovascular outpatient diagnoses, or deaths. Two physicians reviewed all records for independent end-point classification and assignment of every date. Adjudication of events has been previously described.[16] CVD events in the present study were defined as composite events, including myocardial infarction (MI), resuscitated cardiac arrest, definite or probable angina followed by coronary revascularization and definite angina not followed by coronary revascularization, death because of coronary heart disease, stroke, death because of stroke, transient ischemic attack, and congestive heart failure.

Statistical Analysis

Continuous variables are shown as mean±SD unless otherwise specified and categorical variables are shown as percentages. Normality

was evaluated by the Shapiro–Wilk *W* test, histogram, and quantile–quantile (Q–Q) plot. Comparisons between participants with or without CVD events were performed using Student *t* test and Mann–Whitney *U* test for normally and non-normally distributed data, respectively. Categorical variables are presented as frequencies and percentages and analyzed using χ^2 tests. Arch PWV were logarithmically transformed for linear and COX regression models because of its right-skewed distribution ($\log_{PWV}$).

We used Cox proportional hazards regression to analyze the associations between PWV and CVD events. We show the hazard ratio (HR) for a 1-SD increase (*Z* score) of $\log_{PWV}$ levels. Cox regression models using PWV tertile instead of $\log_{PWV}$ were also performed. Model 1 adjusted for demographic factors (age, sex, race, height, and weight) and model 2 adjusted for conventional cardiovascular risk factors (SBP, use of antihypertensive medication, diabetes mellitus, smoking status, total cholesterol, and high-density lipoprotein) adding to model 1. After model 2, further adjustment for measures of subclinical markers—including carotid IMT, ankle–brachial index, CAC, and LV mass individually and all together—was performed. Further adjustment for ascending or descending aortic area was also performed after model 2. Models that alternatively included DBP or pulse pressure instead of SBP were also evaluated. We examined the interaction of arch PWV with the age decade (45–54, 55–64, 65–74, and 75–84 years, with 75–84 chosen as the reference group) in its association with outcome using multiplicative interaction terms. This result showed that there was significant interaction between arch PWV and 45- to 54-year group (HR for interaction, 1.55; 95% confidence interval [CI], 1.13–2.13; *P*=0.007), whereas the interactions between arch PWV and the other groups are not significant (Table S1 in the online-only Data Supplement). Because of the significant interaction between arch PWV and 45- to 54-year group, analysis was repeated in age categories (45–54 and >54 years).

Unadjusted Kaplan—Meier survival curves illustrated the association between arch PWV and CVD events. The log-rank test assessed statistical significance. Receiver-operating characteristic curve analysis was used to determine optimal cutoff value for incident CVD event with arch PWV. The best cutoff point value was defined as the point with the highest sum of the sensitivity and specificity. The incremental predictive value of arch PWV above the Framingham risk score was assessed by comparing the global χ^2 values for each model and differences in Harrell C statistics. We also evaluated the added predictive ability of arch PWV for the distributions of time to CVD events using net reclassification improvement.[19] Net reclassification improvement was calculated from the Framingham predicted risk cut points of 6% and 20% at 10 years.[20]

The cross-sectional association of arch PWV with age was assessed by the piecewise linear regression model.

A 2-tailed *P* value of <0.05 was considered statistically significant. All statistical analyses were performed using Stata, version 12.0 (Stata Corp LP, College Station, TX). Net reclassification improvement and integrated discrimination improvement were calculated with the help of a STAT add-on from the Uppsala Clinical Research Center (http://www.ucr.uu.se/en/index.php/ucr-statistics/program-code/306-nri-and-idi).

Results

MESA Participant Characteristics

Demographic and clinical parameters at baseline for participants is presented in Table 1. The study population was 47% men, 36% white, 15% Chinese American, 29% African American, and 20% Hispanic, with mean age of 62±10 years. MESA participants with aortic data more often tended to be white or Hispanic and overall had a mildly lower risk profile than participants without aortic MRI data (Table S2). The median value of arch PWV was 7.4 m/s (interquartile range, 5.6–10.2). A total of 456 participants (13%) experienced CVD events for an average of 10.3-year follow-up. Participants with CVD were older and more likely to be hypertensive, diabetic, active smokers, and more likely to have increased weight, body mass index, and blood pressures, decreased high-density lipoprotein, and increased Framingham CVD risk score compared with participants without events. Arch PWV and aortic area were greater in participants with CVD events. Carotid IMT, CAC, and LV mass were greater; ankle–brachial index was smaller in participants with events.

Age-Related Change in Arch PWV

Arch PWV was greater with increasing age; however, the association of arch PWV with age was nonlinear (Figure S1). In the piecewise linear regression model, B coefficients for $\log_{PWV}$ per 10 years of age were 0.36 (standard error, 0.03) at 45 to 54 years of age and 0.10 (0.01) >55 years. The difference in slope was significant between 45 to 54 and >54 years (*P*<0.001; Figure 2). This association and slope difference remained significant even after adjusting for cardiovascular risk factors.

