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Permalink

<https://escholarship.org/uc/item/0b0578d9>

Journal

Angiology, 69(5)

ISSN

0003-3197

Authors

Cohoon, Kevin P
Criqui, Michael H
Budoff, Matthew J
et al.

Publication Date

2018-05-01

DOI

10.1177/0003319717730636

Peer reviewed

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Angiology
1-6
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DOI: 10.1177/0003319717730636
journals.sagepub.com/home/ang

Kevin P. Cohoon, DO, MSc^{1,*}, Michael H. Criqui, MD, MPH²,
Matthew J. Budoff, MD³, Joao A. Lima, MD⁴, Michael J. Blaha, MD⁵,
Paul A. Decker, MS⁶, Ramon Durazo, PhD⁷, Kiang Liu, PhD⁸,
and Holly Kramer, MD⁷

Abstract

Data are limited on whether valvular calcification is associated with aortic wall stiffness. We tested whether aortic valve calcification (AVC) and/or mitral valve calcification (MVC) is inversely associated with aortic distensibility (AD). Cross-sectional study conducted in a subset of the Multi-Ethnic Study of Atherosclerosis (MESA) included 3676 MESA participants aged 44 to 84 years with AD measured with magnetic resonance imaging and with AVC and MVC measured with noncontrast cardiac computed tomography scans. Both AVC and MVC were divided into 3 categories: zero, < median values (low), and $\geq$ median values (high) for patients with nonzero values. Overall, 88% (n = 3256) and 92% (n = 3365) of participants had zero AVC and MVC, while 6% (n = 211) and 4% (n = 156) had low, and 6% (n = 209) and 4% (n = 155) had high values of AVC and MVC, respectively. The AVC was independently associated with AD after adjusting for age, gender, and ethnicity ($P = .035$). No association was noted between AVC groups and AD after adjustment for all covariates or MVC groups and AD in any model.

Keywords

aortic wall distensibility, mitral valve calcification, aortic valve calcification, Multi-Ethnic Study of Atherosclerosis

Introduction

Aortic distensibility (AD) participates in preserving normal function of the left ventricle and coronary blood flow.¹⁻³ The aorta develops rigidity when the normal aortic function is compromised, resulting in less AD.⁴ There is cultivating evidence that reductions in AD reflect premature atherosclerosis⁴⁻⁹ and predict future risk of hypertension¹⁰ and cardiovascular events,^{11,12} independent of traditional risk factors. Decreased AD has also been associated with increased microvascular disease¹³ within the heart,¹⁴ brain,¹³ and kidneys.¹⁵⁻¹⁷ Moreover, a recent report demonstrated that reductions in AD are independently associated with all-cause mortality and hard cardiovascular death (ie, myocardial infarction, death from coronary heart disease, resuscitated cardiac arrest, stroke, or stroke death) among individuals without overt cardiovascular disease (CVD) at baseline.¹⁸

Mitral valve calcification (MVC) and aortic valve calcification (AVC) are more often detected in the elderly patients and are frequently accompanied by coronary artery disease, aortic atheroma, or peripheral artery disease. Individuals older than 65 years have a 25% prevalence of developing AVC.¹⁹ Despite the well-established association between AD and future risk of

¹ Department of Cardiovascular Diseases, Gonda Vascular Center, Mayo Clinic, Rochester, MN, USA

² Department of Family Medicine and Public Health, University of California, San Diego, San Diego, CA, USA

³ Department of Internal Medicine, LA Biomedical Research Institute at Harbor-UCLA, Torrance, CA, USA

⁴ Division of Cardiology and Radiology, Johns Hopkins University, Baltimore, MD, USA

⁵ The Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore, MD, USA

⁶ Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA

⁷ Department of Preventive Health Sciences, Stritch School of Medicine, Loyola University Chicago, Chicago, IL, USA

⁸ Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Corresponding Author:

Kevin P. Cohoon, Department of Cardiovascular Diseases, Gonda Vascular Center, Mayo Clinic, 200 First Street, SW, Rochester, MN 55905, USA.
Email: cohoon.kevin@mayo.edu

