CHEST

Original Research

PULMONARY VASCULAR DISEASE

Brachial Artery Diameter and the Right Ventricle

The Multi-Ethnic Study of Atherosclerosis-Right Ventricle Study

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Background: **Endothelial dysfunction is associated with left ventricular morphology and long-term cardiovascular outcomes. The purpose of this study was to assess the relationship between both baseline brachial artery diameter and peripheral endothelial function (assessed by brachial artery ultrasonography) and right ventricular (RV) mass, RV end-diastolic volume (RVEDV), and RV ejection fraction (RVEF).**

Methods: **The Multi-Ethnic Study of Atherosclerosis (MESA) performed cardiac MRI and brachial artery ultrasonography on participants without clinical cardiovascular disease. Baseline brachial artery diameter and flow-mediated dilation were assessed.**

Results: **The mean age was 60.9 years, and 49.4% of subjects were men (n = 2,425). In adjusted models, larger brachial artery diameter was strongly associated with greater RV mass (β = 0.55 g, *P* < .001), larger RVEDV (β = 3.99 mL, *P* < .001), and decreased RVEF (β = −0.46%, *P* = .03). These relationships persisted after further adjustment for the respective left ventricular parameters. Flow-mediated dilation was not associated with RV mass or RVEF and was only weakly associated with RVEDV.**

Conclusions: **Brachial artery diameter is associated with greater RV mass and RVEDV, as well as lower RVEF. Changes in the systemic arterial circulation may have pathophysiologic links to pulmonary vascular dysfunction or abnormalities in RV perfusion.** ***CHEST 2012; 142(6):1399–1405***

Abbreviations: BD = baseline brachial artery diameter; FMD = flow-mediated dilation; LV = left ventricular; MESA = Multi-Ethnic Study of Atherosclerosis; RV = right ventricular; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; SDB = sleep-disordered breathing

The importance of systemic hypertension and endothelial dysfunction in causing left ventricular (LV) hypertrophy is well defined.[1,2] In contrast, data regarding the association between peripheral endothelial dysfunction and right ventricular (RV) structure and function are scarce. Patients with idiopathic pulmonary arterial hypertension demonstrate peripheral vascular endothelial dysfunction and commonly have RV hypertrophy, dilation, and systolic dysfunction.[3-5] Furthermore, peripheral endothelial function is linked to the pulmonary vascular response to vasodilators.[6] Despite these associations, there has been little investigation of the relationship between peripheral vascular endothelial dysfunction and RV morphology, even though endothelial dysfunction may precede clinical cardiovascular disease and is potentially modifiable.[7-9]

Brachial artery ultrasonography can assess peripheral vascular structure and function. Larger baseline brachial artery diameter (BD) is independently associated with cardiovascular risk factors and an increased risk of cardiovascular events.[10,11] The change in brachial arterial diameter following occlusion of blood flow divided by the BD (known as flow-mediated dilation [FMD]) reflects the capacity for endothelial nitric oxide production and is a significant predictor of cardiovascular events in population-based cohort studies, heart failure, and coronary disease, and after elective vascular surgery.[11-16] Systemic

vascular structure and function may be linked to RV morphology by reflecting right coronary perfusion, the neurohormonal milieu, and/or pulmonary vascular dysfunction and increased RV afterload.[17,18] The purpose of this study was to evaluate the relationship between BD and FMD and RV mass, RV end-diastolic volume (RVEDV), and RV ejection fraction (RVEF) in a population free of clinical cardiovascular disease.

Materials and Methods

The Multi-Ethnic Study of Atherosclerosis (MESA) is a multicenter prospective cohort study to investigate the prevalence, correlates, and progression of subclinical cardiovascular disease in whites, blacks, Hispanics, and Chinese.[19] In 2000-2002, MESA recruited 6,814 men and women aged 45 to 84 years old from six US communities: Forsyth County, North Carolina; Northern Manhattan and the Bronx, New York; Baltimore City and Baltimore County, Maryland; St. Paul, Minnesota; Chicago, Illinois; and Los Angeles, California. Exclusion criteria included clinical cardiovascular disease (physician diagnosis of heart attack, stroke, transient ischemic attack, heart failure, angina, current atrial fibrillation, any cardiovascular procedure), weight > 136 kg (300 lbs), pregnancy, or impediment to long-term participation. Hypertension, diabetes mellitus, and hyperlipidemia were not considered as clinical cardiovascular disease by the design of the parent study, and subjects with these conditions were therefore eligible for inclusion. Informed consent was obtained from all participants. The studies described herein were approved by the institutional review board of the University of Pennsylvania (No. 808374).