Relationship of Arch PWV With CVD Events

Cox proportional hazard models for all participants and for each age category are presented in Table 2. In univariate analysis, arch PWV was associated with incident CVD among all participants; however, this association was not present after adjustment for demographic variables. In age group, only 45- to 54-year-old participants had significant association of arch PWV with incident CVD in both univariate analysis (HR, 1.59; 95% CI, 1.23–2.06; *P*<0.001; per 1-SD increase for $\log_{PWV}$) and multivariate analysis adjusted for CVD risk factors (HR, 1.47; 95% CI, 1.10–1.97; *P*=0.009), whereas participants >54 years of age did not (*P*=0.93). HR for the highest tertile group for PWV was 2.37 (95% CI, 1.13–4.96) compared with lowest tertile in 45- to 54-year-old participants (Table S3). This association of arch PWV with incident CVD in 45- to 54-year-old participants was maintained after further adjusting for measures of other subclinical markers individually and together (carotid IMT, ankle–brachial index, CAC, and LV mass; Table S4). This association was maintained in models further adjusted for ascending or descending aortic area as potential confounders. Similar results were obtained in models using DBP, or pulse pressure instead of SBP (data not shown).

Goodness-of-fit and discriminatory values for arch PWV in the 45- to 54-year age group are shown in Table 3. When arch PWV was added to the Framingham risk score-adjusted model in the 45- to 54-year age group, arch PWV had an incremental predictive value, as indicated by an increase in global χ^2 values (57.9–62.7; *P*=0.03; Table 3); however, the C statistic was unchanged (0.788–0.799; *P*=0.42; Table 3). Addition of arch PWV to the Framingham risk score-adjusted model resulted in overall estimated net reclassification improvement of 0.154 (*P*=0.005; Table 3). Together, these findings indicate that the addition of arch PWV to the Framingham risk score resulted in improved risk discrimination and risk reclassification in the 45- to 54-year age group.

The area under the receiver-operating characteristic curve was 0.643 for $\log_{PWV}$ to CVD events (95% CI, 0.574–0.711; *P*=0.001) in the 45- to 54-year age group. The optimal cutoff value of arch PWV for the prediction of CVD was 6.4 m/s (sensitivity of 67% and specificity of 61%). The cumulative hazard of CVD was significantly higher in participants with arch

Table 1. Baseline Characteristics Stratified by Age Categories

Characteristics	All Participants (n=3527)	No Events (n=3071)	CVD Events (n=456)	*P* Value
Age, y	62±10	61±10	67±9	<0.001
Men, %	47	45	59	<0.001
Ethnicity, %				<0.001
White	36	35	44	
Chinese	15	16	9	
Black	29	29	27	
Hispanic	20	20	20	
Height, cm	166±10	166±10	167±10	0.19
Weight, kg	77±16	76±16	79±16	0.001
BMI, kg/m^2	27.5±4.9	27.5±4.9	28.3±4.9	0.001
Hypertension, %	45	42	66	<0.001
Antihypertensive medication, %	38	35	53	<0.001
Diabetes mellitus, %	12	11	21	<0.001
Current smoking status, %	13	12	18	0.001
Total cholesterol, mg/dL	194±34	194±34	194±36	0.99
HDL cholesterol, mg/dL	52±15	52±15	49±14	<0.001
Blood pressures				
SBP, mm Hg	126±22	125±21	137±23	<0.001
DBP, mm Hg	72.0±11	71.7±10	74±11	<0.001
PP, mm Hg	54±17	53±17	63±18	<0.001
Heart rate, bpm	63±10	63±9	64±10	0.01
PWV, m/s; median (IQR)	7.4 (5.6–10.2)	7.2 (5.5–10.1)	8.0 (6.1–11.6)	<0.001
Ascending aortic area, cm^2	7.9±2.0	7.8±1.9	8.6±2.2	<0.001
Descending aortic area, cm^2	4.5±1.3	4.5±1.3	5.0±1.3	<0.001
Framingham risk score	14.3±9.6	13.3±9.3	20.8±8.6	<0.001
Maximum internal carotic IMT, mm	1.05±0.59	1.02±0.56	1.30±0.71	<0.001
ABI	1.11±0.12	1.11±0.11	1.08±0.15	<0.001
CAC score, median (IQR)	0 (0–82)	0 (0–54)	92 (5–369)	<0.001
LV mass, g	120±30	118±28	131±36	<0.001

Values are mean (SD) or %. ABI indicates ankle–brachial index; BMI, body mass index; CAC, coronary calcium score; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein; IMT, intima media thickness; IQR, interquartile range; LV, left ventricular; PP, pulse pressure; PWV, pulse wave velocity; and SBP, systolic blood pressure.

PWV >6.4 m/s by the log-rank test in this age group (P<0.001; Figure 3A). In participants >54 years of age, the cumulative incidence of CVD events was similar between 2 groups divided by median value (PWV=8.1 m/s; P=0.40; Figure 3B).

Discussion

The present study evaluates the association of arch PWV assessed by MRI with incident CVD event in a large multiethnic population with middle age to elderly participants. Arch PWV had incremental predictive value for incident CVD above traditional CVD risk factors in participants 45 to 54 years of age. Arch PWV was not associated with incident CVD events in participants >54 years of age.

The aorta is not a simple conduit for blood distribution. The structure of aorta is regionally heterogeneous; the proximal aorta has more elastic fiber, and the distal aorta has more smooth muscle cells. The viscoelastic property of the proximal aorta provides a cushioning function that absorbs the energy of LV ejection and dampens the pulsatile flow.[21] Cf-PWV assessed by tonometry—the standard marker for arterial stiffness—omits the aortic arch,[8] so aortic arch PWV assessed by MRI may have a unique value as central aortic stiffness and could provide complementary information on aortic stiffness.