*Current Address: Kevin P. Cohoon; Division of Cardiology and Vascular Surgery, University of Wisconsin School of Medicine and Public Health; 600 Highland Avenue; Madison, WI 53705, USA.
Email: kpcphoon@medicine.wisc.edu

cardiovascular events,¹⁸ there is a paucity of data assessing whether MVC or AVC is associated with stiffness of the aortic wall and decreased AD. Increased AVC and MVC serves as risk factors for CVD and atherosclerosis-hyperlipidemia, hypertension, elevated C-reactive protein, tobacco use, and diabetes mellitus. Combining magnetic resonance imaging (MRI) and cardiac computed tomography (CT) for participants in the Multi-Ethnic Study of Atherosclerosis (MESA) afforded us the opportunity to evaluate the association between AD and MVC and AVC with adjustment for covariates including demographics and cardiovascular risk factors such as hypertension, diabetes mellitus, and cigarette use, among adults without established CVD. We hypothesized that AD will be inversely associated with the presence and severity of AVC and MVC.

Methods

Study Population

The MESA study methods have been previously described in detail.²⁰ In summary, the MESA is a population-based study of 6814 men and women aged 45 to 84 years who were free of clinical CVD at enrollment. Participants were enrolled from 6 field site communities located in the United States, including Los Angeles County, California (UCLA); Chicago, Illinois (Northwestern University); Baltimore/Baltimore County, Maryland (Johns Hopkins University); St Paul, Minnesota (University of Minnesota); Forsyth County, North Carolina (Wake Forest University); and Northern Manhattan/Bronx, New York (Columbia University). Race/ethnicity was based on self-report questionnaires including 2622 (38%) non-Hispanic white, 1893 (28%) African, 1496 (22%) Hispanic, and 803 (12%) Chinese American who enrolled between August 1, 2000, and July 30, 2002. Of the 6814 participants in MESA, we limited the analyses of participants who underwent an MRI of the heart ($n = 3676$) for calculation of AD. All 3676 participants in MESA who had an MRI for AD measurement also underwent a cardiac CT scan to evaluate for AVC and MVC. Institutional review board approval was obtained at all MESA field sites, and all participants provided written informed consent.

Measurements of AD

Magnetic resonance imaging was performed at baseline to consenting participants with no contraindications using 1.5-T scanners. Magnetic resonance imaging of the aorta was performed with electrocardiographic gating using a double inversion recovery black-blood fast spin-echo sequence. Gradient echo phase-contrast cine MRI was performed to evaluate the distensibility of the aorta. Images of the ascending and descending aorta were obtained perpendicular to aortic lumen at the level of the right pulmonary artery in the transverse plane. To determine AD, the maximum and minimum cross-sectional areas of the ascending aorta were acquired using an automated contour routine using the software FLOW (Medis Medical Imaging Systems, Leiden, the

Netherlands). The AD was calculated as (maximum area – minimum area)/(minimum area $\times$ pulse pressure $\times$ 1000).²⁰ The MRI reader was blinded to all variables of the study except their identification numbers.

Measurements of AVC and MVC

Both AVC and MVC were measured by cardiac CT as part of the baseline MESA examination and were performed in duplicate in all participants. The details about the equipment, scanning methods, image calibration, interstudy reproducibility of measurements, and quality control in MESA have been previously described in detail.^{21,22} In summary, electron beam tomography (Imatron C150 scanner; GE Medical Systems, Milwaukee, Wisconsin) or multidetector CT scanners (4-slice) were used at 6 field sites. Electron beam tomography (0.68 mm $\times$ 0.68 mm $\times$ 3.00 mm) spatial resolution was 1.38 and 1.15 mm³ for the multidetector CT (0.68 mm $\times$ 0.68 mm $\times$ 2.50 mm). The CT scans were examined by a single blinded reader (J.T.) at a central reading center in Los Angeles, California (Harbor–UCLA Research and Education Institute). The AVC was identified as any calcified lesion within the aortic valve leaflets, as described previously.^{23–25} Calcified lesions that involved the coronary arteries, annulus, sinuses, or wall of the ascending aorta were not classified as AVC.^{23–25} The AVC was computed for each individual lesion using the method of Agatston et al.²⁶ Individual lesion measurements were then summed to generate an overall Agatston score. In the absence of AVC, the Agatston score was documented as 0. The MVC was defined in a similar manner. We categorized AVC and MVC into 3 groups: zero calcium (zero), <median (low), and $\geq$ median (high) for nonzero calcium scores. Annular calcification was not included in any of the analysis.