Of the 6,814 participants, 5,098 agreed to undergo MRI and had no contraindications. LV morphology was interpretable in 5,004 participants (98%). Of these, the MESA-Right Ventricle ancillary study targeted the interpretation of 4,484 scans and successfully read 4,204 scans for RV morphology.[20-25] Brachial artery ultrasonography was measured in 6,489 participants. A randomly selected sample of 2,844 participants plus 182 participants who had a cardiovascular event within 5 years of follow-up had ultrasound measurements interpreted (n = 3,026). Therefore, our study sample (n = 2,425) was composed of the participants with complete covariate data from the intersection of the 3,026 with brachial artery ultrasound measurements and the 4,204 with interpretable RV function (Fig 1).

MRI Protocol and Brachial Artery Ultrasonography

The cardiac MRI protocol and methods for interpretation of LV and RV parameters in MESA have been reported (e-Appendix 1).[23,25,26] BD and FMD were determined using high-resolution ultrasonography of the brachial artery.[11,16,27] In brief, participants were asked to abstain from food, consumption of vitamin E or C, and smoking for ≥ 6 h before the scan. A standard BP cuff was positioned around the right arm, 2 in below the antecubital fossa, and the brachial artery of the right arm was imaged 5 to 9 cm above the antecubital fossa using a 9-MHz linear array transducer (M12L transducer; GE Healthcare). Digitized images of the right brachial artery were captured continuously for 30 s before cuff inflation (BD). To induce reactive hyperemia, the brachial artery was occluded for 5 min at an occlusion cuff pressure of ≥ 50 mm Hg above the participant's systolic BP. Digitized images were recorded for 2 min beginning immediately before cuff deflation to document the vasodilator response. Data were analyzed using a validated semiautomated system.[16,28] FMD was expressed as the percentage of increase in the brachial artery diameter (media-adventitial interface to the media-adventitial interface) with reactive hyperemia: FMD = ([peak brachial artery diameter after cuff deflation − BD]/BD) × 100.

Intrasubject variability was evaluated by comparing results from repeated examinations of 19 subjects on 2 days, 1 week apart. The intraclass correlation coefficients for BD, peak diameter, and FMD were 0.90, 0.90, and 0.54, respectively. The intrareader intraclass correlation coefficients for BD, peak diameter, and FMD were 0.99, 0.99, and 0.93, respectively, from 40 scans. Percentage technical errors of measurement for BD, peak diameter, and FMD were 1.39%, 1.47%, and 28.4%, respectively.[16]

Covariates and Statistical Analysis

See e-Appendix 1 for information on the covariates. Multivariable linear regression was used to assess the relationship of BD and FMD (independent variables) with RV mass, RVEDV, and RVEF (dependent variables) (e-Appendix 1). All analyses were adjusted for height, weight, and waist circumference, so it was not necessary to index the RV parameters to account for differences in body size. Analyses were performed using STATA 11.0 (StataCorp LP). P values < .05 were considered statistically significant.

Results

There were 2,455 participants with measurement of RV morphology and brachial artery ultrasonography. We excluded 30 participants with missing covariate data, leaving 2,425 in the final study sample (Fig 1). The mean age was 60.9 years, and 49.4% were men (Table 1). Approximately one-third were white, 21.0% were black, 25.1% were Hispanic, and

Manuscript received January 4, 2012; revision accepted April 24, 2012.
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Funding/Support: This work was supported by the National Institutes of Health [Grants and Contracts HL086719, HL103844, HL077612, N01-HC95159 through HC95165, and HL007891]. This research was also supported (in part) by the Intramural Research Program of the National Institutes of Health (National Institute of Biomedical Imaging and Bioengineering).
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DOI: 10.1378/chest.12-0028