Maroules et al[22] reported that arch PWV assessed by MRI was not associated with CVD events in the Dallas heart study. This result is consistent with the present study that shows no significant association of arch PWV with CVD events in the overall MESA population. However, the present study showed that there was a strong age interaction for arch PWV with CVD. In the present study, arch PWV predicted future incidence of CVD events in 45- to 54-year-old participants but not in those >54 years in the general

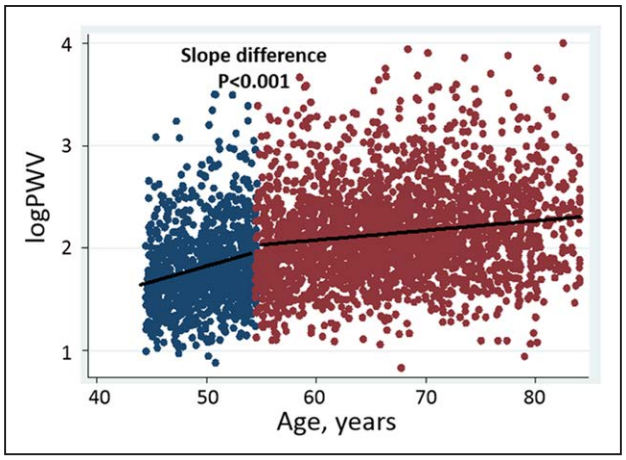

Figure 2. Association of arch pulse wave velocity (PWV) with age (blue dots, <50 years of age; red dots, ≥55 years of age).

population. For individuals 45 to 54 years of age, arch PWV is an independent predictor even after adjustment for CVD risk factors and other subclinical markers, such as ankle–brachial index, CAC, carotid IMT, and LV mass, and had incremental predictive value above Framingham risk scores. These results suggest that arch PWV may be useful for risk stratification for CVD in middle age. Along with this association of arch PWV with incident CVD, the increase in arch PWV was particularly marked in participants 45 to 54 years of age compared with those >54 years of age. This lower increase of arch PWV with advancing age is not consistent with a study that indicated a steep increase in arch PWV in the elderly compared with young adults[14] but might, in part, contribute to results in the present study.

Cf-PWV assessed by tonometry is associated with incident CVD events in the general population within a broad range of age, especially the elderly.[1,4] On the other contrary, in the present study, arch PWV can predict future incident CVD events only in middle age. This finding is partially consistent with the result of meta-analysis that demonstrated cf-PWV was a stronger risk factor among younger population, although it was still predictive in older population.[4] Cf-PWV has information on aortic stiffness, including distal aorta; therefore, including additional information in cf-PWV might contribute to the different impact on CVD event seen for cf- and arch PWV. Hickson et al[23] reported that the greater age-related increase in aortic PWV occurred in the abdominal aorta compared with the ascending aorta. Stiffening in the distal segment might be mainly caused by localized calcification, which is strongly correlated with increasing PWV.[24] This may also be important because abdominal aortic calcium deposits have been linked with independently predicting cardiovascular morbidity and mortality.[25] In addition, PWV in the proximal segment of the aorta showed the smallest association with older age, whereas this segment also showed the greatest increase in diameter with increased age, which may help offset an increase in PWV.[23]

Redheuil et al[13] reported that ascending aorta distensibility as a measure of proximal aortic stiffness is a strong predictive marker for CVD events in the MESA population. Although both arch PWV and ascending aorta distensibility represent proximal aortic stiffness, PWV indicates increased regional aortic wall stiffness, whereas distensibility, which is calculated using cross-sectional aortic area change through the cardiac cycle, represents local aortic function and is more sensitive to load. In this regard, aortic area changes across the cardiac cycle may better reflect the specific role of the proximal aorta, dampening the effect of pulsatile flow from the heart on the arterial system as a whole.[26] PWV reflects more advanced alterations of material properties involving the regional vessel. These differences might contribute to the differences in predictive power between arch PWV and ascending aorta distensibility.

Our study has limitations. Because our sample group was a relatively elderly cohort (mean age, 60 years at baseline), it is unsuitable to assess how arch PWV is associated with CVD in younger populations. We had only a modest number of events; therefore, we lacked power to examine threshold models or to analyze specific types of CVD events. We might have inflated type I error because of multiple testing. Because MESA participants had no overt CVD at baseline, the participants at baseline represent a relatively healthy sample of the population. Thus, generalization of the study results is limited by selection and survival bias. Because we did not have the cf-PWV in MESA, we could not compare arch PWV with cf-PWV regarding an association of CVD events to elucidate the impact of aortic stiffness in a differential segment on future events. We assessed only aortic arch PWV, and PWV of other segments, such as abdominal aortic PWV, was not measured in MESA. We did not assess the other variables that relate to aortic stiffness, such as augmentation index or reflection magnitude that