Demographic and Clinical Information

Medical history, laboratory data, and anthropometric measurements for the present study included data from Exam1. Information about sex, age, and medical history was acquired by standardized questionnaires. Resting systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured 3 times with participants in the seated position using an automated oscillometric sphygmomanometer; the average of the second and third measurements was used in the analysis. Hypertension was defined as SBP $\geq$ 140 mm Hg, DBP $\geq$ 90 mm Hg, or current use of blood pressure-lowering medication. Cholesterol and glucose levels were measured from blood samples obtained after a 12-hour fast. The Friedewald equation was used to calculate low-density lipoprotein (LDL) cholesterol.²⁷ Elevated levels of total cholesterol, LDL cholesterol, and triglycerides were defined as $\geq$ 240 mg/dL, $\geq$ 160 mg/dL, and $\geq$ 150 mg/dL, respectively. Reduced levels of high-density lipoprotein (HDL) cholesterol were defined as <40 mg/dL. Hyperlipidemia was defined as presence of abnormal lipid levels or use of lipid-lowering medications. The lipid levels were defined according to third report of the National Cholesterol Education Program (Adult Treatment

Panel III).²⁸ Smoking status was reported as current smoking, former smoking, or never smoking. Diabetes was defined as a fasting plasma glucose ≥ 126 mg/dL or use of glucose-lowering medications.

Statistical Methods

The associations of participant characteristics with AVC and MVC groups were assessed using multinomial logistic regression with a generalized logit to determine whether patient characteristics differentiated AVC/MVC groups; age was included as a covariate. Aortic distensibility was log transformed for all analyses, and unadjusted geometric means with 95% confidence intervals (95% CIs) were presented when appropriate. Categorical data were expressed as counts (percentages) and continuous data as means (standard deviation [SD]) or median (range). The association of AVC and MVC with AD was assessed using multivariable regression models with AD as the dependent variable and AVC and MVC groups as independent variables. For each predictor, AVC and MVC, 2 models were assessed; model 1 included age, gender, and race as covariates, and model 2 included diabetes, hypertension, body mass index, and smoking status as covariates in addition to model 1 variables. Assumptions of linearity were evaluated using generalized additive models. Two-way interactions were assessed in each model as appropriate. Analyses were conducted in SAS version 9.02 (SAS Institute, Cary, North Carolina). In all cases, P values $< .05$ were considered statistically significant.

Results

Participant Population

Among the 3676 MESA participants, the mean (SD) participant age was 60.5 (10) years (range: 44–84 years); 54% of participants were female (Table 1); and race/ethnicity distribution was 43% white, 29% African American, 17% Hispanic, and 11% Chinese.

Observed Valvular and AD Comparisons

Table 2 provides the demographic and clinical characteristics, stratified by AVC and MVC groups (zero, low, high). Overall, 88% ($n = 3256$) and 92% ($n = 3365$) had zero AVC and MVC, respectively, while 6% ($n = 211$) and 4% ($n = 156$) had low AVC and MVC, respectively. High AVC and MVC were noted in 6% ($n = 209$) and 4% ($n = 155$), respectively. While severe aortic stenosis has been defined using CT scan,²⁹ the number of patients in the MESA cohort with AVC > 1274 AU (292 AU/cm²) in women ($n = 3$) and > 2065 AU (476 AU/cm²) in men ($n = 3$) was insufficient for us to study. Age significantly increased from noncalcified aortic and mitral valves compared to those with high calcification. Those with high AVC were significantly more likely to be male and a former smoker compared to zero AVC. The LDL cholesterol was found to be significantly higher in the nonzero AVC and only in the high MVC group (not all nonzero MVC groups) when compared to the zero AVC and MVC groups, respectively. In contrast, HDL