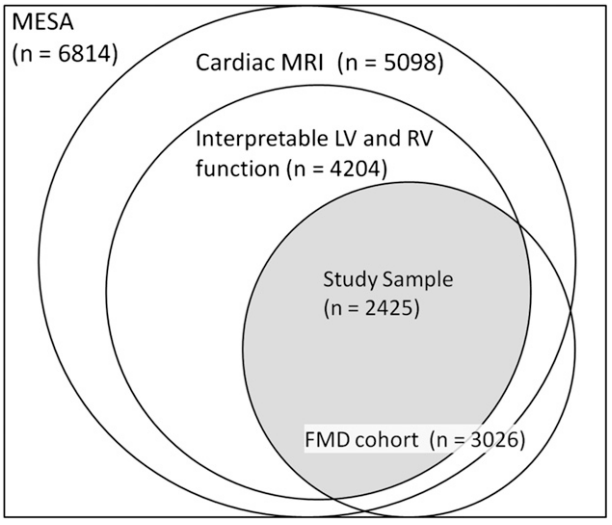

FIGURE 1. Study sample. FMD = flow-mediated dilation; LV = left ventricular; MESA = Multi-Ethnic Study of Atherosclerosis; RV = right ventricular.

19.9% were Chinese. The mean BMI was 27.3 kg/m². Those included were somewhat more likely to be male, Chinese, and nonsmokers, and less likely to be black than were those excluded, but were generally similar (Table 1). Formal hypothesis testing for these comparisons (*P* values) is not appropriate and was not performed. Table 2 shows the results of the cardiac MRI and brachial artery ultrasonography. The mean RVEF was 70.2% ± 6.5%. The mean BD and FMD were 4.30 mm and 4.41%, respectively.

Larger BD was significantly associated with greater RV mass in the limited and adjusted models (both $P < .001$) (Fig 2A, Table 3). A 1-mm increase in BD corresponded to a 0.55-g higher RV mass in the adjusted model. This relationship was attenuated but persisted after adjusting for LV mass ($P = .001$), suggesting a relationship between BD and RV mass independent of LV mass. Similarly, larger BD was significantly associated with greater RVEDV in limited and adjusted models (both $P < .001$) (Fig 2B, Table 3). A 1-mm increase in BD corresponded to a 3.99-mL-larger RVEDV in the adjusted model. This relationship was attenuated but persisted after adjusting for LV end-diastolic volume ($P = .001$). Larger BD was associated with lower RVEF after adjustment for covariates ($P = .03$) (Fig 2C, Table 3). Adjustment for LV ejection fraction attenuated this association, which still appeared to be present ($P = .07$). There were no differences in these associations by sex or race/ethnicity. The relationships between BD and RV parameters were present in models without adjustment for height, weight, and waist circumference and with adjustment for only the corresponding LV parameter (eg, RVEF adjusted for LV ejection fraction) (data not shown).

FMD was not significantly associated with RV mass and RVEF. Higher FMD was associated with statistically significantly lower RVEDV in the limited and adjusted models. However, the effect estimates were small (Table 3, e-Fig 1).

We repeated these analyses after adjusting for spirometry, urine cotinine, and extent of emphysema by CT scan in those with available data (n = 2,300), with findings nearly identical to those from the full cohort (e-Table 1). Larger BD was significantly associated with greater RV mass and larger RVEDV in the limited and adjusted models (both $P < .001$). This relationship was attenuated but persisted after adjustment for the corresponding LV parameter. BD appeared to be associated with RVEF in this subset but did not reach statistical significance.

In those unlikely to have sleep-disordered breathing (SDB) (n = 743), the effect estimates were similar (or larger) compared with those from the main analysis (e-Table 2). Larger BD was significantly associated with greater RV mass and larger RVEDV in the limited and adjusted models (e-Table 2). Finally, approximately one-third of our cohort (n = 839) were not obese, were nonsmokers, and did not have hypertension, diabetes mellitus, or impaired fasting glucose. Again, the relationships seen between BD and RV parameters in this healthy subset were similar to

Table 1—*Characteristics of the Study Sample Compared With Those Excluded*

Characteristic	Study Sample (n = 2,425)	Excluded (n = 4,389)
Age, y	60.9 ± 9.9	62.8 ± 10.4
Male	49.4	45.9
Race/ethnicity		
White	34.2	40.9
Black	21.0	31.6
Hispanic	25.1	20.2
Chinese	19.9	7.3
Height, cm	166.2 ± 9.9	166.5 ± 10.1
Weight, kg	75.8 ± 16.0	80.2 ± 17.8
BMI, kg/m²	27.3 ± 4.8	28.9 ± 5.8
Educational attainment		
No high school degree	17.4	18.4
High school degree	24.6	25.8
Some college	20.2	22.0
College degree	18.5	16.6
More than bachelor's degree	19.3	17.3
Cigarette smoking status		
Never	55.5	47.5
Former	33.4	38.4
Current	11.1	14.1
Hypertension medication use	30.5	34.8
Statin use	13.9	15.3
Systolic BP, mm Hg	124.2 ± 19.9	127.9 ± 22.1
Diastolic BP, mm Hg	71.9 ± 10.0	71.9 ± 10.4
Diabetes mellitus (treated or untreated)	10.5	13.9

Data are presented as mean ± SD or %.