Table 2. HRs of the Log_{PWV} for Cardiovascular Events Stratified by Age Groups

Participants Group	No. of Events	Unadjusted		Model 1		Model 2	
		HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
All participants (n=3527)	456	1.27 (1.16–1.38)	<0.001	1.07 (0.98–1.18)	0.14	1.03 (0.94–1.14)	0.5
Age categories							
45–54 y old (n=1027)	54	1.56 (1.20–2.02)	<0.001	1.52 (1.15–2.00)	0.003	1.44 (1.07–1.95)	0.018
55–84 y old (n=2500)	402	1.08 (0.98–1.19)	0.11	1.02 (0.92–1.13)	0.64	0.99 (0.90–1.10)	0.93

HRs are indicated per 1-SD increase for log_{PWV}. Adjustment was performed for the following risk factors: model 1=adjusted for age, sex, race, height, and weight; model 2=model 1+systolic blood pressure, antihypertensive medication use, diabetes mellitus, smoking, total cholesterol, and high-density lipoprotein cholesterol. CI indicates confidence interval; and HR, hazard ratio.

Table 3. Measures of Model Fit and Discrimination for Models With and Without PWV in 45 to 54 y of Age

Models		Estimate	*P* Value
Model without PWV	C statistic	0.788 (95% CI, 0.723–0.853)	<0.001
	LR χ^2	57.9	
Model with PWV	C statistic	0.799 (95% CI, 0.738–0.860)	<0.001
	LR χ^2	62.7	
Comparing models with or without $\log_{PWV}$			
Difference between C statistics			0.42
LR test		4.8	0.03
NRI		0.154	0.006

Model without PWV was adjusted for Framingham risk score (FRS). Model with PWV was adjusted for FRS and $\log_{PWV}$. CI indicates confidence interval; LR, likelihood ratio; NRI, net reclassification in improvement; and PWV, pulse wave velocity.

represents wave reflections, and characteristic impedance that is the highly recommended measurement in assessment of arterial stiffness.[27,28] Future study should be conducted to assess whether other variables will have impact on future cardiac events and how other variables relate to arch PWV. The increased wave reflection with greater age might have differential influence on ascending and descending flow wave forms,[29] resulting in increased difficulty to reliably assess short transit times. However, the impact of reflected waves on global flow curves is usually seen after systolic peak flow[30] and minimally alters the upslopes that are used to calculate transit time in the present study. We acknowledge moderate temporal resolution to be a potential limitation in the present study. The strength of our study is a large sample size and the assessment for arch PWV by a sophisticated methodology using MRI.

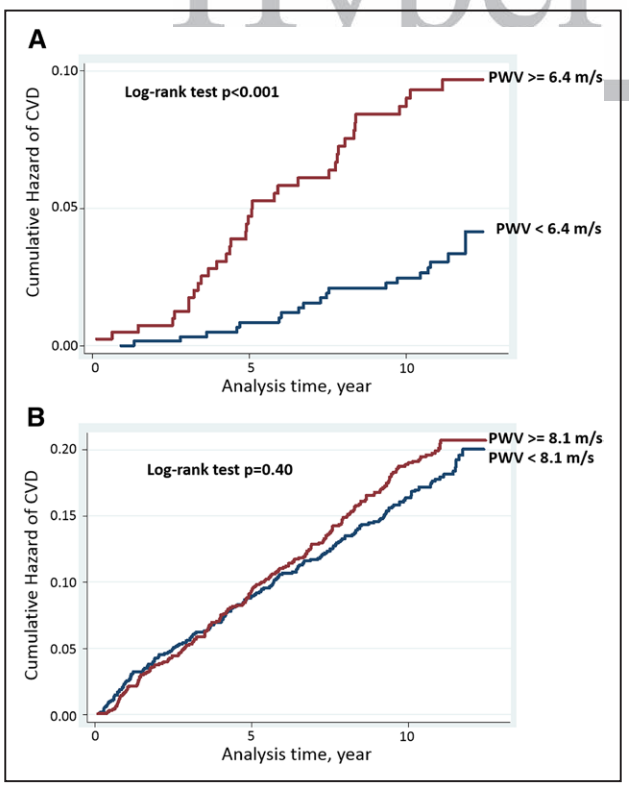

Figure 3. Kaplan—Meier curve for cardiovascular disease (CVD) event according to pulse wave velocity (PWV) in participants aged 45 to 54 (**A**) and >55 years (**B**).

Perspective

Previous studies demonstrated a steep increase in cf-PWV in the elderly compared with young adults, whereas the present study showed that the increase in arch PWV was particularly marked in a middle-aged population compared with an elderly population. Along with this association of age with arch PWV, arch PWV was associated with incident CVD only in participants 45 to 54 years of age in the present study. Other arterial stiffness markers, such as cf-PWV, are associated with incident CVD in the general population. These findings imply that proximal aortic stiffness would occur earlier compared with distal and arch PWV assessed by MRI would be more helpful to stratify the risk for incident CVD among middle-aged population compared with other arterial stiffness markers. Moreover, measurement for arch PWV by MRI has high interstudy reproducibility,[31,32] so arch PWV would be used as an surrogate measure for CVD in the evaluation of pharmacological treatment.

Conclusion

The present study demonstrates that arch PWV assessed by MRI is a significant predictor of CVD events in a middle-aged population but is not associated with CVD among an elderly population. The incremental value of arch PWV was seen in a 45- to 54-year-old population. The differential segment of aortic stiffness may have a different impact on outcomes among a different population. Future studies need to assess the association of arch PWV with CVD in younger adults.