Table 1. Baseline Characteristics of the Participants With Aortic Wall Distensibility and Valvular Calcification Measured.^a

Patient Characteristics (n = 3676)	
Age, mean (SD)	60.5 (10.0)
Gender	
Female	1993 (54.2%)
Male	1683 (45.8%)
Race	
White	1574 (42.8%)
Chinese	399 (10.9%)
Black	1075 (29.2%)
Hispanic	628 (17.1%)
Hypertension	1526 (41.5%)
Diabetes	373 (10.2%)
Cigarette smoking status	
Never	1876 (51.2%)
Former	1303 (35.6%)
Current	483 (13.2%)
BMI, mean (SD)	27.8 (5.0)
Total cholesterol, mean (SD)	194.0 (34.6)
LDL cholesterol, mean (SD)	117.0 (30.6)
HDL cholesterol, mean (SD)	51.9 (15.2)
Aortic distensibility, median (range)	0.46 (-1.95 to 3.2)
Aortic valve calcium, median (range)	0 (0–5029)
Mitral valve calcium, median (range)	0 (0–9844)

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation.

^aValues are n (%) unless indicated.

cholesterol was found to be significantly lower in the AVC and only in the high MVC group (not linear for MVC) when compared to the noncalcified group. We also evaluated the association of AD with atrial fibrillation using Cox proportional hazards regression model adjusting for age, gender, and race and found no association (hazard ratio [HR] = 1.07; 95% CI: 0.75–1.52; $P = .71$).

Adjusted Relationship of AD by AVC and MVC

Table 3 provides the unadjusted geometric means of AD by no calcium, low calcium, and high calcium of AVC and MVC. A multivariable regression analysis indicated that log AD was significantly associated with AVC groups after adjusting for age, gender, and ethnicity ($P = .035$). Increased AVC was associated with decreased AD. After adjusting for age, gender, ethnicity, diabetes, hypertension, body mass index, and smoking status, AD was not significantly associated with AVC groups ($P = .23$). The age $\times$ AVC group interaction was also assessed and there was no significant interaction ($P = .36$). The MVC was not associated with AD in either model.

Discussion

This cross-sectional study demonstrates that AD is significantly lower in adults with nonzero AVC and MVC compared to those with zero AVC and MVC, respectively ($P < .001$ in each case). To our knowledge, this is the first study to assess AD by the presence of AVC and/or MVC among adults without

Table 2. Participant Characteristics Across Aortic and Mitral Valve Calcification Groups.^{a,b}