Table 2—*MRI and Brachial Artery Ultrasonography Results*

Parameter	Study Sample (n = 2,425)
RVEDV, mL	125.4 ± 31.4
RV mass, g	21.1 ± 4.3
RVEF, %	70.2 ± 6.5
LVEF, %	69.3 ± 7.2
Baseline brachial artery diameter, mm	4.30 ± 0.82
FMD, %	4.41 ± 2.80

Data are presented as mean ± SD. FMD = flow-mediated dilation; LVEF = left ventricular ejection fraction; RV = right ventricular; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction.

those from the full study sample (e-Table 3). Power to detect significant differences in these smaller subsets was more limited than in our main study sample.

Discussion

We have shown that larger BD is associated with greater RV mass, larger RVEDV, and lower RVEF in individuals free of clinical cardiovascular disease. These findings were present both before and after adjustment for height, weight, and LV mass and volume, indicating that the relationship was not attributable to differences in body size or changes in the LV. Our findings were not affected by adjustment for spirometry, cotinine levels, and extent of emphysema, indicating that the relationship is not due to confounding by tobacco use or parenchymal lung structure or function. Finally, the results were similar in those individuals at low risk of SDB and without other common medical conditions. These data suggest that systemic vascular structure may be associated with RV morphology independent of any concomitant lung, sleep, medical, or LV disorders, implying that the peripheral vasculature could be an indicator of pulmonary vascular remodeling. The relative changes in RV mass with a 1- to 2-mm difference in BD are similar to those seen for LV mass in relation to active smoking or diabetes mellitus in MESA.[25] RV hypertrophy and enlargement may be associated with increased risks of heart failure and cardiovascular death, suggesting clinical relevance.[29] However, just as with the LV, it is likely overly simplistic to designate increased RV mass as "good" or "bad." There are likely adaptive and maladaptive forms of ventricular hypertrophy, which are not necessarily easy to discriminate morphologically.

The association of larger BD with greater RV mass and volumes seemingly runs counter to the notion that diseased arteries become narrowed. However, a large body of human and nonhuman primate research suggests that systemic arteries remodel and dilate in response to cardiovascular risk factors.[30] In an autopsy