Acknowledgments

We thank the other investigators, staff, and participants of the MESA study (multi-ethnic study of atherosclerosis) for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

Sources of Funding

This research was supported by contracts N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, and N01-HC-95168 from the National Heart, Lung, and Blood Institute.

Disclosures

None.

References

1. 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;55:1318–1327. doi: 10.1016/j.jacc.2009.10.061.
2. Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, Vita JA, Levy D, Benjamin EJ. Arterial stiffness and cardiovascular events: the Framingham heart study. *Circulation*. 2010;121:505–511. doi: 10.1161/CIRCULATIONAHA.109.886655.
3. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, Ducimetiere P, Benetos A. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension*. 2001;37:1236–1241.
4. Ben-Shlomo Y, Spears M, Boustred C, et al. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant

meta-analysis of prospective observational data from 17,635 subjects. *J Am Coll Cardiol*. 2014;63:636–646. doi: 10.1016/j.jacc.2013.09.063.
5. Mancia G, De Backer G, Dominiczak A, et al. 2007 Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European society of hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2007;28:1462–1536. doi: 10.1093/eurheartj/ehm236.
6. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H; European network for non-invasive investigation of large arteries. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J*. 2006;27:2588–2605. doi: 10.1093/eurheartj/ehl254.
7. Chiu YC, Arand PW, Shroff SG, Feldman T, Carroll JD. Determination of pulse wave velocities with computerized algorithms. *Am Heart J*. 1991;121:1460–1470.
8. Mitchell GF. Arterial stiffness and wave reflection: biomarkers of cardiovascular risk. *Artery Res*. 2009;3:56–64. doi: 10.1016/j.artres.2009.02.002.
9. Grotenhuis HB, Westenberg JJ, Steendijk P, van der Geest RJ, Ottenkamp J, Bax JJ, Jukema JW, de Roos A. Validation and reproducibility of aortic pulse wave velocity as assessed with velocity-encoded MRI. *J Magn Reson Imaging*. 2009;30:521–526. doi: 10.1002/jmri.21886.
10. Fielden SW, Fornwalt BK, Jerosch-Herold M, Eisner RL, Stillman AE, Oshinski JN. A new method for the determination of aortic pulse wave velocity using cross-correlation on 2D PCMR velocity data. *J Magn Reson Imaging*. 2008;27:1382–1387. doi: 10.1002/jmri.21387.
11. Cavalcante JL, Lima JA, Redheuil A, Al-Mallah MH. Aortic stiffness: current understanding and future directions. *J Am Coll Cardiol*. 2011;57:1511–1522. doi: 10.1016/j.jacc.2010.12.017.
12. Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. *Am J Epidemiol*. 2002;156:871–881.
13. Redheuil A, Wu CO, Kachenoura N, Ohyama Y, Yan RT, Bertoni AG, Hundley GW, Duprez DA, Jacobs DR Jr, Daniels LB, Darwin C, Sibley C, Bluemke DA, Lima JA. Proximal aortic distensibility is an independent predictor of all-cause mortality and incident CV events: the MESA study. *J Am Coll Cardiol*. 2014;64:2619–2629. doi: 10.1016/j.jacc.2014.09.060.
14. Redheuil A, Yu WC, Wu CO, Mousseaux E, de Cesare A, Yan R, Kachenoura N, Bluemke D, Lima JA. Reduced ascending aortic strain and distensibility: earliest manifestations of vascular aging in humans. *Hypertension*. 2010;55:319–326. doi: 10.1161/HYPERTENSIONAHA.109.141275.
15. Dogui A, Redheuil A, Lefort M, DeCesare A, Kachenoura N, Herment A, Mousseaux E. Measurement of aortic arch pulse wave velocity in cardiovascular MR: comparison of transit time estimators and description of a new approach. *J Magn Reson Imaging*. 2011;33:1321–1329. doi: 10.1002/jmri.22570.
16. Bluemke DA, Kronmal RA, Lima JA, Liu K, Olson J, Burke GL, Folsom AR. The relationship of left ventricular mass and geometry to incident cardiovascular events: the MESA (multi-ethnic study of atherosclerosis) study. *J Am Coll Cardiol*. 2008;52:2148–2155. doi: 10.1016/j.jacc.2008.09.014.
17. Folsom AR, Kronmal RA, Detrano RC, O'Leary DH, Bild DE, Bluemke DA, Budoff MJ, Liu K, Shea S, Szklo M, Tracy RP, Watson KE, Burke GL. 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;168:1333–1339. doi: 10.1001/archinte.168.12.1333.
18. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham heart study. *Circulation*. 2008;117:743–753. doi: 10.1161/CIRCULATIONAHA.107.699579.
19. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;27:157–172, discussion 207. doi: 10.1002/sim.2929.
20. Polak JF, Pencina MJ, Pencina KM, O'Donnell CJ, Wolf PA, D'Agostino RB Sr. Carotid-wall intima-media thickness and cardiovascular events. *N Engl J Med*. 2011;365:213–221. doi: 10.1056/NEJMoa1012592.
21. O'Rourke MF, Hashimoto J. Mechanical factors in arterial aging: a clinical perspective. *J Am Coll Cardiol*. 2007;50:1–13. doi: 10.1016/j.jacc.2006.12.050.
22. Maroules CD, Khera A, Ayers C, Goel A, Peshock RM, Abbara S, King KS. Cardiovascular outcome associations among cardiovascular magnetic resonance measures of arterial stiffness: the Dallas heart study. *J Cardiovasc Magn Reson*. 2014;16:33. doi: 10.1186/1532-429X-16-33.
23. Hickson SS, Butlin M, Graves M, Taviani V, Avolio AP, McEniery CM, Wilkinson IB. The relationship of age with regional aortic stiffness and diameter. *JACC Cardiovascular Imaging*. 2010;3:1247–1255. doi: 10.1016/j.jcmg.2010.09.016.
24. McEniery CM, McDonnell BJ, So A, Aitken S, Bolton CE, Munnery M, Hickson SS, Yasmin, Maki-Petaja KM, Cockcroft JR, Dixon AK, Wilkinson IB; Anglo-Cardiff Collaboration Trial Investigators. Aortic calcification is associated with aortic stiffness and isolated systolic hypertension in healthy individuals. *Hypertension*. 2009;53:524–531. doi: 10.1161/HYPERTENSIONAHA.108.126615.
25. Wilson PW, Kauppila LI, O'Donnell CJ, Kiel DP, Hannan M, Polak JM, Cupples LA. Abdominal aortic calcific deposits are an important predictor of vascular morbidity and mortality. *Circulation*. 2001;103:1529–1534.
26. Redheuil A. Cardiovascular aging: insights from local and regional measures of aortic stiffness using magnetic resonance imaging. *Artery Research*. 2014;8:66–72.
27. Townsend RR, Wilkinson IB, Schiffrin EL, Avolio AP, Chirinos JA, Cockcroft JR, Heffernan KS, Lakatta EG, McEniery CM, Mitchell GF, Najjar SS, Nichols WW, Urbina EM, Weber T, American Heart Association Council on Hypertension. Recommendations for improving and standardizing vascular research on arterial stiffness: a scientific statement from the American Heart Association. *Hypertension*. 2015;66:698–722. doi: 10.1161/HYP.0000000000000033.
28. Adji A, Kachenoura N, Bollache E, Avolio AP, O'Rourke MF, Mousseaux E. Magnetic resonance and applanation tonometry for noninvasive determination of left ventricular load and ventricular vascular coupling in the time and frequency domain. *J Hypertens*. 2016;34:1099–1108. doi: 10.1097/HJH.0000000000000925.
29. Miyashita H, Ikeda U, Tsuruya Y, Sekiguchi H, Shimada K, Yaginuma T. Noninvasive evaluation of the influence of aortic wave reflection on left ventricular ejection during auxotonic contraction. *Heart Vessels*. 1994;9:30–39.
30. Bensalah MZ, Bollache E, Kachenoura N, Giron A, De Cesare A, Macron L, Lefort M, Redheuil A, Redheuill A, Mousseaux E. Geometry is a major determinant of flow reversal in proximal aorta. *Am J Physiol Heart Circ Physiol*. 2014;306:H1408–H1416. doi: 10.1152/ajpheart.00647.2013.
31. Noda C, Ambale Venkatesh B, Ohyama Y, Liu CY, Chamera E, Redheuil A, Teixido-Tura G, Chugh AR, Wu CO, Hundley GW, Bluemke DA, Lima JA. Reproducibility of functional aortic analysis using magnetic resonance imaging: the MESA. *Eur Heart J Cardiovasc Imaging*. 2016;17:909–917. doi: 10.1093/ehjci/jev215.
32. Ohyama Y, Teixido-Tura G, Ambale-Venkatesh B, et al. Ten-year longitudinal change in aortic stiffness assessed by cardiac MRI in the second half of the human lifespan: the multi-ethnic study of atherosclerosis. *Eur Heart J Cardiovasc Imaging*. 2016;17:1044–1053. doi: 10.1093/ehjci/jev332.