	Aortic Valve (n = 3676)				Mitral Valve (n = 3676)			
	Zero (n = 3256)	Low (n = 211)	High (n = 209)	P	Zero (n = 3365)	Low (n = 156)	High (n = 155)	P
Aortic valve calcium, median (range), AU	0 (0-0)	21 (1.9-57)	137 (58-5029)	-	0 (0-1790)	0 (0-4417)	0 (0-5029)	-
Mitral valve calcium, median (range), AU	0 (0-6591)	0 (0-6735)	0 (0-9844)	-	0 (0-0)	22 (1.9-61.7)	253 (62.2-9844)	-
Age, mean (SD), years	59.3 (9.5)	69.7 (8.1) ^c	70.4 (8.1) ^c	<.001	59.5 (9.5)	70.7 (8.4) ^c	72.2 (7.5) ^c	<.001
Gender				<.001				.25
Female	1829 (56.2%)	85 (40.3%) ^c	79 (37.8%) ^c		1813 (53.9%)	86 (55.1%)	94 (60.6%)	
Male	1427 (43.8%)	126 (59.7%) ^c	130 (62.2%) ^c		1552 (46.1%)	70 (44.9%)	61 (39.4%)	
Race				.01				<.001
White	1350 (41.5%)	109 (51.7%)	115 (55.0%)		1385 (41.2%)	98 (62.8%)	91 (58.7%)	
Chinese	373 (11.5%)	18 (8.5%)	8 (3.8%) ^c		386 (11.5%)	7 (4.5%)	6 (3.9%) ^c	
Black	968 (29.7%)	50 (23.7%) ^c	57 (27.3%)		1004 (29.8%)	35 (22.4%)	36 (23.2%)	
Hispanic	565 (17.4%)	34 (16.1%)	29 (13.9%)		590 (17.5%)	16 (10.3%)	22 (14.2%)	
Hypertension	1262 (38.8%)	127 (60.2%) ^c	137 (65.6%) ^c	<.001	1347 (40.0%)	77 (49.4%)	102 (65.8%) ^c	.028
Diabetes	310 (9.5%)	28 (13.3%)	35 (16.9%) ^c	.035	324 (9.7%)	22 (14.2%)	27 (17.4%) ^c	.042
Cigarette smoking status				.001				.44
Never	1700 (52.4%)	91 (43.3%)	85 (41.3%)		1719 (51.3%)	75 (48.4%)	82 (53.2%)	
Former	1111 (34.2%)	94 (44.8%)	98 (47.6%)		1184 (35.3%)	64 (41.3%)	55 (35.7%)	
Current	435 (13.4%)	25 (11.9%)	23 (11.2%)		450 (13.4%)	16 (10.3%)	17 (11.0%)	
BMI, mean (SD), kg/m ²	27.8 (5.0)	27.3 (4.3)	28.6 (4.6) ^c	<.001	27.8 (5.0)	27.0 (4.2)	29.1 (5.1) ^c	<.001
Total cholesterol, mean (SD), mg/dL	193.7 (34.5)	197.1 (36.3)	195.6 (33.7)	.077	193.8 (34.3)	195.0 (39.7)	197.3 (35.8)	.11
LDL cholesterol, mean (SD), mg/dL	116.7 (30.4)	119.6 (33.2) ^c	119.3 (30.6) ^c	.006	117.0 (30.5)	114.9 (32.5)	120.4 (30.7) ^c	.043
HDL cholesterol, mean (SD), mg/dL	52.1 (15.3)	51.4 (15.1) ^c	49.1 (13.9) ^c	<.001	51.8 (15.2)	55.0 (16.1)	50.0 (14.0) ^c	.009
Framingham global CVD risk per CIRC 2008 paper, mean (SD)	12.1 (8.9)	20.3 (8.8) ^c	21.5 (8.4) ^c	<.001	12.6 (9.1)	17.0 (9.2)	21.0 (9.1) ^c	.003

Abbreviations: AU, Agatston units; BMI, body mass index; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation.

^aValues are n (%) unless indicated.

^bP value is from multinomial logistic regression adjusting for age.

^cP < .05 relative to zero group.

clinical CVD. Individuals with nonzero AVC are more likely to be male, smoke, hypertensive, diabetic, obese, with decreased HDL, and increased LDL and Framingham risk score. Participants with nonzero AVC and MVC were also significantly older than adults with zero AVC and MVC, respectively. These findings are not surprising as the prevalence of valvular calcification increases with age and is uncommon before the age of 65 years.^{19,30} After adjustment for age, sex, and race, AVC was significantly associated with log-transformed AD, while no significant difference was noted by MVC groups.

Previous studies from MESA have shown that decreased AD is associated with smoking status, older age, hypertension, African American ethnicity, increased thoracic aortic calcium, and HDL cholesterol.^{31,32} Two previous studies^{33,34} reported on the relationship between AD or carotid artery distensibility and valvular calcification. In 143 patients referred for trans-thoracic echocardiography and carotid artery echo Doppler,

carotid artery distensibility was decreased among those with higher AVC and MVC.³³ Among 60 patients with end-stage renal disease treated with peritoneal dialysis,³⁴ aortic stiffness was associated with AVC, but not MVC. Due to marked differences in prior study populations, data sources, and methods to quantify AD and valve calcification, these prior studies cannot be compared to our findings in the MESA study.