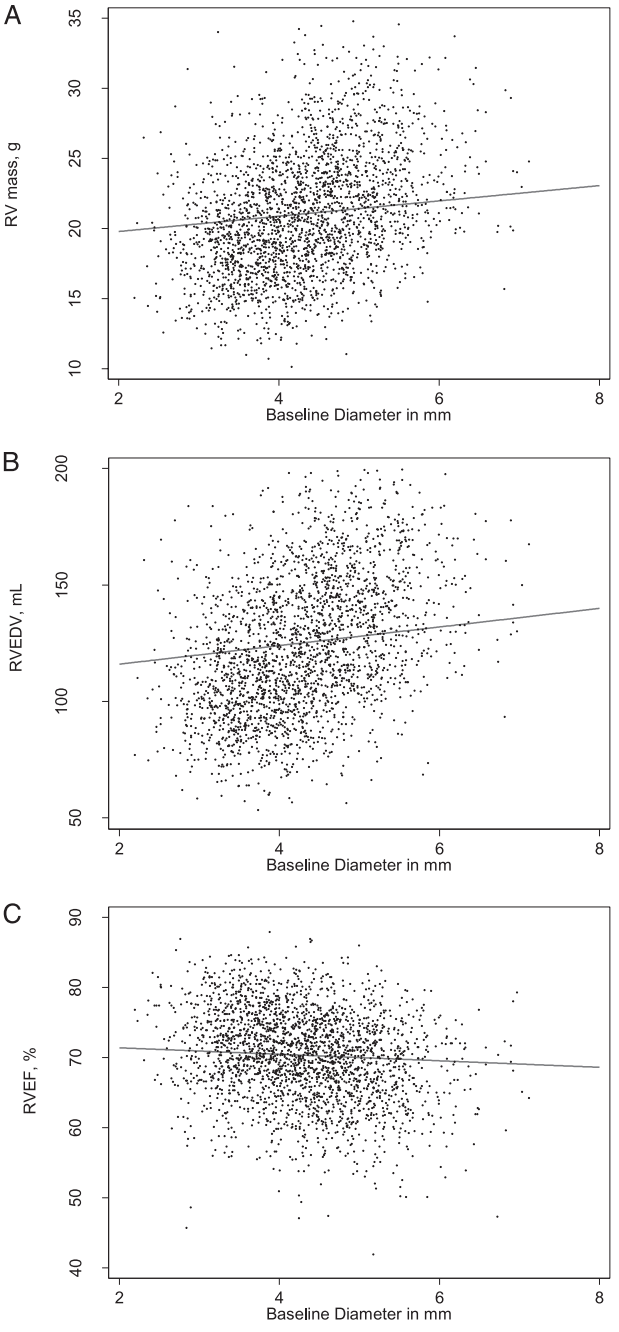

Figure 2. Fully adjusted linear relationship between baseline diameter and RV mass, RVEDV, and RVEF. A, RV mass. B, RVEDV. C, RVEF. RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction. See Figure 1 legend for expansion of other abbreviations.

study, early atherosclerosis was characterized by enlargement of coronary vessel and luminal diameter.[31] Several studies have linked cardiovascular risk factors and atherosclerosis with larger luminal diameters of the brachial artery and other vascular structures.[10,32-34] In MESA, larger BD was strongly associated with wider retinal venular caliber and smaller retinal arteriolar caliber, both validated markers of systemic vascular disease.[35] Chung et al[33] found that larger

Table 3—*Linear Regression Models of the Association Between Brachial Artery Ultrasonography and RV Parameters (n = 2,425)*

	Limited Model[a]			Adjusted Model[b]			Adjusted Model + LV[c]		
Parameter	β	95% CI	*P* Value	β	95% CI	*P* Value	β	95% CI	*P* Value
RV mass									
Baseline diameter	0.53	0.33-0.74	< .001	0.55	0.34-0.76	< .001	0.35	0.15-0.55	.001
FMD	−0.04	−0.09-0.01	.08	−0.04	−0.09-0.01	.09	−0.01	−0.06-0.04	.67
RVEDV									
Baseline diameter	3.83	2.34-5.33	< .001	3.99	2.50-5.48	< .001	1.86	0.77-2.95	.001
FMD	−0.36	−0.68-−0.04	.03	−0.37	−0.69-−0.05	.02	−0.07	−0.31-0.17	.56
RVEF									
Baseline diameter	−0.39	−0.81-0.03	.07	−0.46	−0.89-−0.04	.03	−0.35	−0.74-0.03	.07
FMD	0.05	−0.05-0.30	.31	0.05	−0.04-0.15	.28	0.04	−0.05-0.13	.34

β represents the change in the respective RV parameter (g for RV mass, mL for RVEDV, and % for RVEF) associated with a 1-unit increment of the vascular parameter (1 mm for baseline diameter, 1% for FMD). LV = left ventricular. See Table 2 legend for expansion of other abbreviations.

[a]Limited model includes age, sex, race/ethnicity, height and weight, waist circumference, systolic BP, and diastolic BP.

[b]Adjusted model includes all covariates from limited model with the addition of statin use, hypertension medication use, diabetes, smoking status, pack-years, education level, and exercise.

[c]Indicates the addition of the relevant LV parameter (eg, LV mass for model with RV mass).

postsublingual nitroglycerin brachial artery diameter (reflecting maximal vasodilation) was associated with cardiovascular risk factors, suggesting the importance of arterial remodeling (rather than vascular tone). Larger vessels had proportional increases in blood flow, consistent with flow-induced adaptive remodeling.

Larger BD also predicts worse cardiovascular outcomes. In the Women's Ischemia Syndrome Evaluation study, larger BD (but not FMD) was an independent predictor of coronary artery disease in women with chest pain.[36] The Cardiovascular Health Study demonstrated a relationship between larger BD and an increased risk of cardiovascular events.[11] In MESA, BD was associated with cardiovascular events independent of the Framingham risk score; however, the relationship was not seen in the final multivariable model.[16]

There are several possible explanations for the associations between BD and RV parameters in our study. Peripheral endothelial dysfunction has been linked with increased LV mass in MESA and other cohorts, independent of BP.[1,2,37-39] Nitric oxide signaling is also associated with cardiac remodeling and hypertrophy.[40,41] Therefore, an afterload-independent relationship between the peripheral vasculature and cardiac morphology (eg, mediated by neurohormonal activation) may provide a potential explanation for associations with RV morphology in this study.