Novelty and Significance

What Is New?

- We measured arch PWV by a sophisticated methodology using MRI in a large multiethnic cohort. We showed significant interaction of arch PWV with the age in its association.

What Is Relevant?

- Arch PWV increased steeply in a middle-aged population compared with an elderly population. Along with this finding, arch PWV was associated with incident CVD events only in a middle-aged population.

Summary

Aortic arch PWV assessed by MRI is a significant predictor of CVD events among middle-aged (45–54 years old) individuals, whereas arch PWV is not associated with CVD among an elderly in a large multiethnic population.

Hypertension
Journal of the American Heart Association

Aortic Arch Pulse Wave Velocity Assessed by Magnetic Resonance Imaging as a Predictor of Incident Cardiovascular Events: The MESA (Multi-Ethnic Study of Atherosclerosis)

Yoshiaki Ohyama, Bharath Ambale-Venkatesh, Chikara Noda, Jang-Young Kim, Yutaka Tanami, Gisela Teixido-Tura, Atul R. Chugh, Alban Redheuil, Chia-Ying Liu, Colin O. Wu, W. Gregory Hundley, David A. Bluemke, Eliseo Guallar and Joao A.C. Lima

Hypertension. published online July 3, 2017;
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0194-911X. Online ISSN: 1524-4563

ONLINE SUPPLEMENT

Aortic Arch Pulse Wave Velocity Assessed by MRI as a Predictor of Incident Cardiovascular Events: The Multi-Ethnic Study of Atherosclerosis (MESA)

Yoshiaki Ohyama[1], Bharath Ambale-Venkatesh[2], Chikara Noda[1], Jang-Young Kim[1], Yutaka Tanami[1], Gisela Teixido-Tura[1], Atul R.Chugh[1], Alban Redheuil[3], Chia-Ying Liu[4], Colin O.Wu[5], W.Gregory Hundley[6], David A. Bluemke[4], Eliseo Guallar[7], Joao A.C. Lima[1].