Participants with higher AVC and MVC demonstrated higher Framingham risk scores, reflecting the burden of cardiovascular risk factors in those with nonzero AVC and MVC is significantly higher than individuals with zero AVC or MVC (AVC: $P < .001$; MVC: $P = .003$). These findings corroborate with the well-established association between AD and future risk of cardiovascular events,¹⁸ where individuals older than 65 years have a 25% prevalence of developing AVC and are associated with a 50% increased risk of cardiovascular mortality.¹⁹ Among our study, individuals with low or high AVC or MVC

Table 3. Association of Aortic and Mitral Valve Calcification With Aortic Distensibility.^{a,b,c}

	Aortic Distensibility			Model 1			Model 2		
	n	Unadjusted Geometric Mean (1/mm Hg) (95% CI)	P	Parameter Estimate	Standard Error	P ^d	Parameter Estimate	Standard Error	P ^d
Aortic valve calcification			<.001			.035			.23
Zero	3256	1.64 (1.61-1.67)		Ref	-	-	Ref	-	-
Low	211	1.16 (1.08-1.25)		-0.09	0.04	.017	-0.06	0.04	.097
High	209	1.19 (1.11-1.27)		-0.05	0.04	.2	-0.02	0.04	.5
Mitral valve calcification			<.001			.64			.73
Zero	3365	1.61 (1.58-1.65)		Ref	-	-	Ref	-	-
Low	156	1.27 (1.18-1.36)		0.04	0.04	.39	0.03	0.04	.43
High	155	1.16 (1.07-1.26)		-0.01	0.04	.77	0.01	0.04	.87

^aModels 1 and 2 show differences in aortic distensibility (1/mm Hg) by the presence of low or high AVC or low or high MVC compared to zero AVC or MVC, respectively.

^bModel 1 adjusts for age, gender, and race.

^cModel 2 adjusts for age, gender, race, diabetes, hypertension, BMI, and smoking status. Age was modeled with a natural spline with 2 knots for each model.

^dP value for aortic valve calcification or mitral valve calcification categories in the overall model.

were found to have a higher Framingham risk score compared to those with zero AVC or MVC. Thus, finding AVC indicates lower AD and higher CVD risk due to the higher burden of cardiovascular risk factors. Based on previous study,³⁵ older individuals, and increased Framingham risk in those with AVC and MVC, we evaluated the association of AD with atrial fibrillation using Cox proportional hazards regression model adjusting for age, gender, and race and found no association (HR = 1.07; 95% CI: 0.75-1.52; $P = .71$). Therefore, lower AD is associated with nonzero AVC reflecting higher burden of cardiovascular risk factors, especially in older aged individuals, but does not equate to atrial fibrillation risk. This may reflect that AD is confounded by older age and increased cardiovascular risk factors that result in worse outcomes.

Strengths of MESA include the standardized and validated measures of multiple CVD risk factors and AVC and MVC in a multiethnic cohort free of CVD at baseline. The MESA also includes 4 different racial/ethnic groups. Our study has important limitations. Due to the cross-sectional design, we cannot discern temporal associations. One of the limitations is the exclusion of morbidly obese adults because AD was measured using MRI and these participants were excluded from MRI. Furthermore, there may have been additional confounders not evident in this analysis, which was thereby not accounted for and could have changed the results. The MESA also excluded individuals with clinical CVD, and the number of participants with high AVC and MVC was small. The MESA cohort was not a random sample of the US population, but MESA was structured for multiethnic representation. Our study may not be generalized to very young or those with established CVD.

In conclusion, in a multiethnic cohort, AD is lower in adults with nonzero AVC and MVC but this association is due to higher age and comorbidities. Future studies should examine other potential determinants of AD and whether modifiable risk factors and medication may affect AD.

Authors' Note

A full list of participating MESA investigators and institutions can be found at <http://www.mesa-nhlbi.org>. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses.

Acknowledgments

The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was supported by R01 HL071739 and contracts N01-HC-95159 through N01-HC-95165 and N01 HC 95169 from the National Heart, Lung, and Blood Institute.

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