Larger BD may also be a surrogate marker for pulmonary vascular remodeling, which could impact the RV through subclinical increases in afterload. Studies using a variety of methodologies have linked peripheral endothelial function with pulmonary vascular disease.[4-6,42] Given the relationship between systemic and pulmonary vascular function (and the shared milieu of circulating mediators), it is possible that remodeling in the systemic and pulmonary vessels may also occur in concert.

Finally, BD is associated with coronary artery calcification, which suggests that altered right coronary perfusion could explain the RV morphologic changes.[43] Abnormal RV perfusion and ischemia adversely affect the ventricle in pulmonary vascular disease, even in the absence of epicardial coronary artery disease.[44] Subclinical RV perfusion variability has not been well studied in participants without clinical cardiovascular disease.

We did not find a consistent relationship between FMD and RV parameters. The variability of FMD was much greater than of BD, likely because of compounding of the errors from the two measurements necessary to compute this variable. Therefore, it is possible that measurement error in FMD accounts for the discordant results between FMD and BD.

There were some limitations in our study. As with all measures, error in the assessment of brachial artery diameters and RV morphology is possible. However, potential error in either measurement (as long as nondifferential) should bias our results toward the null hypothesis, so that the associations may be even stronger than we have shown. We attempted to account for multiple covariates and perform additional analyses of healthy subsets; however, residual or unmeasured confounding is possible. FMD has been linked to the presence of obstructive lung disease[45]; however, our findings were similar after adjustment for lung function, suggesting that lung disease did not account for the associations. Two studies have shown a link between BD and SDB; however, the effect estimates were unchanged after

exclusion of participants who may have had SDB.[32,46] We did not have brachial artery or RV measures available in all participants; however, we incorporated weighting into our analysis and those included in the study sample were similar to those excluded.

In summary, we have described a strong association between brachial artery BD and RV morphology. The relationship between RV mass and function and peripheral vascular structure warrants further studies to determine how these findings impact subclinical and clinical heart and lung disease. Future investigation of the relationships between brachial artery BD and RV afterload and perfusion may elucidate the mechanisms that explain these findings.

Acknowledgments

Author contributions: Dr Kawut is the guarantor of the entire manuscript.
Dr Dibble: contributed to study concept and design, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content, and takes responsibility for the integrity of the work as a whole.
Dr Shimbo: contributed to study concept and design, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content.
Dr Barr: contributed to study concept and design, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content.
Dr Bagiella: contributed to study concept and design, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content.
Dr Chahal: contributed to study concept and design, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content.
Dr Ventetuolo: contributed to study concept and design, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content.
Dr Herrington: contributed to study concept and design, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content.
Dr Lima: contributed to acquisition and interpretation of MRI data, study concept and design, and critical revision of the manuscript for important intellectual content.
Dr Bluemke: contributed to acquisition and interpretation of MRI data, study concept and design, and critical revision of the manuscript for important intellectual content.
Dr Kawut: contributed to study concept and design, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content.
Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following conflicts of interest: Dr Ventetuolo has received grant funding from Pfizer, Inc and has served on advisory boards for Actelion Pharmaceuticals Ltd, Gilead, and United Therapeutics Corp. Drs Dibble, Shimbo, Barr, Bagiella, Chahal, Herrington, Lima, Bluemke, and Kawut have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.
Role of sponsors: The sponsors coordinated data collection, provided editorial assistance, and approved final versions of the manuscript.
Other contributions: This manuscript has been reviewed by the MESA Investigators for scientific content and consistency of data interpretation with previous MESA publications, and significant comments were incorporated prior to submission for publication. The authors thank the other investigators, staff, and participants of the MESA for their valuable contributions. A full list of participating MESA Investigators and institutions can be found at http://www.mesa-nhlbi.org. The authors thank Laurel Kalman, BA, for editorial assistance.
Additional information: The e-Appendix, e-Figure, and e-Tables can be found in the "Supplemental Materials" area of the online article.

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