[1]Department of cardiology, Johns Hopkins University, Baltimore, MD, USA

[2]Department of radiology, Johns Hopkins University, Baltimore, MD, USA

[3]Imagerie Cardiovasculaire/Cardiovascular Imaging DICVRI, Institut de Cardiologie, Groupe Hospitalier Pitié Salpêtrière, Paris

[4]National Institutes of Health Clinical Center, Bethesda, MD

[5]National Heart, Lung and Blood Institute, Bethesda, MD

[6]Department of Epidemiology and Prevention, Wake Forest School of Medicine, Winston-Salem, NC

[7]Departement of Epidemiology, Johns Hopkins University, Baltimore, MD, USA

Corresponding author:

Joao A.C. Lima

600 N. Wolf St. / Blalock 524, Baltimore, MD, 21287

Phone: +01 443-529-7537

Fax: +01 410-614-8222

E-mail: jlima@jhmi.edu

Table S1. Interaction of arch PWV with the age decade (45-54, 55-64, 65-74, 75-84 years, with 75-84 chosen as the reference group) in its association with incident CV events.

Dependent variables	HR (95% CI)	p
zlogPWV	0.97 (0.82-1.16)	0.76
Age categories (ref: age 75-84)		
age1 (45-54)	0.23 (0.16-0.34)	<0.001
age2 (55-64)	0.37 (0.27-0.50)	<0.001
age3 (65-74)	0.59 (0.46-0.76)	<0.001
Interaction term (ref: (age 75-84)*zlogPWV)		
age1*zlogPWV	**1.55 (1.13-2.13)**	**0.007**
age2*zlogPWV	1.00 (0.77-1.32)	0.97
age3*zlogPWV	1.05 (0.84-1.32)	0.66

Adjustment was performed for gender, race, height, weight, systolic blood pressure, diabetes, total cholesterol, HDL, anti-hypertensive medication.

Table S2. Baseline Characteristics Stratified by Participants with and without Aortic MRI

Characteristics	Participants with Aortic MRI (n=3,527)	Participants without Aortic MRI (n=3,287)	p value
Age, y	62 ± 10	62 ± 10	0.65
Men, %	47	47	0.89
Ethnicity, %			<0.001
White	36	41	
Chinese	15	8	
Black	29	27	
Hispanic	20	24	
Height, cm	166 ± 10	167 ± 10	0.19
Weight, kg	77 ± 16	81 ±18	<0.001
BMI, kg.m-2	27.5 ± 4.9	29.2 ± 5.9	<0.001
Hypertension, %	45	45	0.37
Antihypertensive medication, %	38	37	0.79
Diabetes mellitus, %	12	13	0.08
Current Smoking status, %	13	13	0.77
Total cholesterol, mg/dl	194 ± 34	194 ± 37	0.41
HDL cholesterol, mg/dl	52 ± 15	50 ± 15	0.002
Blood pressures			
SBP, mmHg	126 ± 22	127 ± 21	0.5

DBP, mmHg	72 ± 11	72 ± 10	0.62
MBP, mmHg	90 ± 13	90 ± 12	0.91
PP, mmHg	54 ± 17	55 ± 17	0.26
Heart rate, bpm	63 ± 10	63 ± 10	0.05
PWV, m/s, median (IQR)	7.4 (5.6-10.2)	n/a	
Ascending aortic area, cm2	7.9 ± 2.0	n/a	
Descending aortic area, cm2	4.5 ± 1.3	n/a	
Framingham risk score	14.3 ± 9.6	14.7 ± 9.6	<0.001
Maximum internal carotic IMT, mm	1.05 ± 0.59	1.09 ± 0.62	0.008
ABI	1.11 ± 0.12	1.12 ± 0.12	<0.001
CAC score, median (IQR)	0 (0-82)	1.4 (0-96)	0.09
LV mass, g	120 ± 30	n/a	

Values are expressed by mean and SD.

Abbreviation as in Table 1.

Table S3. Hazard Ratios of the PWV tertile for Cardiovascular Events Stratified by Age Groups

PWV tertile	no.of events	Unadjusted HR (95% CI)	p	Model1 HR (95% CI)	p	Model2 HR (95% CI)	p
Whole pupulation (n=3,527)	456						
PWV tertile 1 (n=1,176)	115	ref		ref		ref	
PWV tertile 2 (n=1,176)	159	**1.43 (1.13-1.83)**	**0.003**	1.09 (0.85-1.39)	0.515	1.04 (0.81-1.33)	0.778
PWV tertile 3 (n=1,175)	182	**1.72 (1.36-2.17)**	**<0.001**	1.14 (0.89-1.45)	0.296	1.05 (0.82-1.35)	0.681
Age group							
45-54 years old (n=1,027)	54						
PWV tertile 1* (n=343)	10	ref		ref		ref	
PWV tertile 2* (n=342)	13	1.33 (0.58-3.04)	0.495	1.13 (0.49-2.59)	0.774	0.93 (0.40-2.15)	0.866
PWV tertile 3* (n=342)	31	**3.32 (1.63-6.78)**	**0.001**	**3.07 (1.48-6.35)**	**0.003**	**2.37 (1.13-4.96)**	**0.022**
55-84 years old (n=2,500)	402						
PWV tertile 1† (n=833)	129	ref		ref		ref	
PWV tertile 2† (n=834)	125	0.96 (0.74-1.23)	0.773	0.94 (0.73-1.20)	0.613	0.91 (0.71-1.17)	0.464
PWV tertile 3† (n=833)	148	1.21 (0.96-1.54)	0.108	1.08 (0.85-1.37)	0.541	1.02 (0.80-1.30)	0.869

PWV tertile 1 corresponds to low tertile and tertile 3 to high tertile for PWV. In age stratified analysis, PWV tertile was defined in each age group (* for 45-54 years old, † for 55-84 years old). Adjustment was performed for the following risk factors: model 1 = adjusted for age, gender, race, height, and weight; model 2 = model 1 + systolic blood pressure, antihypertensive medication use, diabetes, smoking, total cholesterol, HDL cholesterol, BMI.

Abbreviation as in Table 1 and 2.

Table S4. Hazard Ratios of the logPWV for Cardiovascular Events after adjusting measures of subclinical markers in age 45-54 group.

Subclinical CVD markers	Model1		Model2		Model3		Model4		Model5	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
PWV	**1.48 (1.09-2.00)**	**0.01**	**1.49 (1.10-2.01)**	**0.009**	**1.50 (1.11-2.03)**	**0.008**	**1.47 (1.09-1.97)**	**0.012**	**1.52 (1.12-2.08)**	**0.008**
CAC (present)	1.74 (0.98-3.10)	0.06							1.64 (0.91-2.96)	0.098
ABI (<1.0 or ≧1.4)			**2.55 (1.15-5.63)**	**0.021**					**2.44 (1.11-5.36)**	**0.026**
Carotid IMT					0.93 (0.63-1.35)	0.69			0.91 (0.61-1.36)	0.65
LV mass							1.00 (0.99-1.01)	0.45	1.00 (0.99-1.01)	0.71

Hazard ratio for PWV is indicated per 1SD increase for logPWV. Adjustment was performed for the risk factors (age, gender, race, height, weight, systolic blood pressure, antihypertensive medication use, diabetes, smoking, total cholesterol, HDL cholesterol, BMI) and subclinical markers individually (CAC; model1, ABI; model2, Carotid IMT; model3, LV mass; model4) and all together (model5).

Abbreviation shown as in Table 1 and Table2.

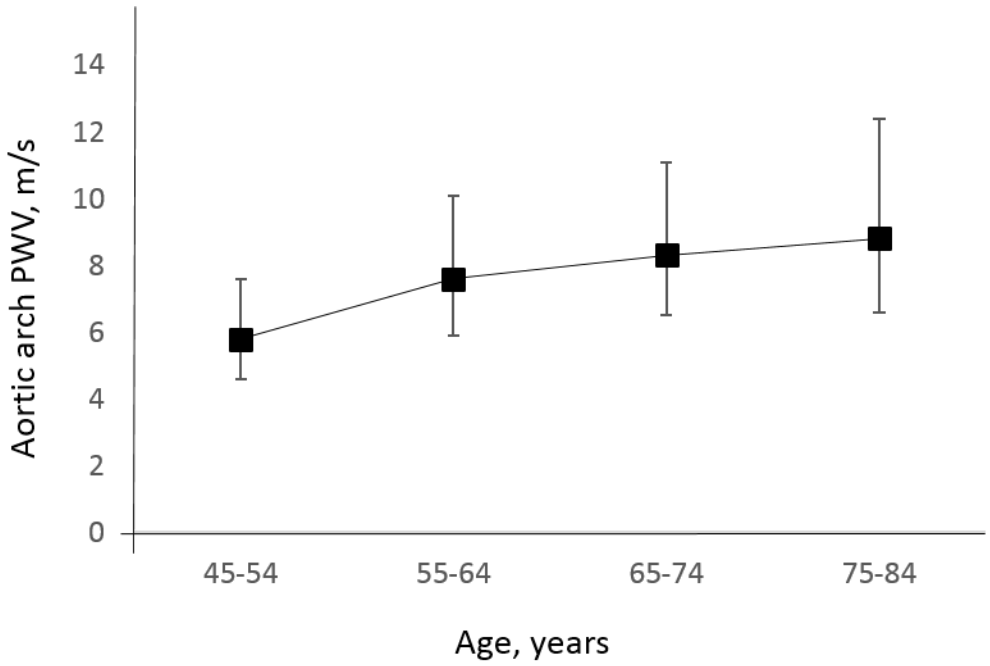

Figure S1. The association of arch PWV (original value) with age decade

Dots indicate median value and bars indicate 25%ile and 75%ile for each age decade. Lines connect each dots.